Sociedad de Bioquímica
y Biología Molecular de Chile

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From Molecules to Cells and Disease

Abstract Book

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XLI Reunión Anual SBBMCH
25-28 de Septiembre 2017, Iquique

“THE WAY OF DOING SOCIETY".

Last year, our Society celebrated its 40th anniversary in an uninterrupted manner and we celebrated it in a big way. Many members joined us and we had a rich discussion of various topics. This year we continue with the same enthusiasm that we had since the first meeting in Talca back in 1977 and we prepared a high quality congress that will be for the first time in the “Norte Grande de Chile, Iquique”.

As a directive we know that it is important to show the members that our Society has been built with the contribution of great people, and that each congress has had a special stamp. In order to honor and value our previous directives, remembering their impressions and experiences, we invited each past-president to deliver an account of his period to share with the other members and know firsthand how each previous directive boosted the growth of our beloved society. Thus, looking to the past and supported by our history, we can build together a prosperous future for our beloved society. We hope that these stories fill you with the passion with which the different periods of the Society were gestated and that they serve as a guide to continue growing.

We hope this year will be a new opportunity to get even closer and invite more partners to participate in the discipline of Biochemistry and Molecular Biology, making our beloved society an inclusive platform of scientific reflection and friendship.

Directive,

“LA MANERA DE HACER SOCIEDAD.

El año pasado nuestra Sociedad cumplió 40 años realizando su congreso anual de manera ininterrumpida y lo celebramos en grande. Muchos socios nos acompañaron y tuvimos una muy buena discusión de variados temas.
Este año seguimos con el mismo entusiasmo que se tuvo desde la primera reunión en Talca en 1977 y preparamos un congreso de gran calidad que será por primera vez en el Norte Grande de Chile.

Como directiva sabemos que es importante mostrar a los socios que nuestra Sociedad se ha ido construyendo con el aporte de grandes personas, y que cada congreso ha tenido un sello especial. Con la finalidad de homenajear y valorar a nuestras anteriores directivas, recordando sus impresiones y vivencias, invitamos a cada ex-presidente a entregar un relato de su periodo para compartir con los demás socios y conocer de primera fuente como, cada directiva anterior impulsó el crecimiento de nuestra querida sociedad. Así, mirando hacia el pasado y apoyados en nuestra historia, podemos construir juntos un prospero Futuro para nuestra querida sociedad. Esperamos que estos relatos los llenen de la pasión con la cual se fueron gestando los diferentes periodos de la Sociedad y que nos sirvan de guía para seguir creciendo.

Este año esperamos sea una oportunidad de acercarnos y de invitar a participar a más socios en la disciplina de la Bioquímica y Biología Molecular, haciendo de nuestra querida sociedad una instancia inclusiva de reflexión científica y de amistad.

DIRECTORY

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Past President	: Marcelo López-Lastra
Vice President	: Luis F. Larrondo
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Past Presidents Brief Memoirs (in spanish)

Dr. Marcelo López-Lastra (Presidente 2015-2016)
Ilona Concha, Vicepresidente; Luis Larrondo Secretario; Christian Wilson, Tesorero; Sergio Lavandero, Presidente anterior; Claudia Stange, Directora Santiago; Lorena Garcia, Directora Santiago; Violeta Morin, Directora Concepción; Patricio Ramos, Director Talca; Claudia Quezada, Directora Valdivia;

"Me declaro culpable" es con esta auto-denuncia que mi directiva inicio su periodo en la dirección de la Sociedad de Bioquímica de Chile. Así, se asumió ante el Ministerio de Justicia la responsabilidad de nuestra Sociedad de no haber dado cumplimiento desde el año 1975 a la obligación legal de informar anualmente de sus actividades a dicho Ministerio. Es necesario sin embargo aclarar que desde su inicio nuestra Sociedad dio cumplimiento a todas sus obligaciones institucionales llevando las actas al día, registros de socios, balances financieros y demás antecedentes societarios. A pesar de ello la Sociedad de Bioquímica se encontraba en un estado de "inactividad" ante el Ministerio de Justicia debido a la omisión de la obligación legal de entrega de información anual de sus actividades. Bien se comprendió lo complejo de esta situación la cual se agravaba aún más por el surgimiento de la Ley 20.500 la cual establecía la nueva normativa de las Sociedades sin fines de lucro. Por ello y con el fin de evitar una fiscalización forzosa o bien el ingreso en causal de disolución de nuestra Sociedad se decidió apersonarse al Ministerio y reconocer de manera propia este grave error de omisión. Como consecuencia a este acto de auto-denuncia el Ministerio de Justicia nombró a un fiscal de la causa iniciándose así el proceso de regularización de nuestra Sociedad. Durante todo el proceso nuestra directiva trabajo codo a codo junto un grupo de talentosos abogados y a nuestro contador recopilando toda la información asociada a nuestra Sociedad solicitada por el fiscal del caso. Es así como se recuperaron y digitalizaron todos los libros resúmenes de las reuniones anuales desde el año 1977, se realizó un recuento histórico de las diversas actividades realizadas desde sus inicios, se actualizo la lista de Socios activos, y se realizó un balance detallado de las cuentas históricas de la Sociedad entre otras actividades. El proceso resulto largo y en ciertas etapas muy complejo. En ocasiones, que normalmente se asociaban con una nueva solicitud aclaratoria o de la presentación de más documentación por parte del fiscal del caso, se presentaba con un final incierto. Sin embargo, el 21 de Diciembre del año 2016 el proceso de legalización de nuestra Sociedad culminó de manera exitosa dándose inicio a la etapa siguiente que consistía en la modificación de los Estatutos de la Sociedad para poder así ajustarlos a la nueva normativa legal impuesta por la Ley 20.500.

Saludos cordiales,
Marcelo López-Lastra.

Dr. Sergio Lavandero (Presidente 2013-2014)
Marcelo López-Lastra, Vicepresidente; Andrew Quest Secretario; Lorena Norambuena, Tesorero; Victoria Guixé, Presidente anterior; Eduardo Kessi, Director Santiago; Luis Larrondo, Director Santiago; Ariel Castro, Director Concepción; Raúl Herrera, Director Talca; Ilona Concha, Directora Valdivia.

Esta historia comienza en una mañana de Octubre del 2010 en Dallas donde realizada mi estadía sabática en la University of Texas Southwestern Medical Center. Recibo la sorpresiva y grata llamada de la Prof. Victoria Guixé (Vicky), invitándome a ser Vice-Presidente durante su Presidencia entre 2011-2013 junto a los socia/os Marcelo Lopez Lastra (Tesorero), Lorena Norambuena (Secretaria) y los delegada/os Eduardo Kessi, Luis Larrondo, Ilona Concha, Ariel Castro y Raúl Herrera. Me encantó la idea pero de a poco me fui enterando que asumiría una gran responsabilidad mayor cuando asumiera como próximo Presidente de nuestra Sociedad, ni más ni menos la organización de la XX Reunión de la PABSMB a realizarse en Chile. Además todos recordábamos la reunión de la PABMB, casi épica, realizada en Pucón bajo la dirección del Prof. Jorge Babul. En especial su sobresaliente programa científico y cóctel inaugural. La vara y expectativas estaban puestas muy altas. Acepté este desafío con una sola condición. Excepcionalmente no haría una renovación de la directiva, sino sólo cambios internos, pues las desafiantes exigencias requerían de un grupo humano de experiencia, afiatado en el trabajo en equipo y sin tiempo para improvisaciones. A nuestro equipo se incorporó Andrew Quest para facilitar el contacto con investigadores extranjeros. Las tareas de conseguir recursos, búsqueda de un lugar con la infraestructura óptima para m congreso científico y también hotelera, sumado a la realización de este evento junto a otras Sociedades, en especial la Sociedad de Biología de Chile y la Protein Society fueron algunas de las tareas más complejas sumado a mi simultáneo desempeño como Vicerrector de Investigación de la Universidad de Chile. Este encuentro se realizó en Puerto Varas, usando dos sedes y varios hoteles, asistiendo cerca de 1000 personas. Tuvimos 20 conferencias, destacando la Opening FEBS Lecture realizada por Robert Huber (Nobel Prize), la Closing Lecture dictada por Carlos Bustamante y las dos excepcionales Plenary Lectures realizadas por Fabián Jaksic y María Teresa Ruiz. Además se realizaron 29 simposios, 3 sesiones de paneles y una feria científica. Este evento internacional organizado por nuestra Sociedad fue un éxito. Ahora miro hacia atrás y medito que salió adelante, esencialmente gracias al equipo humano que formamos. Mis infinitas gracias y reconocimiento a esa inolvidable Directiva.

Saludos cordiales,

Sergio Lavandero

Dr. Victoria Guixé (Presidente 2011-2012)
Sergio Lavandero, Vicepresidente; Lorena Norambuena, Secretario; Marcelo López-Lastra, Tesorero; Juan Olate, Presidente anterior; Eduardo Kessi, Director Santiago; Gino Corsini, Director Santiago; Roxana Pincheira, Directora Concepción; Raúl Herrera, Director Talca; Ilona Concha, Directora Valdivia.

Tuve el honor y el privilegio de presidir la SBBM durante el período 2011-2012. Asumí el cargo con mucho entusiasmo, alegría y ganas de hacer las cosas bien, con el genuino interés de contribuir a la Sociedad. Sin embargo, en el transcurso del año 2011 tuve un serio problema de salud que me obligó a permanecer en cama sin posibilidad de moverme. No obstante, eso no fue impedimento para que, con la gran e incondicional ayuda de Lorena y Eduardo, pudiera dirigir la Sociedad desde mi cama. Largas horas de conversación telefónica con Lorena me permitían estar al tanto y discutir las directrices de lo que pensábamos debía ser el rumbo de la Sociedad, así como discutir hasta los más mínimos detalles.

Al asumir, nuestra Directiva se hizo el propósito de revitalizar la Sociedad, haciéndola más atractiva para nuevos miembros y al mismo tiempo modernizarla en su gestión. Fue así, como el año 2011 la Directiva de la SBBM se reunió con la encargada de Becas de Conicyt con el fin de plantearle nuestras inquietudes sobre la forma y ejecución de los concursos relacionados con el financiamiento para asistencia a congresos nacionales, reunión que no tuvo el éxito esperado. Asimismo, se reformuló y modernizó la página web. Instauramos el Ciclo de Charlas Encuentros con la Ciencia,las que se realizaban durante el año y ofrecían una instancia adicional de encuentro entre socios y estudiantes. El año 2011 esta actividad estuvo a cargo del Dr. Tito Ureta y el Dr. Alfredo Jadresic, quienes expusieron “Los primeros pasos de la Bioquímica en Chile”. El año 2012esa actividad correspondió al homenaje póstumo al Dr. Tito Ureta.

Instauramos el Premio Dr. Tito Ureta como una forma de mantener vivo el recuerdo de nuestro maestro, socio y ex presidente y de reconocer su gran labor científica y académica. El Premio Tito Ureta 2012 se otorgó al Dr. Jorge Allende Rivera, y su entrega se efectuó en una ceremonia que tuvo lugar durante la Reunión Anual de aquel año, a la que asistió el Dr. Jorge Allende y su esposa. Por otra parte, nuestra Sociedad, a través de su presidenta, participó de la nueva edición del libro en homenaje a Hermann Niemeyer.

En las Reuniones Anuales de los años 2011 y 2012 incorporamos una conferencia denominada Diálogos con la Ciencia, la que tenía por objeto escuchar una conferencia científica fuera del ámbito de la Bioquímica y Biología Molecular. Durante esas mismas reuniones se desarrolló una actividad denominada Almuerzo con los Expertos, la que tenía por objeto que los científicos jóvenes y con planes de post doctorados y/o estadías en el extranjero, o simplemente interés en el área de investigación del invitado, tuviesen la posibilidad de interactuar de manera más directa con los invitados extranjeros que asisten a la Reunión Anual.

En el interés de descentralizar nuestras actividades, realizamos visitas a las filiales regionales reuniéndonos con las filiales Concepción en el 2011 y Talca el 2012. El socio José Martínez Oyanedel fue nombrado Coordinador de Educación de la Sociedad de Bioquímica y Biología Molecular de Chile. El 2012 nuestra Reunión Anual coincidió con la semana de la Ciencia y Tecnología organizada por Explora-Conicyt, por lo que invitamos a nuestros socios a participar de ella en Puerto Varas y alrededores. Las charlas brindadas en esta actividad fueron dirigidas a estudiantes de enseñanza media, básica y preescolar.

Nuestra Sociedad participó el año 2011 en el congreso “*Exploring beyond the shore: a transatlantic meeting beyond the shore*”, una iniciativa organizada por la Sociedad Española de Bioquímica y Biología Molecular (SEBBM) en colaboración con la sociedad Portuguesa de Bioquímica (SPB) y la Sociedad Marroquí de Bioquímica y Biología Molecular, destinada a detectar científicos emergentes no solo de España, Portugal y Marruecos sino también de América Latina. Esto con miras a la organización del “*22nd IUBMB International Congress of Biochemistry and Molecular Biology&37th FEBS congress*” a realizarse en Sevilla, España, el año 2012. Para ello,la Sociedad de cada país debió proponer entre 4-6

nombres que pudieran participar en los temas propuestos. De entre estos nombres la SEBBM elegiría dos de cada país. De Chile los seleccionados fueron los Drs. Rodrigo Gutiérrez y Marcelo López-Lastra. En nombre de la sociedad chilena asistió el Vice-Presidente, Dr. Sergio Lavandero con la charla:"*The current status and challenges of Biochemistry in Chile*". Además, establecimos un protocolo para la participación recíproca de nuestra Sociedad con la SSBQ, Sociedad Brasilera de Bioquímicay Biología Molecular. El primer simposio conjunto se realizó el año 2013 Reunión Anual de la SBBq, donde participaron los Drs. Andrew Quest y Roxana Pincheira.

Los esfuerzos de la directiva por revitalizar y modernizar la gestión de la sociedad se vieron reflejados por una parte en que establecimos contacto formal con la empresa 4ID y en que tuvimos un alto número de nuevos socios, 39, en el periodo 2011/2012 por otra. Además, aumentó significativamente el número de asistentes a las reuniones anuales, alrededor de 290 cada año, esto sin mencionar el personal de las empresas que siempre nos acompañaron.

La reunión Anual del 2011 se realizó con mucho éxito en Valdivia. Sin embargo, para el año siguiente decidimos cambiar el lugar, pues el año 2013 debíamos organizar la Reunión PABM la que requería de una infraestructura y apoyo logístico muy superior a lo que estábamos acostumbrados. Por ello, y como posible lugar para el año 2013, el 2012 realizamos nuestra reunión en Puerto Varas, lugar que de ahí en adelante fue el preferido de nuestraSociedad hasta hoy, en que la reunión 2018 se realizará en Iquique. Bien por el norte de Chile y sus científicos.

La reunión PABMB del 2013 requirió de mucho trabajo y esfuerzo. Es así como durante el 2012 la Directiva de la Sociedad se volcó con gran entusiasmo a esa ardualabor que muchas veces no fue fácil y tampoco estuvo exento de dificultades. Sin embargo, todos entendimos que la imagen del nuestra Sociedad y también la del país estaba en juego, por lo que supimos superar los obstáculos y trabajar en conjunto para tener una exitosa reunión, de la que sin duda les hablará Sergio Lavandero, a quien le correspondió presidir nuestra Sociedad en aquel periodo.

Al escribir este apretado resumen, me asiste la convicción que nuestra Sociedad experimentó cambios importantes y trascendentes durante el período en que fui su presidenta. Creo genuinamente haber cumplido mis propias expectativas y las de aquellos que me otorgaron ese alto honor y, porque no decirlo, esa enorme responsabilidad. Dichos cambios no representan, ciertamente, el esfuerzo de una sola persona sino el trabajo de un equipo que, debo decirlo, tuve el privilegio de dirigir. Dicho eso, sólo resta seguir trabajando, seguir mejorando, seguir contribuyendo con excelencia a la actividad científica de nuestro país.

Dra. Victoria Guixé

Dr. Juan Olate (Presidente 2009-2010)

Victoria Guixé, Vicepresidente; José Martínez, Secretario; Soraya Gutiérrez, Tesorero; Xavier Jordana, Presidente anterior; Gino Corsini, Director Santiago; Rodrigo Gutiérrez, Director Santiago; Marcia Puchi, Directora Concepción; Simón Ruíz, Director Talca; Alejandro Reyes, Director Valdivia.

Esta maravillosa pero exigente aventura comenzó en el año 2007, cuando el Dr. Xavier Jordana, Presidente de la Sociedad de Bioquímica en ese entonces, me solicitó que aceptara el cargo de Vicepresidente. Así el año 2009 asumí la Presidencia de la Sociedad de Bioquímica, con la gran responsabilidad de continuar el gran trabajo realizado por Xavier. Recuerdo que lo más arduo era llegar a un consenso en la directiva sobre donde realizar la Reunión Anual, pues había que balancear costos y lugar de manera muy armónica. Después de realizar varios viajes visitando distintos lugares y principalmente debido al éxito obtenido por Xavier en el Hotel Termas de Chillán y lo hermoso del entorno, decidimos continuar realizando ambas reuniones (2009 y 2010) en el mismo lugar.

La reunión del año 2010 fue muy difícil de estructurar debido a las repercusiones que tuvo el terremoto de ese año, que afectó gravemente a diferentes Universidades en su infraestructura, equipamiento y por lo tanto su trabajo científico y presupuesto. Se sumo a esto, el recelo de viajar a Chile de profesores extranjeros invitados al evento para no sufrir la experiencia traumática de un movimiento telúrico. Sin embargo, algunos invitados entre ellos Heidi Hamm, presidenta de la Sociedad de Bioquímica de Estados Unidos, aceptó dar la Conferencia PABMB.

Todas las dificultades a que nos enfrentamos ese año 2010, fueron olvidadas rápidamente en la cena de clausura, donde junto al Dr. José Martínez, secretario de la Sociedad, elaboramos una ceremonia de entrega de los “Premios Fermelo” muy entretenida y novedosa que causó total sorpresa y diversión en los asistentes.

Solamente me queda por decir en esta breve reseña, la extraordinaria experiencia que fue para mi persona dirigir por dos años una Sociedad Científica tan prestigiosa e importante como la Sociedad de Bioquímica y Biología Molecular de Chile junto a los restantes componentes de la directiva cuyo trabajo fue fundamental para llevar a cabo esta magna tarea.

Dr. Juan Olate Aravena.

Dr. Xavier Jordana (Presidente 2007-2008)

Juan Olate, Vicepresidente; Marcelo López-Lastra, Secretario; Ana Preller, Tesorero; Claudio Vásquez, Presidente anterior; Gino Corsini, Directora Santiago; Pilar Carvallo, Director Santiago; José Martínez, Director Concepción; Simón Ruíz, Director Talca; Gloria León, Directora Valdivia.

Creo que una decisión estratégica de la directiva que encabecé fue tomar ciertos riesgos financieros para organizar reuniones anuales atractivas, en lugar de privilegiar "abaratar costos". Como ejemplo, además de hacernos cargo como de costumbre del viaje y/o estadía de los conferencistas (Inaugural, PABMB, Severo Ochoa), invitamos a los socios a organizar simposios asumiendo nosotros el financiamiento de un invitado, e incitándolos a invitar a algún otro con sus proyectos. Ello redundó en programas muy interesantes, en un aumento del número de inscritos, socios y estudiantes, y en que no tuvimos pérdidas económicas. Pienso también que gracias a ello y a las directivas siguientes aumentó significativamente la incorporación de nuevos socios, ya sea por trabajo de incorporación o, muy importante, de académicos consolidados que hasta entonces no habían participado en la Sociedad (ingreso por CV). No puede dejar de mencionarse que en ese período Conicyt financiaba la asistencia de un gran número de estudiantes de doctorado, un factor que también contribuyó en forma importante al éxito de las Reuniones Anuales.

Otro aspecto que quisiera destacar es la fraternidad, la cordialidad con que funcionamos como directiva, y aprovechar de agradecer a todos los que me acompañaron en la tarea (Claudio Vásquez como presidente anterior, Juan Olate como vicepresidente, Marcelo López como secretario, Ana Preller como tesorera, y los directores Pepe Martínez por Concepción, Simón Ruiz por Talca, Gloria León por Valdivia, y Pilar Carvallo y Gino Corsini por Santiago). El compromiso de las secciones de Valdivia, Talca y Concepción fue fundamental, y especial mención merece el trabajo de Concepción en la logística de las Reuniones en las Termas de Chillán.

Por último quisiera señalar que entre los hitos de las Reuniones Anuales están la emocionante ceremonia de homenaje a los ex-presidentes de la Sociedad (Reunión del 2007), y el inicio de las conferencias Ciencia de Frontera en colaboración con la Academia de Ciencias (Reunión del 2018, astronomía). También, si mi memoria no me engaña, se institucionalizaron los premios Fermelo al mejor trabajo de incorporación y a las mejores comunicaciones libres, con un aporte complementario de la Sociedad.

Dr. Xavier Jordana

Dr. Claudio Vásquez (Presidente 2005-2006)

Xavier Jordana, Vicepresidente; María Antonieta Valenzuela, Secretario; Marco Álvarez, Tesorero; Luz María Pérez, Presidente anterior; Ana Preller, Directora Santiago; Marcelo López-Lastra, Director Santiago; Marta Bunster, Directora Concepción; Simón Ruíz, Director Talca; Gloria León, Directora Valdivia.

Luego de ser Director por Santiago junto al Dr. Xavier Jordana durante la presidencia de la Dra. Pilar Carvallo (2001-2002) y estando en Texas, USA, en una estadía sabática, recibí un llamado de la futura Presidenta de la Sociedad, Dra. Luz María Pérez. La idea era que la acompañase como Vicepresidente, a lo que accedí gustosamente. Ello conllevó a que fuese Presidente de la misma el período siguiente, 2005-2006. Con cierta antelación, había solicitado a Xavier que oficiase de Vicepresidente, quien felizmente aceptó. El sería el próximo Presidente. Nos acompañaron en la Directiva de aquel entonces la Dra. María Antonieta Valenzuela (Secretaria) y el Dr. Marco Álvarez (Tesorero).

Aun cuando las actividades relativas a la Reunión Anual se desarrollaron normalmente, el año 2005 cabe destacar una anécdota que en su momento generó alguna polémica. La Presidenta anterior, Dra. Pérez, había acordado con el Dr. Juan J. Cazzulo llevar a cabo una reunión conjunta con la sociedad homóloga en Argentina y así potenciar la Reunión Anual de ambas Sociedades. Por una de esas cosas que uno nunca llega a entender bien, pasó el tiempo y aquella idea no prosperó, lo que obligó a la Directiva a organizar aceleradamente el Congreso de aquel año, que finalmente terminó llevándose a cabo en el Centro de Conferencias Paso Pehuenche, de la Universidad de Talca, del 9-12 de Enero de 2006 (se puede revisar el programa completo en la siguiente dirección http://www.sbbmch.cl/wp-content/uploads/2015/04/SBBMCH-2005.pdf).

Fue así como técnicamente hablando la Sociedad no tuvo Reunión Anual el 2005 año pero sí tuvo, y dos el 2006, una curiosidad por cierto. Aquella XXVIII Reunión Anual recibió a los participantes en La Casa Colorada, Colbún, con un bello y torrencial aguacero. Hubo -entre otros- distinguidos invitados como los Dres. Alberto Podestá (Argentina) Manuel Guzmán (España), quienes ofrecieron las conferencias PABMB y Severo Ochoa, respectivamente. La conferencia Osvaldo Cori estuvo a cargo precisamente de la Secretaria de nuestra Sociedad, Dra. María Antonieta Valenzuela. También se llevó a cabo un interesante taller sobre el Estado de la Bioquímica en Chile, que fue coordinado por el Dr. Jorge Babul y tuvo una gran participación de socios y asistentes.

Más tarde, ese mismo año 2006, se llevó a cabo la XXIX Reunión Anual de la SBBMCH, en conjunto con la XLIX Reunión Anual de la Sociedad de Biología de Chile y la XVIII Reunión Anual Sociedad de Botánica de Chile en el Gran Hotel Pucón (https://scielo.conicyt.cl/scielo.php?script=sci_arttext&pid=S0716-97602006000400002). En esta oportunidad, las conferencias PABMB y Severo Ochoa fueron dictadas por los Dres. Anibal Vercesi (Brasil) y José M. Valpuesta (España), respectivamente. Esta XXIX Reunión la Sociedad se contó con la visita del Dr. Joan Guinovart, de la Universidad de Barcelona, España, quien dictó la conferencia Sociedad de Bioquímica y Biología Molecular de Chile.

El suscrito agradece el compromiso y aporte de todos aquello/as, quienes -directa o indirectamente- hicieron posible que el resultado de las referidas reuniones haya sido más que exitoso.

Saludos, Claudio.

Dr. Luz María Pérez (Presidente 2003-2004)

Claudio Vásquez, Vicepresidente; María Estela Andrés, Secretario; Victoria Guixé, Tesorero; Pilar Carvallo, Presidente anterior; María Antonieta Valenzuela, Director Santiago; Patricio Arce, Director Santiago; Marta Bunster, Directora Concepción; Gloria León, Directora Valdivia.

Me tocó presidir la Sociedad de Bioquímica y Biología Molecular los años 2003 y 2004, en los que realizamos las tradicionales reuniones anuales de la Sociedad: en Valle Dorado, Villa Alemana (2003) y en Conference Town, Reñaca (2004). Estas reuniones se realizaron en forma independiente de otras sociedades. La Reunión Anual realizada en el Hotel Valle Dorado incluyó un simposio sobre modelamiento molecular de proteínas, en una época en la que recién se iniciaban estos tipos de estudio. De allí surgiría el interés por desarrollar proyectos y capacitar recurso humano competente para enfrentar ese tipo de trabajos. Esa reunión atrajo a un gran número de socios y de estudiantes, y se pudo visualizar una creciente representación de trabajos de Talca. Ello nos motivó a visitarlos en el año 2004 para evaluar su disponibilidad para incorporar un representante al Directorio de la Sociedad de Bioquímica y Biología Molecular de Chile. La disposición de los científicos del área en Talca y los antecedentes disponibles de su actividad de investigación, permitieron aprobar en el directorio la incorporación de un representante de esa región. Esta incorporación se concretó en el año 2005, donde el Dr. Simón Ruiz es designado el primer director por Talca en nuestra sociedad. La Reunión Anual realizada en el Conference Town de Reñaca, contó con un Taller sobre Educación en Bioquímica, en el que se pudo analizar la disponibilidad de recursos virtuales para dictar las asignaturas de Bioquímica incluidas en diferentes programas de pregrado, la conveniencia de uso y nuevas herramientas de evaluación. Adicionalmente, durante el período 2003-2004, la Sociedad aprobó la incorporación de otros cinco investigadores.

Saludos,
Luz María Pérez Roepke

Dr. Pilar Carvallo (Presidente 2001-2002)

Luz María Pérez, Vicepresidente; Jenny Fiedler Secretario; Victoria Guixé, Tesorero; Juan Carlos Slebe, Presidente anterior; Claudio Vásquez, Director Santiago; Xavier Jordana, Director Santiago; María Imschenetzky, Directora Concepción; Alejandro Reyes, Director Valdivia.

Al finalizar la XXIII Reunión Anual en Valdivia, recibí la invitación de la Directiva y de algunos socios a ser candidata a la Vice-Presidencia de la SBBMCh, lo cual acepté con gran alegría ya que recientemente había sido parte del Directorio por 4 años, como directora y como tesorera.

Asumí la presidencia de la Sociedad en 2001, ingresando a la directiva 4 de los futuros presidentes de la Sociedad, Luz María Pérez, Victoria Guixé, Xavier Jordana y Claudio Vásquez. Ese primer Congreso lo realizamos en las Termas de Chillán que era un sueño (personal) guardado desde unos años. El viaje a las Termas lo hicimos la mayoría de los participantes en el tren Santiago-Chillán y luego en buses previamente arrendados. Otros fueron directamente en auto desde sus ciudades, y otros en avión a Concepción. El Congreso tuvo 4 simposios y 4 conferencias plenarias, entre éstas la "PABMB", "Severo Ochoa" y "Osvaldo Cori". Una triste anécdota es que la 5a conferencia, que prometía ser excelente, no se realizó ya que nuestro invitado no pudo viajar por el reciente atentado a las Torres Gemelas. En esa reunión ganó la Medalla Hermann Niemeyer el actual director por Concepción Leonardo Gutiérrez. En esta Reunión tuvimos 60 estudiantes de pre y postgrado becados completamente por la Sociedad, alojados en las Termas.

En este Congreso planeamos una tarde libre (miércoles), en la cual se organizaron paseos a diferentes lugares de alrededor de las Termas, con lo cual no todo fue trabajo. El tiempo también fue nuestro aliado, ya que los tres primeros días hubo muy buen tiempo. La noche del 26 de septiembre mientras realizábamos nuestra cena, hermosos y silenciosos copos de nieve se empezaron a ver detrás de los ventanales del comedor, fue maravilloso, casi como si lo hubiéramos programado. Al día siguiente un lindo paisaje blanco nos recibió al desayuno, y nos acompañó a nuestro regreso a Chillán.

La XXV Reunión Anual la realizamos en conjunto con nuestra Sociedad Madre, la Sociedad de Biología, junto a las Sociedades de Botánica, Ecología e Inmunología, en las Termas de Puyehue. Nuestro programa propio fue más reducido por temas de espacio y tiempo, pero ganamos en diversidad de temas como "Invasiones biológicas en Chile", "Causas y consecuencias de El Niño", "Inmunoterapia" entre otros. En esta Reunión Anual se entregó la Medalla Hermann Niemeyer a nuestro Vicepresidente actual Luis Larrondo.

Durante este periodo 2001-2002 se incorporaron 9 nuevos socios. Se realizó la primera conferencia "Severo Ochoa" en las Termas de Chillán y la primera "Conferencia hermana" Hermann Niemeyer en la Sociedad Española de Bioquímica y Biología Molecular, a cargo de nuestro Past-President Juan Carlos Slebe. El año siguiente, 2002, fui invitada a la segunda Conferencia Hermann Niemeyer en el Congreso de la SEBBM.

Como una actividad habitual, implementada con anterioridad en la Presidencia de Jorge Babul, se realizaron tres reuniones de socios con el fin de celebrar hechos especiales. El primer encuentro fue el 21 de junio de 2001 para felicitar al Dr. Jorge Allende, por su incorporación a la Academia de Ciencias de Estados Unidos. En julio de 2002 nuestra reunión fue para celebrar a la Dra. Cecilia Hidalgo, por su incorporación a la Academia de Ciencias del Instituto de Chile, y para felicitar al Dr. Pablo Valenzuela, por la designación del Premio Nacional de Ciencias Aplicadas. Nuevamente nos reunimos en octubre de 2002 ya que otro socio el Dr. Ramón Latorre fue galardonado con el Premio Nacional de Ciencias Naturales.

En estos años, adquirimos el primer equipo data show de nuestra Sociedad, que reemplazaría a las antiguas proyectoras de diapositivas, y comenzamos nuestra primera página Web.

¡¡Gracias a todos los que me acompañaron en esta importante tarea!!

Pilar Carvallo

Dr. Juan Carlos Slebe (Presidente 1999-2000)

Pilar Carvallo, Vicepresidente; Javier Puente, Secretario; Cecilia Rojas, Tesorero; Rafael Vicuña, Presidente anterior; Eduardo Kessi, Director Santiago; Jenny Fiedler, Director Santiago; Juan Olate, Director Concepción; Alejandro Reyes, Director Valdivia.

En la década de los 90 empezó a advertirse de que las computadoras y ordenadores no lograrían diferenciar entre 1900 y 2000. Muchos no tenían claro qué consecuencias tendría esto, pero se llegó a especular que dejarían de funcionar al iniciarse el año 2000, dando lugar a numerosos vaticinios fatalistas. Lo cierto es que hubo fallas, pero sin importancia, y para nuestra Sociedad de Bioquímica y Biología Molecular de Chile (SBBMCh), el período que tuve el honor de presidir (1999-2000), fue especialmente importante y exitoso en estrechar las relaciones entre nuestra Sociedad con otras sociedades de Latino América e Iberoamérica. Este nuevo impulso y fortalecimiento en la internacionalización de la SBMBCh consideró el valor que en años anteriores habían tenido las reuniones Cono-Sur y aquellas que han perdurado en el tiempo, me refiero a las reuniones de la Pan-American Association for Biochemistry and Molecular Biology (PABMB).

Como resultado de estas relaciones surgió un Programa de Intercambio recíproco de conferencistas invitados a nuestros respectivos Congresos Anuales, que logró establecerse en una reunión realizada el año 1999 en Mendoza, Argentina, entre los Presidentes de la Sociedad Española de Bioquímica y Biología Molecular (SEBBM), Dr. Joan J. Guinovart, el suscrito por la SBBMCh y la Directiva de la Sociedad Argentina de Investigación Bioquímica y Biología Molecular (SAIB), dirigida en esa época por el Dr. Ricardo A. Wolosiuk, Dentro de este marco, las conferencias que llevan el nombre de dos distinguidísimos investigadores de Chile y España, Dr. Hermann Niemeyer y Dr. Severo Ochoa, respectivamente, son organizadas con España. De igual modo, la SEBBM y SAIB organizan las conferencias Dr. Luis Leloir y Dr. Alberto Sols. Así, desde el año 2001 y hasta el año 2018 han intervenido en este programa 18 distinguidos científicos de Chile, en las reuniones anuales de la SEBBM y 18 distinguidos científicos de España, en nuestras reuniones anuales. Este programa no solo ha permitido dar a conocer los avances científicos realizados en cada país si no que, lo más importante, impulsar y fortalecer la formación de redes de colaboración e intercambio en nuestra disciplina.

Otro hito importante de nuestro período, derivado de los mismos esfuerzos antes descritos, es la organización y ejecución de la 1era Reunión Iberoamericana de Bioquímica, Biología Molecular y Biología Celular, realizada entre el 30 de Octubre y el 03 de Noviembre de 2000, en Viña del Mar, Chile, en conjunto con la XXIII Reunión Anual de la SBBMCh, XXXVI Reunión Anual de la SAIB, y la XIV Reunión Anual de la Sociedad de Biología Celular de Chile (SBCCh), y en asociación con la SEBBM. En esta magnífica reunión se contó con más de 750 participantes, entre los cuales destacan alrededor de 30 investigadores de España, 300 investigadores y estudiantes de Argentina y un gran número de invitados de diversos otros países, con una masiva concurrencia de investigadores y estudiantes de Chile.

Estas y numerosas otras actividades realizadas no podrían haberse concretado con éxito sin el esencial compromiso y apoyo de todos nuestros socios y el gran esfuerzo y trabajo desplegado por todos los integrantes de la Directiva que me acompañó en ese período. Vaya mi gratitud a cada uno de ellos.

Saludos cordiales,

Juan Carlos Slebe

Dr. Rafael Vicuña (Presidente 1997-1998)

Juan Carlos Slebe, Vicepresidente; Omar Orellana – Javier Puente, Secretario; Cecilia Rojas, Tesorero; Jorge Babul, Presidente anterior; Javier Puente, Director Santiago; Loreto Holuigue, Director Santiago.

Fui presidente hace unos 20 años, sucediendo al Dr. Jorge Babul. Transcurridas ya dos décadas, solo puedo indicar cuales fueron las principales iniciativas que promovió la directiva que tuve el honor de presidir.

En primer lugar, el eje central de nuestro trabajo fue hacer crecer el número de afiliados, para lo cual promovimos una campaña de postulaciones y además invitamos a varios nuevos miembros por méritos propios. Además, con el fin de fortalecer nuestro funcionamiento como Sociedad, nos preocupamos de realizar actividades adicionales a la reunión anual, la que por razones obvias siempre ha sido nuestra principal actividad. Para ello organizamos un par de comidas anuales, en las que típicamente se daba la bienvenida a los nuevos miembros y luego uno de los asistentes ofrecía una conferencia. En tercer lugar, seguimos con la política de directivas anteriores respecto a privilegiar la asistencia de estudiantes a la reunión anual, la que según recuerdo, dio resultados muy satisfactorios.

Por último, estimo importante destacar nuestra actitud favorable a realizar la reunión anual en conjunto con otra sociedad científica cercana disciplinariamente a la SBBM. Nuestra reunión anual de 1998 en conjunto con la Sociedad de Biología Celular fue particularmente muy exitosa.

Saludos cordiales,
Rafael Vicuña

Dr. Jorge Babul (Presidente 1995-1996)

Rafael Vicuña, Vicepresidente; Ana Preller, Secretario; Pilar Carvallo, Tesorero; Emilio Cardemil, Presidente anterior; Cecilia Rojas, Director Santiago; Jorge Ferreira, Director Santiago.

Durante el periodo que me correspondió coordinar la Directiva, se realizaron dos reuniones anuales de la sociedad de Bioquímica de Chile,

IX REUNIÓN ANUAL SOCIEDAD DE BIOLOGÍA CELULAR DE CHILE

XVIII REUNIÓN ANUAL SOCIEDAD DE BIOQUÍMICA Y BIOLOGÍA CELULAR

La Reunión Anual conjunta de estas sociedades se realizó desde el 27 al 30 de septiembre de 1995, en el Hotel Pacífico de Algarrobo, Avenida Carlos Alessandri 1930, Algarrobo, Chile.

1. PROGRAMA

- Comunicaciones libres (sólo diapositivas)
- Trabajos de incorporación
- Avances de Tesis de Doctorado
- Conferencia Dr. Osvaldo Cori a cargo del Dr. Hernán Chaimovich, Presidente de la Sociedad Brasilera de Bioquímica y Biología Molecular.
- Conferencia a cargo de la Dra. Mirtha Flawiá, Presidenta de la Sociedad Argentina de Investigación en Bioquímica y Biología Molecular.
- Conferencia Dr. Luis Izquierdo a cargo del Dr. Federico Leighton.
- Simposios:

  Genética Molecular: aspectos básicos y clínicos. Coordinadora Dra. Pilar Carvallo. Receptores y transducción de señales. Coordinador Dr. Alfonso González.
- Entrega del Premio Medalla Dr. Hermann Niemeyer al alumno más destacado de los programas de Doctorado en Bioquímica y áreas afines.
- Entrega del Premio Fundación Chilena para Biología Celular a la mejor Tesis de Pregrado y Postgrado en el área de la Biología Celular

Como se puede observar, se dio cumplimiento al acuerdo entre las sociedades de Argentina, Brasil y Chile de invitar a los presidentes de las sociedades en las reuniones que cada país organizara. Como otros acuerdos, se desvaneció con el tiempo.

Durante este año fui fue invitado a las reuniones de las sociedades de Argentina y Brasil con motivo de la organización de la reunión de la Asociación Panamericana de Sociedades de Bioquímica, que se realizaría en Pucón (originalmente Valdivia) el año siguiente. En esas oportunidades se presentó el Programa de la reunión y se dieron a conocer las bondades de Pucón como lugar apropiado para la interacción entre científicos y para un buen pasar.

También se destaca la sesión en la que los estudiantes de doctorado presentaban sus avances ante los asistentes. Por cierto el número de ellos, en esos años, lo permitía (quizás hoy, también)

El 25 de octubre de 1996 el Presidente recibe una carta del Presidente de la Sociedad Española de Bioquímica y Biología Molecular (disponible en el sitio de nuestra sociedad) en la que comunica la decisión de la Junta Directiva de proponer la puesta en marcha de un programa de colaboración entre nuestras sociedades: “la SEBBM está abierta a

cualquier fórmula de interacción que resulte eficaz y que pueda conducir a resultados positivos, aunque sea a largo plazo", indicó el Dr. Guinovart. Como se ve en el relato del Dr. Rafael Vicuña, durante su periodo estas proposiciones se concretaron y aún permanecen con fuerza.

También durante este periodo comenzamos a realizar reuniones durante el año sobre diferentes temas de interés para la Sociedad y para dar a conocer a los nuevos miembros. El muy recordado Club Suizo en la calle Dublé Almeyda, de Ñuñoa, donde se realizaron estas reuniones, ha sido retomado recientemente.

VIII PABMB CONGRESS

The Pan-American Association for Biochemistry and Molecular Biology

In conjunction with:

XXXII Annual Meeting of the Argentinean Society for Biochemistry and Molecular Biology Research

XIX Annual Meeting of the Society of Biochemistry and Molecular Biology of Chile

Welcome lecture

It is an honor for me to open this Congress and on behalf of its Organizing Committee, I extend to all of you the warmest welcome to this triple event, the Eighth Congress of the Pan-American Association for Biochemistry and Molecular Biology (which used to be known as PAABS, now PABMB), held jointly with the Thirty-second Annual Meeting of the Argentinean Society for Biochemistry and Molecular Biology Research (Sociedad Argentina de Investigación en Bioquímica y Biología Molecular), and the Nineteenth Annual Meeting of the Society of Biochemistry and Molecular Biology of Chile (Sociedad de Bioquímica y Biología Molecular de Chile). Every four years, the Pan-American community of biochemists, professors, post-doctoral fellows, students and collaborators, get together to present and discuss their research in biochemistry and related fields. In the last meeting at Ixtapa, Mexico, the Chilean Society took the responsibility of the organization of the eighth version. Our expectations was to stimulate and strengthen the collaboration and exchange of experiences on the research conducted by members of our societies, by the invited speakers and all participants, especially students. We invited our sister societies of Argentina and Brazil to join us in this effort participating in the Organizing Committee and to celebrate our meetings jointly. Because of the large number of members of the Biochemical Society of Brazil, they could not cancel its annual meeting, but are present in large number here in Pucón.

Before making a decision in respect to the final Program of the meeting we asked each constituent and adherent society to suggest topics for the symposia and plenary lectures and also names of possible invited speakers. The program committee gave preference to those subjects proposed by several societies and which allow, at the same time, the participation of scientists of different countries. The program includes 8 plenary lectures, 26 symposia, and 3 poster sessions. The abstract book is the summary of all these presentations, approximately 620 in total. Many topics were left out because of restrictions such as the length of the meeting, together with our prospects of a meeting with participants secluded in a place with ample time for exchange of experiences. These ideas were important in many decisions taken by the organizers. The beauty of Pucón may ran against our expectations, but the sessions will be so attractive that the lake and volcano will be defeated. The volcano here appears and disappears, and something similar will happens with our students.

I would like say a few words about our scientific community and Dr. Fabian Jaksic will tell you about our country, landscapes and creatures.

Our scientific community is small, not over 3.000. The biological community started up the Biological Society with sections of according to the different areas of Biology cultivated. Now most of the sections became societies and function as an association of biological societies with approximately 700 members.

We also have a Council of Scientific Societies which includes Biology, Chemistry, Physics and Mathematics that also acts as an Association for the Advancement of Science and is a member of Interciencia Association. This council together with our National Academy of Sciences and International Scientific Committees constitute what we call the ICSU National Committee that is our association with the International Council of Scientific Unions. His group has been actively working

on a directory of active researchers in all fields (mainly astronomy, biology, chemistry, earth sciences, environmental sciences, marine sciences, mathematics, and physics). The main subjects of study of the ICSU National Committee has been scientific productivity, undergraduate science training, postgraduate science training, international cooperation in science, and financing of science in Chile. Our recommendations have been related to

1. The creation of mechanisms and procedures to include the variable of science and technology in the political decisions (specially a presidential advisory council)

2. Programs of activities to stimulate the scientific-technological development of the country (specially a program for increasing human resources)

3. A system of financial stimulus for the researchers

4. A program to improve science teaching.

5. Science popularization activities

6. Stimulus to scientific-technological research in the industry

7. Relationship of Chilean science with the international science

8. Fostering of science and technology in the regions

9. And scientific infrastructure.

We have succeeded in any of this subjects but we still have a long, long way to go.

We are convinced that our first priority is to increase of human resources for science and technology through postgraduate studies and to communicate to the national public the great projections of science and technology for the future of our countries, and the need of scientific research to maintain and to be more competitive in international markets as well as for our social development.

We hope that with meeting will provide the opportunity to scientists from several latitudes to learn about our concerns and our hopes and will also help us with ideas, criticism and support. The Chilean scientific community wants and needs closer ties with the international scientific community and is certain that the visit of so many distinguished leaders on the occasion of this meeting will be very helpful

Here in Pucón we open to you the doors of our country and science in what will be a week-long celebration with our colleagues and friends from other countries to share with us the excitement for science and scientific research. We are all convinced that Science is important to know more about us, about everything in Nature, and for the future of our countries.

I would like to thank our colleagues that had the enormous responsibility to make every effort to organize each detail of this meeting. We have decided to do this ourselves, with no professional organization involved. It has been a tremendous task for just a few. Four or five of us answer all your mail, messages, phone calls; we wanted to be as cordial as possible. We think we learn which name or last name of three for or more people use in each country. The eventual success of the Congress will be their best reward.

¡Bienvenidos!

Jorge Babul

Chairman, Organizing Committee

El Programa completo de la reunión se encuentra en el sitio de nuestra sociedad (http://www.sbbmch.cl/wp-content/uploads/2015/04/PABMB-1996.pdf).

Este congreso constituye uno de los eventos científicos internacionales de mayor importancia que se ha desarrollado a la fecha en nuestro país. En dicha instancia se contó con la participación de un total de 890 inscritos, 8 conferencias

plenarias, 26 simposios y la asistencia de científicos provenientes de 22 países diferentes, incluidos Chile y Argentina. Entre todas esas actividades el número de presentaciones fue 620 en total.

Este congreso fue posible gracias a la participación de muchos colegas y colaboradores. Agradezco especialmente a: Tito Ureta, Presidente del Comité de Programa; Ana Preller, Secretaria; Pilar Carvallo, Tesorera; Cecilia Rojas, Prosecretaria y a Patricio Rodríguez, que estuvo al lado mío siempre en una labor que nos tomó más de dos años.

Uno de los logros más importantes fue el científico, especialmente porque dejó la vara muy alto, lo que fue beneficioso para los congresos siguientes, hasta hoy.

Las palabras de Bill Whelan, creador de la Asociación Panamericana, nos sirve como cierre. Se las reenvié como motivo de la reunión PABMB que organizamos el 2013 cuando fui Presidente de la Asociación y se sorprendió que las conservara por más de 17 años.

29 de noviembre de 1996

Dear Jorge,

I am writing to you, as I have just done to Tito, to thank you for inviting me to Pucon, and for arranging such a splendid Congress. It surely will be looked back on with the greatest pleasure and held out as a model of how to do things right. While I was at first apprehensive at the apparent remoteness of Pucon (being someone who always has one foot on the plane), I came to realize that it was the ideal place, where people came together in relaxed and informal surroundings to listen to and talk about excellent science. I did enjoy it and hope you can now take a well-earned rest. All good wishes, Bill Whelan.

Abrazos afectuosos.

Jorge Babul

Dr. Emilio Cardemil (Presidente 1993-1994)

Jorge Babul Vicepresidente; Ana María Jabalquinto, Secretaria; María Antonieta Valenzuela, Tesorero; Octavio Monasterio, Presidente anterior; Paulina Bull, Director Santiago; Pilar Carvallo, Director Santiago.

Bajo esta directiva se realizaron 2 congresos de la Sociedad

XVI Reunión Anual en conjunto con la Sociedad de Biología Celular Valdivia, 26-28 agosto de1993

XVII Reunión Anual La Serena 3-5 agosto de 1994

Dr. Octavio Monasterio (Presidente 1991-1992)

Emilio Cardemil Vicepresidente; Victoria Guixé, Secretaria; Rosalba Lagos, Tesorero; Arturo Yudelevich, Presidente anterior; Loreto Holuigue, Director Santiago; María Antonieta Valenzuela, Director Santiago.

Me correspondió presidir la Sociedad de Bioquímica y Biología Molecular de Chile, que en ese entonces se llamaba Sociedad de Bioquímica, desde agosto de 1991 a mayo de 1993. Para tal efecto la Directiva saliente de la Sociedad, presidencia del Dr. Arturo Yudelevich, me hizo entrega de "Las Cajas de la Sociedad" (eran de cartón), que contenían todos los documentos y útiles de secretaría, incluyendo el timbre de la Sociedad. La nueva Directiva quedó conformada de la siguiente manera: Presidente Octavio Monasterio; Vicepresidente Emilio Cardemil; Presidente anterior Arturo Yudelevich; Secretaria Victoria Guixé; Tesorera Rosalba Lagos; Directoras Loreto Holuigue y María Antonieta Valenzuela, como pueden ver se mantenía un equlibrio de género a favor de la mujer.

Las dos reuniones anuales organizadas por esta directiva fueron la XIV Reunión Anual en conjunto con la Sociedad de Biología de Chile en Puyehue del 27 al 30 noviembre de 1991 y la XV Reunión Anual que la hicimos en forma individual en La Leonera del 6 al 8 agosto de1992. En esta ocasión la Dra Valenzuela se hizo cargo del traslado de los socios en un bus Romanini, contratado por la Sociedad. En esta reunión ocurrió un hecho muy anecdótico. Estaba como invitado el Dr. Nelson Carvajal para participar con una ponencia en el Simposio sobre "Estructura de Proteínas", y como de costumbre tenía su presentación preparada en diapositivas y ocurrió que al inciarla hubo un corte de electricidad que se extendió por un largo tiempo. Mientras esperábamos el retorno de esta, a la luz de los candelabros del hotel, el Dr. Carvajal ofreció hacerla con un plumón y una pizarra especialmente instalada por un maestro del hotel. Su exposición fue todo un éxito dada su capacidad docente y la forma en que entregó los conceptos y resultados, princialmente para los estudiantes. Eran otros tiempos en que lo que primaba era un espíritu de colaboración que permitía una fluida comunicación de nuestro hacer científico, y porque no decirlo de nuestra camaradería. El Programa de esa reunión no apareció en la revista de Archivos de Biología y Medicina Experimentales del año, pero sí en un libro de resúmenes especialmente confeccionado para la ocasión.

Dentro de las tareas que le tocó abordar a la Directiva estuvo la postulación exitosa de Chile como sede del VIII Congreso PAABS, tarea encargada al Dr. Manuel Krauskopf como también la organización de los preparativos para realizar esta reunión en 1996. Esta última gestión se le encargó a una comisión especialmente convocada e integrada por los Drs. Jorge Allende, Jorge Babul, Manuel Krauskopf y Federico Leighton, comisión que se constituyó el primero de abril de 1993.

Otra tarea muy importante fue el cambio del nombre de la Sociedad de Bioquímica de Chile debido al explosivo desarrollo de la Biología Molecular en nuestro país. Así, en octubre de 1992, con el beneplácito de los socios, la Sociedad paso a llamarse Sociedad de Bioquímica y Biología Molecular de Chile. Esto significó un arduo trabajo, pues se tuvo que diseñar un nuevo logo (que es el actual), y que se hizo en base al comportamiento de las enzimas, es decir de tipo Michaeliano o sigmoideo. Estas dos curvas son la que se peresentan juntas en el logo, la primera en azul en la parte superior y la segunda en blanco en la parte inferior, respectivamente. Estas se ecuentran sobre las iniciales solapadas del nombre de la Sociedad. He escuchado muchas interpretaciones del significado del logo, lo cual lo hace de alguna manera exclusivo para iniciados en la enzimología.

El fallecimiento del Dr. Hermann Nemeyer, mi mentor, miembro fundador de la Sociedad ocurrió el dia 7 de junio del año 1991. Fue una gran pérdida para nuestra nuestra Sociedad, pues sus sabios consejos siempre estaban presentes en el laboratorio.

Durante el ejercio de mi cargo ocupaba la antigua oficina del Dr. Niemeyer en el Laboratorio de Bioquímica y Biología Molecular y allí nos reuníamos con la Dra. Lagos para revisar las finanzas y con la Dra. Guixé para revisar las actas y planificar el trabajo societario. Entre estas tareas una muy inolvidable fue el diseño y confección de la Medalla Hermann Niemeyer que tuvimos que diseñarla y producirla. Recuerdo en forma especial los entretenidos y discutidos viajes que hacíamos a la calle Chabuco 40 en la primera cuadra después de la Alameda hacia el norte, donde estaba localizada la casa Milled, para fabricar el cuño necesario para que posteriormente se hicieran las diez medallas enchapadas en oro. Esta medalla se confeccionó para ser entregada anualmente en memoria del Dr. Niemeyer a un estudiante meritorio y sobresaliente de los Programas de Doctorado en Bioquímica y de otras áreas relacionadas. La primera medalla se entregó en la Academia de Ciencias del Instituto de Chile luego del lanzamiento del libro "Hermann Niemeyer y la Ciencia en Chile". Este libro fue solicitado por la Sociedad a una comisión encargada de su edición, integrada por el Dr. Tito Ureta (Presidente), el Dr. Jorge Allende, el Dr. Luis Izquierdo y la Dra. Victoria Guixé. El libro se reeditó en el año 2012 y los editores de esta nueva versión fueron los profesores: Tito Ureta, Jorga Babul, Victoria Guixé, Rosalba Lagos, Octavio Monasterio y Ana Preller.

Es interesante comentar que el velatorio del Dr. Niemeyer se hizo también en La Academia de Ciencias del Instituto de Chile, lugar en el cual se cerró un ciclo de agradecimiento a su enorme contribución a la Ciencia de nuestro país con las acciones antes mencionadas.

Para finalizar debo agradecer a cada uno de los miembros de la Directiva que me acompañaron en esta gestión, a la Dra. Guixé por su contribución y trabajo en la secretaría, a la Dra. Lagos por su proligidad y rigurosidad en las cuentas de la Sociedad, a las directoras, Dra. Holuigue y Dra. Valenzuela por su trabajo incansable en la organización de las actividades de la Sociedad, finalmente a los Drs. Yudelevich y Cardemil por sus oportunos consejos en la conducción de la Sociedad.

Octavio Monasterio O.

Dr. Arturo Yudelevich (Presidente 1989-1990)

Octavio Monasterio Vicepresidente; Loreto Holuigue, Secretaria; Bernardo González, Tesorero; Carlos Jerez, Presidente anterior; Ana María Jabalquinto, Directora Santiago; Javier Puente, Director Santiago.

Bajo esta directiva se realizaron 2 congresos de la Sociedad

XIII Reunión Anual en conjunto con el Congreso Iberoamericano de Biología Celular, Sociedad de Biología, Sociedad de Genética, Sociedad de Biología Celular y la Sociedad Chilena de Reproducción y Desarrollo Viña del Mar, 21-25 noviembre de 1989

XIV Reunión Anual en conjunto con la Sociedad de Biología Celular Termas de Catillo, 30 de agosto al 1 de septiembre 1990.

Dr. Carlos Jerez (Presidente 1987-1988)

Arturo Yudelevich Vicepresidente; Marta Gatica, Secretaria; Sergio Bazâes, Tesorero; Alejandro Venegas, Presidente anterior; Luis Vallada, Directora Santiago; Rosalba Lagos, Director Santiago. Maruja Imschenetzky, Directora Concepción; Juan Carlos Slebe, Director Valdivia.

Recién llegado de mi posdoctorado en el Instituto Roche de Biología Molecular, en New Jersey, Estados Unidos, fui invitado por el Dr. Jorge Allende para incorporarme como Secretario en el Directorio de la Sociedad de Bioquímica de Chile. Como muchos otros colegas bioquímicos, estuve tal vez muchos años (1981 a 1990) formando parte del Directorio. Luego de Secretario, fui Director por Santiago, Vicepresidente, Presidente y Presidente Anterior. Durante todo esta época aprendí mucho y compartí con excelentes colegas y amigos(as) esta labor tan importante para el desarrollo y la promoción de nuestra disciplina científica en el país y en el extranjero. Durante mi período como Presidente, realizamos en 1987 la XI reunión anual de la Sociedad de Bioquímica de Chile en conjunto con la XXX Reunión anual de la Sociedad de Biología de Chile, XX reunión anual de la Sociedad de Genética de Chile, IX reunión anual de la Sociedad de Farmacología de Chile, II reunión anual de la Sociedad Chilena de Ciencias Fisiológicas en La Serena, Chile del 25 al 28 de Noviembre. Esta fue una gran reunión con numerosos simposios y comunicaciones libres y una gran asistencia de invitados(as) extranjeros(as), socios(as) y estudiantes(as).

La XII Reunión Anual de la Sociedad de Bioquímica se llevó a cabo en forma individual en Cartagena del 11 al 13 de Agosto de 1988 en el balneario de Cartagena, Chile, contando con variados simposios y comunicaciones libres y un buen número de socios(as), invitados(as) extranjeros y estudiantes(as).

Agradecido de la experiencia obtenida, les saluda cordialmente

Carlos A. Jerez

Detalles sobre las actividades desarrolladas en estas dos reuniones anuales se pueden encontrar en http://www.sbbmch.cl/?page_id=421

Informe del Directorio de la Sociedad de Bioquímica de Chile 1987-1988

La Sociedad de Bioquímica de Chile rindió un homenaje a la memoria del Prof. Osvaldo Cori, maestro y formador de la mayoría de los bioquímicos del país y destacado miembro fundador de nuestra sociedad. Este homenaje consistió en la edición de un número especial de Archivos de Biología y Medicina Experimentales, con 33 trabajos de incorporación en el área de la bioquímica y que fueron realizados por muchos de sus discípulos y colegas. Este volumen fue entregado a la comunidad científica nacional en un acto solemne realizado en la Academia de Ciencias del Instituto Chile el 4 de noviembre de 1988.

Dr. Alejandro Venegas (Presidente 1985-1986)

Carlos Jerez Vicepresidente; Miguel Bronfmann, Secretaria; Sergio Bazâes, Tesorero; Tito Ureta, Presidente anterior; Emilio Cardemil, Directora Santiago; Luz María Pérez, Director Santiago.

Bajo esta directiva se realizaron 2 congresos de la Sociedad

IX Reunión Anual Centro Perfeccionamiento del Magisterio Lo Barnechea, Santiago, 1-3 agosto de1985

X Reunión Anual en conjunto con el IV PAABS-Cono Sur, la Sociedad de Biología de Chile y la Sociedad de Farmacología, Pucón 26-29 de noviembre de 1986

Dr. Tito Ureta (Presidente 1983-1984)

Arturo Yudelevich Vicepresidente; Jorge Babul, Secretaria; Luz María Pérez, Tesorero; Lionel Gil, Presidente anterior; José Minguell, Director Santiago; Carlos Jerez, Director Santiago.

Bajo esta directiva se realizaron 2 congresos de la Sociedad

VII Reunión Anual Hotel La Bahía Cartagena 11-13 agosto de 1983

VIII Reunión Anual Hotel La Bahía Cartagena 6-8 agosto de 1984

Se firma un convenio entre las Sociedades de Bioquímica de Chile y de Argentina, mediante el cual se considera, ente otros acápites, como socios comunes a los pertenecientes a cada una de las sociedades, con los mismos derechos que establezcan los reglamentos de cada sociedad. Informe del Directorio de la Sociedad de Bioquímica de Chile 1983-1984

Dr. Lionel Gil (Presidente 1981-1982)

Tito Ureta Vicepresidente; Carlos Jerez, Secretario; Luz María Pérez, Tesorera; Jorge Allende, Presidente anterior; Alejandro Venegas, Director Santiago; Eugenio Spencer, Director Santiago.

La Directiva de la Sociedad de Bioquímica para el período 1981-1982 estuvo constituida por los siguientes miembros: Presidente Dr. Lionel Gil, Vice presidente Dr. Tito Ureta, Secretario Dr. Carlos Jerez. Tesorera Dra. Luz María Pérez. Past President Dr. Jorge. Allende. Los años 1981 y 1982 fueron años que coincidieron con una profunda crisis económica en el país, que afectó de manera profunda la actividad académica y que por lo tanto tuvimos que trabajar intensa e imaginativamente para organizar reuniones anuales de buen nivel. En términos de participación de científicos extranjeros recurrimos a investigadores nacionales que disponían de financiamiento internacional para solicitarles organizar los simposios, e invitar a sus partners extranjeros, también recurrimos a embajadas, a sociedades científicas y organismos internacionales (RLA-PNUD,OEA,etc). Por otra parte decidimos ubicar algún lugar de menor costo a los que se usaban habitualmente con el objetivo de financiar la mayor participación en las reuniones de estudiantes de pre y postgrado.En otras palabras decidimos hacer una reunión de tiempos de crisis. Por estas razones se eligió como sitio de reunión para la V y la VI reunión, Punta de Tralca cuyas instalaciones no eran de la calidad utilizadas en las reuniones de 1979(Reunión conjunta PAABS SBqCH , Hotel O ´Higgins Viña del Mar) y 1980(Reunión Conjunta Sociedades de BQ de Chile y Argentina, Mendoza).

En la reunión del año 1981 se realizó un simposio internacional sobre **Mecanismos Bioquímicos a Estímulos Extra Celulares.** Participaron investigadores extranjeros y nacionales .En la reunión del año 1982 se realizaron dos simposios internacionales

En la reunión del año 1982, con el objetivo de estrechar nuestras relaciones con la Sociedad de Bioquímica de España y agradecer el apoyo fundamental para que Chile fuera aceptado en la Unión Internacional de Bioquímica en 1979, invitamos al Presidente de la Sociedad de Bioquímica de España periodo 1981-1982 Dr Carlos Asencio quien recibió una distinción de nuestra Sociedad y dictó la conferencia inicial .

Participaron investigadores de las siguientes Instituciones Extranjeras:

Universidad de Sao Paulo, Departamento de Bioquímica, Brasil,Institut Max Planck, Alemania; Department of Pathology Temple University , Estados Unidos; NIH Bethesda, National Cancer Institut, Institut of Mental Health, Bethesda. Estados Unidos; Department of Biochemistry, University of Miami, Estados Unidos;Institut de Biochemie CNRS, Bordeaux, Francia;Fundación Campomar y Universidad de Buenos Aires, Argentina.

Instituciones Chilenas: Instituto de Bioquímica , Universidad Austral de Valdivia; Departamentos de Bioquímica, Fisiología y Biofísica, y de Biología Facultad de Medicina Universidad de Chile; Departamento de Bioquímica, Facultad de Ciencias Básicas y Farmacéuticas, Universidad de Chile; Departamento de Ciencias Básicas, INTA, Universidad de Chile; Laboratorio de Bioquímica, Pontificia Universidad Católica de Chile.

COMUNICACIONES LIBRES

En la sección comunicaciones libres se presentaron 44 trabajos de investigadores de instituciones chilenas y extranjeras

VI Reunión Sociedad de Bioquímica y Biología Celular. Punta de Tralca. 4-7 de agosto 1982.

PROGRAMA

Conferencia Inaugural: Expositor Dr Carlos Asencio. Instituto de Enzimología, Facultad Medicina, Universidad Autónoma de Madrid . Centro Ramón y Cajal. Presidente Sociedad de Bioquímica de España 1982. Título de la presentación "**Las Microcinas una nueva Familia de Antibióticos."**

Simposios Internacionales:

1. **Nucleótidos Cíclicos en la acción hormonal**. Participaron Investigadores de: la Universidad de Vanderbilt Estados Unidos ; Fundación Campomar y Facultad de Ciencias Exactas y Naturales de Buenos Aires, Argentina; Departamento de Bioquímica de la Universidad de Sao Paulo, Brasil; y del Centro de Investigaciones de la Universidad de Carabobo, Venezuela.
2. **Organización y Expresión Génicas**. Participaron investigadores de la Pontificia Universidad Católica de Chile; de la Universidad Austral de Chile, de la Universidad de Bordeaux. Francia y del Instituto Max Planck, Alemania.

COMUNICACIONES LIBRES

En la sesiones de comunicaciones libres se presentaron 30 trabajos, provenientes de universidades y centros de investigación de Chile y de universidades y Centros de Investigación de instituciones internacionales extranjeras

Comentarios.

Si bien es cierto, las reuniones se organizaron con un presupuesto muy bajo por la crisis económica, se cumplió el objetivo de incentivar la participación de estudiantes de pregrado y postgrado. Desde el punto de vista de la calidad de los expositores internacionales y de la calidad de las conferencias la reunión fue considerada como muy exitosa especialmente por los contactos internacionales que se crearon. Por otra parte el lugar elegido para realizar la reunión, si bien fueaustero,los participantes comprendieron la situación, y otras sociedades siguieron nuestro camino utilizando el mismo lugar por algunos años.

El año 1981 la Sociedad acordó rendir un homenaje al Dr. Héctor Croxatto por su excelente trayectoria académica y por haber obtenido merecidamente el premio Nacional de Ciencias. En su conferencia se refirió a su trayectoria académica especialmente a la dificultad de hacer investigación con muy escasos recursos, una lección muy importante para los estudiantes de pre y postgrado.

La invitación al Dr. Asencio en la reunión del año 1982 tuvo por objetivo incrementar la colaboración con la Sociedad de Bioquímica de España, acordada previamente y agradecer al Dr. Asencio quien jugó un rol fundamental en la sesión realizada en Toronto en 1979, para que la Sociedad de Bioquímica de Chile se incorporara a la UNION INTERNACIONAL DE BIOQUIMICA. Se debe hacer notar que a esta postulación se oponían algunos países de Europa por razones políticas.

Con posterioridad a la visita del Dr. Asencio a Chile,tuve el honor de ser invitado a la Reunión de la Sociedad de Bioquímica de España, que se realizó a fines de Septiembre de 1982 en Santander y a participar en una Meza Redonda sobre Cooperación Científica de España y Sudamérica en diferentes áreas de la Biología.. Actividades desarrolladas por el Programa RLA/78/PNUD/UNESCO que dirigió el Dr. Jorge Allende. Se informó que el programa estaba editando un libro; **La Bioquímica en América del Sur y España. Directorio de investigadores en Bioquímica J. Allende, L. Gil., G. Guzmán Financiado por el Instituto de Cooperación Iberoamericana (1983)**

- Otra actividad de colaboración con la sociedad hispánica se materializó con la estadía de investigación , en el laboratorio del Dr. Alberto Sols ,Universidad Autónoma de Madrid, que realizó el Dr Tito Ureta el año1983, Presidente de nuestra sociedad en el período 1983-1984,

Se debe destacar que el Dr, Asencio fue una científico muy reconocido internacionalmente especialmente en Europa y en Estados Unidos. El estaba muy interesado en incrementar la colaboración científica con Latino América y en especial con Chile. Era una persona muy carismática de un nivel de inteligencia muy elevado , de gran sentido del humor y un distinguido conferencista Lamentablemente al regresar a España para continuar sus vacaciones interrumpidas por su viaje a Chile, falleció al incendiarse su vivienda. Su muerte provocó en España una serie de homenajes. Entre ellos, la sociedad de Bioquímica de España publicó un libro sobre su carrera de investigador y su obra. (Titulo : Carlos Asencio. Correspondencia desde América . Editor Dr. Alberto Sols. Prologo Dr. Severo Ochoa).En este libro se publicó la última correspondencia del Dr Asencio que fue una tarjeta de agradecimiento por las atenciones recibidas en la reunión de la Sociedad de Bioquímica de Chile, enviada el día anterior a su muerte.

Mayor información sobre las actividades desarrolladas en estas dos reuniones , programa , simposios, instituciones participantes, resúmenes de las presentaciones en simposios y en comunicaciones libres se encuentran en las siguientes referencias:

1. Archiv. Biol. Med.Exp . vol.14(2) 1981 y
2. Archiv. Biol. Med, Exp. Vol.15(1) 1982

Dr. Lionel Gil

Dr. Jorge Allende (Presidente 1979-1980)

Lionel Gil Vicepresidente; Marco Arancibia, Secretaria; Luz María Pérez, Tesorero; Jaime Eyzaguirre, Presidente anterior; Hermann Niemeyer, Director Santiago; Osvaldo Cori, Director Santiago. Ruby González, Directora Concepción; Juan Carlos Slebe, Director Valdivia.

Bajo esta directiva se realizaron 2 congresos de la Sociedad

III Reunión Anual en conjunto con el II PAABS-Cono Sur Hotel O´Higgins, Viña del Mar 17- 20 de octubre de 1979

IV Reunión Anual en conjunto con la SAIB Mendoza, 17-20 octubre de 1980

Dr. Jaime Eyzaguirre (Presidente 1977-1978)

Jorge Allende Vicepresidente; Lyllian Clark-Turri, Secretaria; Mario Sapag, Tesorero; Marco Perreta, Presidente anterior; Hermann Niemeyer, Director Santiago; Lionel Gil, Director Santiago.

Asumí la presidencia de la Sociedad de Bioquímica así se llamaba en aquella época) en 1976, sucediendo en el cargo al Dr. Marco Perreta QEPD). Mi nombre fue propuesto por el Dr. Hemnann Niemeyer, y me acompañaron en esta gestión la Dra. Lilian Clark como Secretaria y el Dr. Mario Sapag como Tesorero. Mi gestión duró dos años y me sucedió en el cargo el Dr. Jorge Allende.

Lo más importante que sucedió en este período fue la organización de la Primera Reunión Anual. Ella se efectuó en la entonces Sede Talca de la Universidad entre el 19 y el 21 de mayo de 1977. Las condiciones en que se realizó dicha reunión reflejaban las dificultades económicas en que se desenvolvía el país, con muchas limitaciones, contrastando fuertemente a las reuniones de los últimos años. Hubo numerosos trabajos de incorporación a la Sociedad, avances de Tesis Doctorales, y una importante participación de fisiólogos. Se inició así una actividad que con los años pasó a ser la más importante de nuestra Sociedad.

Posteriormente a mi gestión, y en calidad de Past President, me tocó representar a la Sociedad en el XI Congreso Internacional de Bioquímica que tuvo lugar en Toronto, Canadá, en julio de 1979. El objetivo principal de mi participación era conseguir la admisión de nuestra Sociedad a la International Union of Biochemistry. El Presidente de dicha institución era en ese momento un ruso, que en la sesión en que se discutió nuestra admisión, ofreció la palabra si había alguna oposición a nuestra incorporación. Tomó la palabra el delegado de Polonia que lanzó una diatriba contra nuestro gobierno de la época y por razones políticas estimaba que no podían incorporar a Chile a la organización. Al término de su intervención, el presidente me ofreció la palabra. Yo representaba a la Sociedad y no al gobierno chileno, y no estaba dispuesto a entrar en debate con el polaco, por lo que agradecí al presidente diciendo que no tenía nada que agregar. Este me pidió que saliera de la sala para proceder a la votación. Al cabo de pocos minutos me llamó de vuelta, diciendo que Chile había sido aceptado como miembro, lo que fue acompañado por aplausos de la mayoría de los presentes.

Espero que esta breve presentación sea útil.

Saludos cordiales,

Jaime Eyzaguirre.

Dr. Marco Perreta (Presidente 1974-1976)

Jaime Eyzaguirre Vicepresidente; Lyllian Clark-Turri, Secretaria; Lyllian Clark-Turri, Tesorero; Jorge Allende, Presidente anterior; Hermann Niemeyer, Director Santiago; Lionel Gil, Director Santiago.

Si bien en un comienzo no hubo reunión anual, Es aquí donde se comienza a construir nuestra querida sociedad, fruto del espíritu visionario del Dr. Herman Niemeyer y un grupo de entusiastas jóvenes investigadores, quienes con esfuerzo y dedicación fueron construyendo y forjando los cimientos que hoy transforman a la Sociedad de Bioquímica y Biología Molecular de Chile una sociedad consolidada y reconocida tanto en el plano nacional como internacional. El primer presidente fue el Dr. Jorge Allende desde 1971.

Keynote speakers

Opening lecture: Dr. José Maza, Universidad de Chile, Chile.

After studying at the Internado Nacional Barros Arana, he entered the University of Chile as an astronomy student. He did his doctoral studies in astronomy at the University of Toronto. Since 1968 he has been an academic of the Faculty of Physical and Mathematical Sciences of the University of Chile, and since 1987 he has been a full professor of that house of studies. He was director of the University of Chile's Department of Astronomy from 1997 to 2000. Between 1979 and 1984 he headed the Scientific Project of Search for Supernovas at Cerro El Roble and was part of Project Calán Tololo, a Chilean-American initiative that featured the joint work of the University of Chile with the Cerro Tololo Interamerican Observatory, in the search for supernovas. The Calán Tololo project gave contemporary astrophysics tools for measuring the universe more precisely, calculations that years later would be key for a group of American astronomers to follow these supernova studies, being part of the theory of accelerating expansion of the universe by dark energy. He has not been recognized as such since all his mathematical calculations were provided to Harvard University on the condition that they would only perform a mathematical modeling, which allowed that group of American scientists to win the Nobel Prize in 2011. Apart from being a professor and being a member of the Center for Astrophysics and Related Technologies (CATA), he has given astronomical talks to young people to get them interested in science, one of which he did at the boarding school in which he studied. The astronomer Rafael Ferrando baptized the asteroid 108113 as "Maza", in honor.

Osvaldo Cori lecture: **Dr. Marta Bunster**, University of Concepción, Chile.

At present she is full professor at the Biochemistry and Molecular Biology Department in the Faculty of Biological Sciences of the Universidad de Concepción. Obtained the Biochemistry diploma on April 1974 from the Universidad de Concepción/Universidad de Chile and a Doctor of Sciences degree at the Universidad de Concepción in 1981. She has been Director and co-founder of the Magister in Biochemistry and Bioinformatics, Director of the Department of Biochemistry and Molecular Biology, and has been part of the Doctor of Biological Sciences since its creation. She has guided numerous undergraduate and graduate thesis. She has been member of the Sociedad Chilena de Química, Sociedad de Biología de Chile, Sociedad de Bioquímica y Biología Molecular de Chile, Biophysical Society, Member, Secretary and founder of the Iberoamerican Society of Bioinformatics. SOIBIO, Member of International Society of Computational Biology and Bioinformatics and Member of Latinoamerican Society of Crystallography of recent creation. After obtaining the Biochemistry degree, and a brief stay at the University of Chile, she obtained an academic position at the Biophysics section of the Department of Physiology of the Instituto de Ciencias Médico Biológicas, today the Faculty of Biological Sciences, to teach biophysics to biochemists and biology teachers. Simultaneously she enrolled at the nascent Doctor of Sciences Program of the University of Concepción with a DAAD scholarship working in controlled release anticancer and anti-depression drugs using biodegradable polymer matrices at the Polymer Labs at University of Concepción (Dr. Eckhart Schmidt and Juan Bartulín 1976-1977) and University of Florida with the financial support from OEA (Dr. George B. Butler, 1978-1980). Full returned to the University in 1981, and in a partnership/ friendship with Hilda Cid, she was deeply involved in the area of molecular biophysics specially the investigation of the three dimensional structure of proteins from the theoretical point of view and the beginning of the now called, bioinformatics. At this moment a method to predict the secondary structure of proteins was developed, and continue adding new evidences from that time and until now. More than 10 international courses were given in order to increase the critical mass of investigators in structure and function of proteins and specially Protein crystallography, coordinating biology, physics, mathematics and chemistry. From 1995 the biophysics methodologies were applied to the study of an efficient light harvesting system, the phycobilisome. In 2001, the first 3D structure of R-phycoerythrin determined by a chilean group was published. During those years, also, with a group of young and experienced researchers formed the

Iberoamerican network of Bioinformatics that then would become the Iberoamerican Society of Bioinformatics. The purpose of this society was and is to provide bioinformatic education and resources for the members of the society. From 2005 and on, she had the opportunity to work with an absolutely fantastic group of students at different levels that share a dream to mime the photosynthetic apparatus of algae to develop an energy harvesting system capable to provide clean energy at low cost. Following this purpose, "basic science" has been developed which has been published in many scientific journals.

PABMB lecture: Dr. Andrea Gamarnik, Instituto Leloir, Argentina.

Dr. Andrea Gamarnik is a molecular virologist. She earned her PhD degree in Biochemistry, in the University of Buenos Aires. After a postdoctoral training at UCSF, she returned to Argentina in 2002 where she stablished the first laboratory of Molecular Virology at the Institute Leloir, Buenos Aires. Since then, her laboratory became a reference in dengue virus basic biology and made seminal contributions for understanding flavivirus RNA replication. She is currently a Principal Investigator of the National Research Council (CONICET) and the Director of the Instituto de Investigaciones Bioquímicas de Buenos Aires-CONICET at the Institute Leloir. Her work focuses on understanding the function of viral RNA structures and defining how thee structures modulate viral processes. In this regard, her group identify the promoter for dengue virus RNA replication and uncovered the mechanism of viral RNA synthesis, which was then extrapolated to an extensive group of viruses. In addition, her studies on functional viral RNA structures provided a framework to analyze viral RNA genomes as dynamic molecules. More recently, she became interested in studying adaptation of viral RNAs in mosquito and humans, and proposed new models of viral RNA specialization in different hosts. The achievements of Dr. Gamarnik in virology have been widely recognized internationally. She was HHMI International Research Scholar in the Infectious Disease Program (2005-2011), became a member of the American Academy of Microbiology in 2014 and was recipient of numerous awards such as the L'Oreal-UNESCO 2016 "For Women in Science" in representation of Latin America.

Severo Ochoa lecture: Dr. Mariano Barbacid,

Mariano Barbacid (Madrid, Spain 1949) studied biochemistry at the *Universidad Complutense* (1966-71) and got his Ph.D. degree from the same university in 1974. From 1974-1978 he trained as a postdoctoral fellow at the National Cancer Institute (NIH) in Bethesda, Maryland working on the molecular biology of murine retroviruses. In 1978 he started his own research group to try to unveil the molecular events responsible for the development of human tumours. His work led in the spring of 1982, to the isolation of the first human oncogene and the first mutation associated with the development of human cancer. These findings, also made independently by two other groups, have been seminal to establish the molecular bases of human cancer. During the following decade (1988-1998), he joined Bristol-Myers Squibb where he became Vice President of Oncology Drug Discovery. There he started the concept of what is now known as Precision Medicine by developing inhibitors against FTase and cell cycle Cdks, among other molecular targtes. In 1998, he returned to Spain to build and direct the Spanish National Cancer Research Center (*Centro Nacional de Investigaciones Oncológicas,* CNIO). Under his leadership, the CNIO was ranked within the top 15 leading research centres among more than 3,000 research institutions worldwide by the Scimago Institutions Ranking. In 2011, he stepped down as director to concentrate on his own research on the identification and functional validation of therapeutic strategies to treat K-Ras/TP53 driven lung and pancreatic tumors.

In 2012, he was inducted to the US National Academy of Sciences as a Foreign Member and in 2014, he was elected Fellow of the American Association for Cancer Research. He holds three Honorary Degrees from the International University Menendez y Pelayo (1995), University of Cantabria (2011) and University of Barcelona (2014). His work has also been recognized by several international and domestic awards including the Steiner Prize (Bern, 1988), Ipsen Prize (Vienna, 1994), Brupbaher Cancer Research Prize (Zurich, 2005), the Medal of Honour of the International Agency for

Cancer Research (Lyon, 2007) and the Burkitt Medal (Dublin, 2017). In 2011 he was awarded an Endowed Chair from the AXA Research Fund (Paris). He is one of the few European scientists to receive two Advanced Grants from the European Research Council (2009 and 2015). To date, Dr. Barbacid has authored 303 publications, including 225 original research articles in journals with impact factor. Currently, Dr. Barbacid's Hirsch "h" factor is 112 (Google Scholar) or 106 (Web of Science).

Tito Ureta Prize: Dr. Pablo Valenzuela, Fundación Ciencia & Vida, Chile.

Pablo Valenzuela earned a Biochemistry degree from Universidad de Chile (1965) and a Ph.D. degree in Chemistry at Northwestern University (1970). He did postdoctoral training at University of California, San Francisco and held a position as Professor in the Biochemistry Department of that institution. Despite his interest in developing biotechnology products, Valenzuela has been a champion for basic, curiosity driven research. He has published more than 140 papers, directed more than 20 Ph.D. theses and named as inventor in more than 60 patents. At different times, he has been professor at Universidad de Chile, Universidad Católica, Universidad Andrés Bello and Universidad San Sebastián where presently he is a member of the Junta Directiva. Pablo Valenzuela is responsible for the development of several biotechnology products in USA and Chile. In USA he developed more than 10 products in the area of blood banking diagnostics including key tests for hepatitis C, AIDS virus and hepatitis B virus; and several pharmaceutical products including the hepatitis B vaccine, human insulin, a plateled grow factor derived wound healing cream (Regranex) and beta interferon, all made in yeast. All together, these products have worldwide sales higher than 5 billions of dollars a year. In Chile, he has developed a commercial vaccine for salmoniculture and several products for human and blood bank diagnostics such as Chagas, Helicobacter, Rotavirus, Blood Groups, etc. These products are today commercialed in Chile and Latin America with sales of approximately 10 million dollars per year. Valenzuela is an active entrepreneur. Internationally, he has been the cofounder of several biotechnology companies including Chiron Corporation, Ventria Biosciences, Applied Imaging, Phytotox, Austral Biologicals and Praxis Biotech. In Chile, he has been involved in the founding of GrupoBios (with Arturo Yudelevich and José Codner), Andes Biotechnologies (with Luis Burzio and Arturo Yudelevich) and Fundación Ciencia & Vida (with Mario Rosemblatt and Bernardita Méndez). Through the creation of the Science & Business Park, which harbors 15 national and foreign start-ups. He serves as a board member/advisor of several start-ups such as Algenis, Phage Technologies, NovaMineralis, Merken Biotech, Ango Sciences and Ingalfarma. Among his awards are the Chilean National Award in Applied Sciences & Technology (2002), the University of Chile Rectoral Medal Award (2002), Membership of the Chilean Academy of Sciences (2004), the Orden de la Cruz del Sur Medal from the Chilean Government (2012), the California BayBio Life Time Sciences Achievements Awards (2012), the University of California Medal (2014) and the 2017 Entrepreneur of the Year from the Chilean Association of Venture Funds.

Symposia

Symposium 1. Protein crystallography: from structure, function and beyond

Chair: Víctor Castro-Fernandez and Victoria Guixé, Universidad de Chile, Chile

Dr. Marcos Sotomayor received his B.Sc. in Physics from Universidad de Chile in 2001 and his Ph.D. in Physics from the University of Illinois at Urbana-Champaign in 2007. As a graduate student with Dr. Klaus Schulten in the theoretical and computational biophysics group he did molecular dynamics simulations of proteins involved in mechanotransduction. His computational studies predicted the conductance of the ion channel MscS structure, as well as the elasticity of ankyrin and cadherin repeats. After finishing his Ph.D., he joined the laboratories of David P. Corey and Rachelle Gaudet to do experimental work as a postdoctoral researcher at Harvard University. There he solved the first X-ray crystal structure of a heterophilic cadherin complex essential for hearing and balance. During his postdoctoral tenure he was a Howard Hughes Medical Institute fellow of the Helen Hay Whitney foundation. Marcos received a prestigious NIH K99/R00 award and started at OSU in July of 2013. In 2015 he received a Distinguished Undergraduate Research Mentor award from the undergraduate research office at OSU and was selected as an Alfred P. Sloan Research Fellow in Neuroscience.

Dr. José Martinez-Oyanedel structural biophysic has been involved in crystallographic analysis of proteins to establish the structure-function relationship. Has been involved in the development of protein crystallography in Chile, is author of several crystal structure deposited in the Protein Data Bank and publications on protein crystallography. Since 1991 is academic in the Departamento de Bioquimica y Biologia Molecular from Universidad de Concepción. In the last time the research has been direct to build a model of the phycobilisome from Gracilaria chilensis, solving the protein structure that are presents in this macromolecular structure.

Dr. Sebastián Klinke holds a PhD degree in Biological Chemistry from the University of Buenos Aires (2007) under the supervision of Prof. Fernando Goldbaum, and is Associate Researcher of the Argentinian Research Council (CONICET) at the Laboratory of Immunology and Molecular Microbiology, Leloir Institute, Buenos Aires. His thesis project focused on the structural study of lumazine synthase in the pathogenic bacterium Brucella abortus, applying X-ray crystallography as well as other biophysical and biochemical techniques. Lumazine synthase is an enzyme involved in the biosynthesis of riboflavin (vitamin B2), which corresponds to a very promising target for the development of vaccines and antimicrobial compounds against this pathogen. Through his thesis work, the laboratory became a pioneer in Argentina in the application of macromolecular crystallography both in know-how and in instrumentation. In the last years his projects have been focused on the structural study of several Brucella virulence factors related to the biosynthesis and metabolism of riboflavin, which are interesting antibacterial targets, since Brucella is unable to acquire vitamin B2 from the external environment with efficiency and depends exclusively of its endogenous synthesis. Since 2013, Dr. Klinke is director of the Crystallography Node of the Argentinian Platform for Structural Biology and Metabolomics PLABEM. Within the Platform, the first three-dimensional protein structure obtained entirely in Argentina by X-ray diffraction was solved in 2014. As general achievements of his career, Dr. Klinke has published 21 articles in international peer-reviewed journals (h-index = 10), with over 90 presentations to congresses and more than 30 protein structures solved to date. Additionally, he holds academic positions in Argentinian and international scientific associations (Vice-president of the Argentinian Association of Crystallography and Member of the Deliberative Council of the Latin American Association of Crystallography, respectively). To finish, he has been recently involved in science outreach projects in Argentina aimed for primary school and high school students, organizing workshops, seminars and competitions related to crystallization and crystal growth with other colleagues throughout the country.

Dr. Victor Castro-Fernandez studied Biochemistry at the University of Concepción. His undergraduate thesis was directed by Dr. Elena Uribe, in which he worked in enzymology of ureahydrolases. In 2010 he started his PhD in Biological Science at the Faculty of Science of University of Chile under the direction of Dr. Victoria Guixé. During his PhD thesis, he implemented the methodology of ancestral protein reconstruction and worked on specificity of substrates of kinases. During his PhD he made several research stays in the group of Dr. Richard Garrat at University of Sao Paulo in Brazil, where he worked in protein crystallography. After finish his PhD thesis, he awarded a postdoctoral grant Fondecyt with the sponsorship of Dr. Jorge Babul at the University of Chile and his postdoctoral work focused on the evolution of protein stability through evolution and development of protein crystallography from Chile. In collaboration with Dr. Victoria Guixé they have studied the adaptation of proteins to extreme environments such as halophiles, psychrophiles and thermophiles. Since 2017 is academic of the Department of Biology, Faculty of Science of the University of Chile.

Symposium 2. Symposium Sbbq-Brazil: Bioactive compounds with potential health benefits, biotechnological approaches.

Chairs: Dr. Luis Morales-Quintana, Universidad Autónoma de Chile, Chile and Dr. Patricio Ramos, Universidad de Talca, Chile.

Dr. Patricio Ramos studied Biochemistry at the University of Concepción and obtained his professional degree in 2003. He obtained his PhD in engineering in plant genetics from the University of Talca in 2010 and then he performed a post-doctoral training at the Institute of Biological Sciences (ICB) at University of Talca. In 2011 started an insertion in the academy program (PIA) and now he works at University of Talca in "The scientific multidisciplinary nucleus" and is part of the academic team of the ICB and PhD program. One of the main research lines is focusing in the study of phenylpropanoid metabolic pathway regulation and the relationship with hormonal signaling. Phenolic compounds, specifically flavonoids, display wide biological effects such as modulation of the interaction between plants and microorganisms, stress response, pigmentation as well as the hormonal transport regulation in several plant tissues. Homeostasis of those compounds within the subcellular compartment and balance between lignin and flavonoid is part of his scientific research interest. On the other hand, phenylpropanoid displays several health's benefit to consumers, the study of biosynthesis and accumulation in fruits and other edible plant tissues are also part of his research line.

Dr. Luis Morales Quintana studied Engineering in Bioinformatic at the University of Talca and received his degree in 2009. He performed a PhD in Science with mention in plant genetic engineering from the University of Talca and received the degree at 2013. After that he worked as professor at the Institute of Biological Sciences of U. of Talca (2014-2017). He is currently associate professor of Biochemistry and Molecular biology at the Instituto de Ciencias Biomédicas of the Universidad Autónoma de Chile, Talca, Chile. His research main topic focuses in the study of molecular aspects in the formation and degradation of primary plant cell wall. The strategies used involve: structural bioinformatics, biochemical characterization, kinetics studies, and functional genomics. To describe genes, proteins, enzymes and how they modulate the response to different events occurring in the plant cell wall. It has also been approached the study of enzymes involved in the study of quality traits of fruits, specifically in biosynthesis of volatile compounds related with aroma in strawberry and mountain papaya fruits.

Dr. Paulo A. S. Maurao obtained his MD (1975) and PhD (1975) at the Federal University of São Paulo. Postdoc at Baylor College of Medicine (USA) with a fellowship from the US NIH/ Fogarty International Research Fellow. Since 1981, he has been a Professor of Biochemistry at Federal University of Rio de Janeiro, Full Professor since 1992. He coordinates the "Connective Tissue Laboratory", located at the University Hospital, in a project to integrate basic and clinical areas of the institution. He is responsible for an innovative postgraduate program that combines the MD with the PhD. His research theme is glycobiology, especially aimed at the study of structure, biological activity and metabolism of sulfated polysaccharides, including pharmaceutical preparations of heparin and chondroitin sulfate. His research work has been

funded with regular grants from national and international agencies such as the World Health Organization (WHO), Mizutani Foundation for Glycoscience, British Council, Natural Sciences and Engineering Research Council (Canada) and COFECUB (France). Former Fellow of the John Simon Guggenheim Memorial Foundation, he is a member of the Brazilian Academy of Sciences, the Academy of Sciences of Developing Countries, and the National Order of Scientific Merit. In 2003-04 he was president of the Brazilian Society of Biochemistry and Molecular Biology.

Dra. Aparecida Sadae Tanaka studied undergraduate Chemistry at the Universidade Estadual Paulista (UNESP) in Araraquara, São Paulo – Brazil. She obtained her Ph.D. in Sciences from the Universidade Federal de São Paulo in 1993, under the supervision of Claudio A. M. Sampaio. She did a postdoctoral in the Ludwig Maximilian University of Munich (LMU) in Germany (1993-1995). In 1997, she got a position of Adjunct Professor in the Department of Biochemistry in the Escola Paulista de Medicina (EPM) –UNIFESP. In 2006, she obtained the title of Associate Professor - "Livre Docente" in the same Department, were she is currently Full Professor. The focus of the Tanaka's Lab is biochemistry and molecular biology of diseases' vectors. The group already described several new molecules from insects and ticks belonging to proteases and protease inhibitors families. In the present, the group has been focused in the role of those molecules in the vector-parasite or mosquito-virus interactions; and in the development of tools to vector control.

Dr. Leonel Rojo is an Associate Professor and Head of the Pharmacy Academic Program at Universidad de Santiago de Chile. He has developed research on bioactive molecules from botanical sources with applications in metabolic syndrome and skin regeneration. Prior to pursuing postdoctoral training in Biotechnology at Rutgers University (New Jersey, USA), He served as a visiting scientist at Albert Einstein College of Medicine in New York. Dr. Rojo developed several R&D projects as a member of the multidisciplinary team led by Dr. Ilya Raskin and Dr. Bertold Fridlender at Rutgers University. He also served as a consultant for Nutrasorb LLC, a spinoff biotech company of Rutgers University. Dr. Rojo is co-founder and scientific advisor of Neuroinnovation Ltda., a pioneer startup Company based in Chile specialized in developing and commercializing therapeutic technologies for Neurological diseases. He has been a visiting scientist at Kwantlen Polytechnic University in Vancouver, Canada, and the National Institute of Engineering and Technology (INETI) in Lisbon, Portugal. His work in Chile, USA and Europe has resulted in several scientific ISI publications, book chapters and patent applications. Dr. Rojo served as General Director a drug-development program funded by the Chilean government and as the coordinator of the GIBEX-Chile program.

Symposium 3, Preclinical models for studying pathogenesis and designing therapies for hematologic malignancies

Chair: Ruben Carrasco, Harvard University, USA

Dr. Ruben Carrasco received an MD in 1989 and a PhD in Biochemistry in 1993 from the University of Chile. He then completed clinical training in Anatomic Pathology at the Massachusetts General Hospital, followed by a subspecialty fellowship in Hematopathology at the Brigham and Women's Hospital (BWH), Harvard Medical School (HMS), Boston, Massachusetts. During his postdoctoral work in the Department of Medical Oncology at the Dana-Farber Cancer Institute (DFCI) under Dr. Ronald DePinho, he developed an interest in oncogenomics and the genetic modeling of murine hematologic cancers with emphasis on multiple myeloma (MM), a cancer of plasma cells. He has continued to actively pursue this research interest to this day. He is currently a hematopathologist at BWH and a research investigator at DFCI. Over the years his lab has led, or collaborated with other groups on work that has led to several important and original findings in the field, including: i) characterization of MM genomes using genome-wide array comparative genomic hybridization (a-CGH), ii) generation of a novel murine transgenic model of MM using the X-box binding protein 1 (XBP-1), iii) demonstration that the B-cell lymphoma gene (BCL9) is an oncogenic promoter of MM progression, (iv) acquisition of compelling proof-of-concept support for an innovative pharmacologic strategy to inhibit oncogenic Wnt signaling in MM via targeted disruption of BCL9/b-catenin complex, and v) demonstration that Cyclophilin A (CyPA) is a downstream transcriptional target of the Wnt/b-catenin/BCL9 complex that is secreted by bone marrow endothelial cells and promotes MM progression through via binding to CD147. He has led multi-investigator multi-institution NIH funded Program Project Grants. In 2015, he was named an Associate Professor in Pathology at BMW and HMS. He has published more than 90 articles in peer-reviewed journals, holds 4 U.S. patents, and has been an invited speaker at major international meetings devoted mainly to MM.

Dr. Jon Aster obtained his MD/PhD in 1987 from the University of Michigan, and then did clinical training in Anatomic Pathology and hematopathology at Brigham and Women's Hospital. During his postdoctoral work in the Division of Molecular Oncology with Dr. Jeffrey Sklar, he developed an interest in the role of Notch signaling in cancer and hematopoiesis, areas of research that he has continued to pursue to the present. Over the years his lab has led or collaborated on work that has produced a number of firsts in the field, including: i) production of the first mouse model of Notch leukemia; ii) demonstrating that Notch signals can induce T cell development from bone marrow progenitors; iii) demonstrating that T-ALL cells depend on continuing Notch signaling for growth; iv) detecting and characterizing frequent Notch1 mutations in human and murine T-ALL; v) solving key Notch structures at high resolution, including the structures of Notch transcription complexes on DNA; vi) identification of Myc and mTOR as important downstream targets of leukemogenic Notch signaling; vii) development of the first selective Notch receptor inhibitors, antibodies directed against the negative regulatory domain; viii) report of genome-wide Notch1 binding patterns in cancer cell genomes; and viii) description of Notch1 loss-of-function mutations in human squamous cell carcinomas. His work describing Notch1 mutations in T-cell acute lymphoblastic leukemia is one of the most highly cited in the field (2265 citations). He has led multi-investigator multi-institution NIH funded Program Project Grants and Leukemia and Lymphoma Society sponsored Specialized Center of Research Grants. Since 2007, Aster is full Professor of Pathology at Brigham and Women's Hospital and Harvard Medical School and as of 2017 is the first incumbent Michael A. Gimbrone Chair in Pathology. Aster has published more than 190 manuscripts in peer-reviewed journals that have been cited more than 55,000 times and an *h*-factor of 104. He holds 3 patents. He has been an invited speaker at all major international meetings focused on Notch signaling in cancer to date (the Notch Gordon conference, the International Notch Meeting), and has organized several of these meetings. He leads the division of Hematopathology at Brigham and Women's Hospital, serves as the co-leader of the Lymphoma and Leukemia Program of the Dana Farber/Harvard Cancer Center, and is on the Executive Committee of the Cancer Center. He is a past member of the NIH Cancer and Molecular Pathology study section, and continues to serve as an ad hoc reviewer for the NIH. In 2017, Aster was elected to the Association of American Physicians. He also is the co-editor of the Pathologic Basis of Disease, the most widely used pathology text in the world.

Dr. Andrew Lane is a physician-scientist whose goal is to define novel targets in hematologic malignancies that lead to new therapies. He obtained his MD and PhD degrees from Washington University in 2006. His PhD thesis research with Dr. Timothy Ley studied the pathophysiology of acute promyelocytic leukemia (APL). He created new mouse models to understand why the PML-RARa oncogene specifically transforms early myeloid progenitors but no other cell types. He then completed his internal medicine training at Brigham and Womens Hospital / Harvard Medical School, and fellowships in hematology and medical oncology at Dana-Farber Cancer Institute. His postdoctoral research interrogated patient leukemia genetics and animal models to ask why Down syndrome is associated with increased risk of B-ALL. Using an shRNA screen in primary B cell progenitors, he identified the epigenetic regulator and nucleosome-binding protein HMGN1, encoded on chromosome 21q22, as a novel lymphoid leukemia oncogene. Now an assistant professor at Dana-Farber and Harvard Medical School leading his own laboratory group, he continues to work on AML and ALL to elucidate new therapeutic targets. He now also studies blastic plasmacytoid dendritic cell neoplasm (BPDCN), a rare leukemia/lymphoma of dendritic cells, with projects on BPDCN genetics, dendritic cell transformation mechanisms, and testing novel therapies in animal models and in clinical trials, including BCL-2 inhibition, CAR-T cells, and cell surface receptor-targeted immunotoxins. Dr. Lane is director of a new BPDCN Center at Dana-Farber, a clinical and translational research group that aims to accelerate basic biological understanding and promote rapid clinical evaluation of novel therapeutics in BPDCN.

Dr. Tomasz Sewastianik is a translational scientist with a focus on the molecular biology of normal and malignant lymphoid cells and the clinical exploitation of validated signaling, transcriptional, and metabolic pathways. He obtained his MSc in 2011 from Maria Curie-Sklodowska University in Lublin, Poland, under the auspices of the Nencki Institute of Experimental Biology, Polish Academy of Sciences in Warsaw, where he worked in the area of DNA damage response and T cells death associated with immune system deterioration. He then obtained a PhD in 2015 under Prof. Przemyslaw Juszczynski at the Maria Sklodowska-Curie Memorial Cancer Center – Institute of Oncology and at the Institute of Hematology and Transfusion Medicine in Warsaw, where he studied redox-dependent signaling pathways in diffuse large B-cell lymphoma (DLBCL) and identified the TXN-p300-FOXO1 circuit as the major mediator of oxidative stress response in DLBCL. He also worked on the inhibition of PIM kinases in acute myeloid leukemia and on daunorubicin-resistance in acute lymphoblastic leukemia cells. In 2015, he began postdoctoral training with Dr. Ruben Carrasco at Dana-Farber Cancer Institute, working on mouse models of cancer using, for example, animals with mutated MYD88 protein overexpression, miR-15a/16-1 deletion, and Kras oncogene mutation with concomitant deletion of the Ink4a/Arf tumor suppressor. He has published in peer-reviewed journals and has presented his findings at international meetings including, for example, American Society of Hematology Annual Meetings and the International Conference on Malignant Lymphoma in Lugano, Switzerland.

Symposium 4, Exosomes in cancer disease

Chair: Andrew Quest,Universidad de Chile, Chile & Advanced Center for Chronic Diseases, ACCDiS

Dr. Silke Krol was trained in Chemistry at the Westfälische Wilhelms-University in Münster, Germany where she obtained her Master degree in Chemistry in 1997. This was followed by the PhD with the topic of her thesis on the biophysical characterization of hydrophobic pulmonary surfactant components. She received her PhD in 2000 and continued working as a postdoc until 2001. Then she worked first as a post-doctoral fellow (2001-2003) and then as a junior researcher (2003-2007) at the INFM (Istituto nazionale di fisica materia), Institute of Physics, University of Genoa, Genoa, Italy. She developed nanodrugs and protective nanocoatings for cells in an EU project entitled “Nanocapsules with functionalized surfaces. With this approach she was one of the pioneers in nanomedicine in Genoa. A second EU project used the protective cell coating to protect pancreatic islets for a Bioartificial Pancreas for Type I Diabetes Therapy. From 2007-2010 she established and headed the „NanoBio“lab@LA (NADA) (laboratory of nano analysis, drug delivery, and diagnostics) at CBM in Trieste, Italy, a small enterprise dedicated to technology transfer from bench to bedside. Here her research focused on developing anticancer drugs and vehicles that allow the delivery through the blood brain barrier. In 2010, she established and headed the laboratory for Nanomedicine at the National Institute for Neurology ”Carlo Besta”, Milan, Italy. As a principal investigator and advisor to the director of the Nanomedicine Centre, where research activities focus on the design of nanoparticles for imaging and therapy of neurodegenerative disease, epilepsy and cancer. In this contest, she developed a very strong interest in exosomes and their importance for theranostics and the metastasis of tumors. This work was extended and intensified in the field of liquid biopsy for early diagnosis of cancer in the Institute of Oncology “Giovanni Paolo II”, a research hospital in Bari, Italy where she established the laboratory of translational nanotechnology in 2016.

Dr. Carlos Salomon. I lead the Exosome Biology Laboratory based at The University of Queensland located at the Centre for Clinical Diagnostics (CCD) within UQ Centre for Clinical Research (UQCCR). My research interests include extracellular vesicles, ovarian cancer, pregnancy, preeclampsia, preterm birth and maternal obesity in pregnancy and gestational diabetes mellitus. I have obtained an undergraduate degree, Bachelor in Biochemistry with Honours in Immunology in 2005 (University of Concepcion, Chile) and a Masters degree in Clinical Biochemistry and Immunology in 2008. I began my Ph.D. studies in 2008 (Faculty of Medicine, The Pontifical Catholic University of Chile), and my Ph.D. was awarded December 2012. I have completed training in the regulation of transport system, placental function and mass spectrometry at University of Barcelona (Spain), The University of Texas Health Science Center (USA) and The University of Queensland (Australia), respectively. I have awarded the Chancellor’s Prize for Excellence in the Ph.D. Thesis (2013). I am the author of 77 journal publications (51 in EVs field and 43 as senior/corresponding author) and over 100 abstracts during the period of 2011-2017, many of which appear in high-ranking journals in the field (e.g., Oncotarget, Diabetes, JCEM, Placenta, and FASEB). Currently, I hold appointments at the University of Queensland (Brisbane, Australia), Ochsner Medical Center (New Orleans, USA) and Universidad de Concepcion (Concepcion, Chile). I am a principal investigator on several projects on extracellular vesicles based at the USA (NIH), Australia (NHMRC), U.K (Action Research) and Chile (Fondecyt). I have established and lead the EXOSOME BIOLOGY LABORATORY that conforms the ISO standards (ISO17025 and 13185) and in which human exosomes can be isolated, characterised, and their role elucidated to evaluate their clinical utility as biomarkers of disease and therapeutic interventions.

Dr. Alejandro Corvalán got both MD and MSc from the University of Chile, Santiago, Chile and went on to train as a clinical and research fellow at the Mount Sinai Medical School New York, USA and then at Kagoshima University at Kagoshima, Japan. During this period he characterized the role of Epstein-Barr Virus (EBV) in gastric cancer, a novel etiological agent that took almost 20 years to be recognized. He moved on to a position as an Assistant Professor at the University of Chile in Santiago, Chile and then to the University of Texas MD Anderson Cancer Center in Houston, TX, USA. In 2010, he moved back as an Associate Professor at the Pontificia Universidad Catolica de Chile, Santiago where he turned to the study of epigenetic modifications in pathogenesis and as biomarkers of diseases. His group identified a novel gene Reprimo that functions as a tumor suppressor in gastric cancer cells whose epigenetic modifications, such as methylation of the promoter region, may act as a cell-free DNA biomarker for non-invasive diagnosis of gastric cancer. More recently, his group switched to the study of the role of non-coding genes (i.e. microRNAs) in precancer lesions of the stomach and showed that the microRNA-335 may act as a tumor suppressor gene and by inactivating metastatasis-promoting genes. Currently, his group is exploring how downregulation of the microRNA-335 in exosomes promotes metastasis. Alejandro Corvalan is currently director of Grupo Oncologico Chileno Cooperativo de Investigacion (GOCCHI) and Principal Investigator of the Advanced Center for Chronic Diseases (ACCDiS).

Dr. Lorena Lobos-Gonzalez trained as a Biochemist in the Pontificia Universidad Católica de Valparaiso. She got her Master in Biochemistry from the Universidad de Chile under the supervision of Dr. Amalia Sapag and then her PhD with Dr. Andrew Quest working at the same institution. In her PhD thesis she contributed to development a new *in vivo* surgery model that permitted studying the dual role of Caveolin-1 as a tumor suppressor and promoter of metastasis. Her studies were the first in the literature to show directly the dual role of Caveolin-1 in an *in vivo* model. During her PhD training period, Lorena did a research stage in England at St George's Hospital, University of London in the lab of Dr. Dorothy Bennet (PhD), where she studied the role of CAV1 in different tumor and melanoma cell lines. In 2012, Lorena was awarded a PIA project to work in the *Fundación Ciencia y Vida* as a postdoctoral fellow in the lab of The Dr Luis Burzio, whose interests focus on the development of novel therapeutic approaches for the treatment of different types of cancer based on the knockdown of noncoding mitochondrial RNAs. Thanks to these studies, Lorena obtained several important publications and, importantly, the data obtained in the *in vivo* studies in animals permitted moving on to testing the pharmacogenics in a phase I study in the USA, approved by the FDA. In 2014, Lorena was awarded a *Fondecyt de Inicio* (Young Investigator Award) to study the role of exosomes in promoting breast cancer metastasis and identifying the exosomal miRs and proteins involved.

Symposium 5, Scientific research trajectory and scientist training in Chile

Chairs: Roxana Pincheira and Leonardo Guzmán, Universidad de Concepción, Chile.

Dr. Roxana Pincheira is Biochemist from the University of Concepcion. She performed her undergraduate thesis under direction of Dr. Isolde Rudolph (Neurochemistry), and then moved to Santiago and worked for two years as a Research Assistant in the Pontificia Universidad Catolica. During this period she worked under the supervision of Dr. Gonzalo Bustos (Neurochemistry) and Dr. Paulina Bull (Molecular Biology). She obtained her Doctoral Degree in Biomedical Sciences from the University of Chile (2000), working on the identification and characterization of the major subunit of eukaryotic initiation factor 3, and its involvement with cancer. Her PhD thesis was under the direction of Dr. Jian Ting Zhang from the University of Texas Medical Branch (UTMB) through a Joint Graduate Program between Universidad de Chile and UTMB. After graduation she worked as a postdoctoral fellow in the laboratory of Dr. David Donner (Protein Signaling and cancer) at Indiana University-Purdue University Indianapolis (IUPUI) and in the Surgery Oncology Laboratory (Neurotrophin signaling and oncogene-tumor suppressor network) at the University of San Francisco California (UCSF), where she was appointed as Assistant Researcher. Since 2010 she is working as an Associate Professor of the Biochemistry and Molecular Biology Department at Universidad de Concepcion. Dr. Pincheira's research is aimed at understanding the molecular basis of cancer; currently her group investigates the regulation and function of SALL2, a transcription factor associated with Coloboma and several types of cancer. The Pincheira's group has demonstrated that SALL2 plays a key role in the cellular response to stress, and in cell cycle regulation, which together supports a tumor suppressor role for SALL2. The knowledge of the molecular bases of cancer, and in the specific the understanding of SALL2 function under different genetic contexts, including its p53 - independent functions is crucial for the rationale of cancer treatments and the design of future antitumor drugs. Since 2011 Fondecyt has continuously funded her research. During 2011-2016 Dr. Pincheira was the Director of an institutional regional project aimed at advancing biomedical sciences in the Bio Bio Region. She is currently the Scientific Director of CREAV (Centro Regional de Estudios Avanzados por la Vida). Since 2012 she has been the President of the Bioethics committee from the Faculty of Biological Sciences. Dr. Pincheira has mentored several undergraduate thesis (Biochemistry, Bioengineering and Biology) and graduate thesis from Master and PhD programs at University of Concepcion. Finally, since 2010 she is an active member of the Chilean Biochemistry Society, and acted as the Bio Bio regional director during 2011-2012.

Dr. Juan Olate. Dr. Juan Olate's journey is a very interesting one. After finishing high school he entered to Aviation School in Santiago. There, he become passionate about flights and stayed for 5 years (1966-1970), obtaining the rank of Military Pilot after doing the courses in the Beechcraft T-34 "Mentor" and Cessna T-37 instructional aircraft. In a span of eight months (July 1970 - March 1971) he changed his military life for university life to embrace the career of Biochemistry at the University of Concepción (1971) having in mind to become a scientist. After graduating as a Biochemist (1977), he decided to take the academy path (teaching and research). He obtained a PhD in 1985 at the University of Chile (1981-1985), working under the mentoring of Dr. Jorge Allende (National Award of Natural Sciences, 1992). Between 1985-1987 he performed a post-doctorate at Baylor College Of Medicine, Texas Medical Center, Houston, USA (1985-1987) learning the nascent areas of Molecular Biology and Molecular Genetics. After his postdoctorate, Dr. Olate come back to the Universidad de Chile to the Biochemistry laboratory where he was previously trained to establish his first research laboratory group (1988-1993). Latter, he was contacted by the Dean of the Faculty of Biological Sciences from the University of Concepción who offers him the position of Associate Professor, with the task of establishing a Molecular Biology laboratory that would allow cloning, expressing and understanding the function of genes and that would serve at the same time as a formative unit for pre and post-graduate students of the biological research area. He accepted the offer and returned to the Universidad de Concepcion (1994). In this new and modern laboratory, using cutting-edge techniques, he continued for 21 years (1994-2015). Dr. Olate's research focused on the molecular mechanisms that allow communication between cells. During this period, he held several university administrative positions as Biochemistry Department Director, Director of PhD program in Molecular and Cellular Biology, President

of the Biochemistry Society of Chile and was an active member of the study groups of CONICYT (1995-1997). In 2013, he was awarded the "Municipal Science Award", in recognition of his long scientific trajectory, and for his contribution in the Bio Bio region to the scientific knowledge about the function of genes and their relationship with pathologies, and for training and scientific knowledge dissemination. Over the years he mentored more than 30 professionals, 15 doctors, published more than 60 papers in several high impacts journals and presented at numerous international conferences. He also was investigator in five International Cooperation Projects (Human Frontier with Japan and USA, ECOS with France, 3 NIH with USA). In March of 2015, Dr. Olate decided to leave the academy, hung the pipettes and retired. He now is happily enjoying reading, gardening, astronomy and his new house near Termas de Chillán, in a small town located 82 km east of city of Chillán.

Dr. Victoria Guixé obtained the Biology degree from Facultad de Ciencias, Universidad de Chile in 1978. She performs her undergraduate thesis on "Muscle hexokinase: Compartmental Aspects and Cellular Localization" under Dr. Tito Ureta's direction. She continues her scientific training by performing Ph.D. in Biology at Facultad de Ciencias working on the kinetic mechanism and regulation of wild type and mutants forms of *E. coli* phosphofructokinases, under the direction of Dr. Jorge Babul. After finishing her Ph.D., Dr. Guixé moved to P. Universidad Católica de Chile, where she performed teaching activities and scientific research with Dr. Alejandro Venegas working on yeast pyruvate kinase. Then, she returned to the Facultad de Ciencias to join Dr. Ureta' s group. She actively participates in elucidating an indirect pathway for glycogen synthesis in frog oocytes and other key findings related to the *in vivo* operation of glycolysis and gluconeogenesis in this system. Her research had been focused on the importance of the *in vivo* enzyme regulatory properties using as a model study *E. coli* strains expressing phosphofructokinases with different regulatory characteristics. Currently, her research is aimed to understand how along evolution, enzymes from the archaeal family of ADP-dependent kinases have acquired a vast range of molecular adaptations to thrive in many extreme environments. She has performed research stays at Harvard Medical School, Universidad de Barcelona, and Columbia University. Over the years at Universidad de Chile she mentored numerous undergraduate and graduate students, published more than 50 papers in high impacts journals, book chapters and books, and presented at numerous international conferences. She has been actively involved in teaching as well as in administration duties. She has been President, Secretary and Treasurer of the Sociedad de Bioquímica y Biología Molecular de Chile, Director of the Ph.D. program in Biología Molecular Celular y Neurociencias from University of Chile, Director of Biology 3 study group from Fondecyt, external review for the academic test for admission to the University (PSU), among others. Because of her multidisciplinary work, and complete academic career, in 2009 Dr. Victoria Guixé, the women scientist and mother of two daughters received the "Woman Generation Siglo XXI Distinction of the University of Chile".

Dr. Leonardo Guzmán is currently the Director of the Department of Physiology of the Faculty of Biological Sciences of the University of Concepcion. His area of primary specialty was the signal transduction, to then derive in the analysis of the interactions of these molecular systems with the function of ion channels and drug design. Dr. Guzmán received his degree in biochemist in the University of Concepcion in 1998, after completing his undergraduate thesis in the Molecular Genetic Laboratory directed by Dr. Juan Olate, in the Department of Biochemistry and Molecular Biology of the University of Concepcion. Then he did his doctoral studies under the guidance of the same Dr. Olate. In his thesis, advances were made in the knowledge of molecular aspects of the signal transduction associated with the meiotic maturation process of the Xenopus laevis oocyte. Later, he joined the Neurophysiology Group led by Dr. Luis Aguayo for the realization of a postdoctoral project in the Physiology Department of the University of Concepcion. Here, he participated in the determination of molecular aspects of the regulation of the glycine receptor by the transduction protein Gbg. In parallel, Dr. Guzmán joined the academic plant of this department, and integrated the scientific and academic work of the faculty of biological sciences. In this way, he obtained a FONDECYT Initiation project in 2007. Then, he has been awarded whith two other regular FONDECYT projects and a FONDEF IDeA project. During the years 2012 to 2015 he was the Director of the Doctorate in Biological Sciences area Cell and Molecular Biology of the University of Concepcion, being also director of a MECESUP project for the improvement or update of different aspects of this postgraduate program. Its scientific contribution has focused on the design of small molecules that inhibit the

potentiation of ethanol on the glycine receptor, carried out from the conceptual and bioinformatic to the demonstration in in vitro and in vivo models of animal behavior. On the other hand, it has developed a line of research in the study of drug nanocarriers and the molecular interactions that determine their functionality in biological systems. Dr. Guzmán is currently the Regional Director for the Chilean Pharmacology Society (SOFARCHI) and an active member of the Chilean Biochemistry Society and its scientific productivity includes the publication of 33 scientific articles, six of them as author of correspondence or first author, 2 patents and numerous conferences and posters in national and international symposiums. He has guided the thesis of 10 undergraduate students, mainly in Biochemistry and Bioengineering, 4 master students in Physiology and Biochemistry, and 3 PhD students in Cellular and Molecular Biology.

Dr. Norberto A. Guzman is currently Chief Scientific Officer at Princeton Biochemicals Inc., Princeton, New Jersey, U.S.A. Dr. Guzman's expertise is primarily in biomedicine and biotechnology with emphasis in protein biochemistry and immunochemistry. At present, his main research interest is in the understanding of the function of newly-formed and/or post-translational-modified proteins in inflammatory processes, and the finding of therapeutic agents, such as natural and synthetic proteins/peptides, aimed to alleviate chronic inflammatory diseases. For several years, Dr. Guzman has developed immunoaffinity-analytical separation instrumentation and methodologies for the quantification, identification and characterization of proteins and peptides of relevance to the clinical laboratory, pharmaceutical industry and foodnutraceutical industry (e.g., erythropoietin, antibodies, and collagen). He also has used multiple crosslinking methods to generate scaffold of collagen with other natural or synthetic polymers to generate collagen-based biomaterials for use in tissue engineering applications or microencapsulation technology. Dr. Guzman received a B.Sc. degree in biochemistry (clinical biochemistry) from a Joint Undergraduate Program of the University of Concepcion and the University of Chile, Santiago, Chile; a M.Sc. degree in biochemistry (cell and molecular biology) from the Medical College of Georgia, Augusta, Georgia, U.S.A.; and a Ph.D. degree in biochemistry (protein biochemistry) from a Joint Graduate Program of the University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School (formerly Rutgers Medical School) and Rutgers, The State University of New Jersey, New Brunswick, New Jersey, U.S.A. Dr. Guzman has worked for the last 30 years in academic medical institutions, diagnostic and pharmaceutical companies, including Mount Sinai School of Medicine, Roche Diagnostic Systems, Hoffman-La Roche, and Johnson & Johnson. He also has worked in a collagen food-nutraceutical industry. Dr. Guzman is the author or co-author of more than 130 scientific publications, including manuscripts, patents and book chapters. He has delivered over 300 oral presentations in Europe, the Americas, the Far East, and Australia. According to Google Scholar Citations, Dr. Guzman's publications have been cited more than 5600 times, having an h-index of 38, and an i10 index of 69. One publication alone has has more than 1400 citations. Nine figures of his publications have appeared on the front cover of prestigious scientific journals and books. One presentation at Google Headquarters in New York City has been viewed more than 2100 times (https://www.youtube.com/watch?v=1QnTrcYWk-o). He is the editor of 2 two widely referenced books on the subject of capillary electrophoresis and collagen prolyl hydroxylase. Dr. Guzman holds numerous worldwide patents on capillary electrophoresis and microchip technology, and his accomplishments have been recognized by being the recipient of many national and international awards in science and technology innovation. Dr. Guzman is a member of several international scientific organizations. He serves on the editorial board of Electrophoresis (European journal), and the Journal of Liquid Chromatography and Related Technologies (American journal). Dr. Guzman is the founding editor of the Journal of Capillary Electrophoresis and Microchip Technology and one of the pioneers in this field. He is also the founder of the international symposia series known as LACE (Latin-American Capillary Electrophoresis).

Dr. Juan Carlos Slebe was born and educated - primary and secondary school - in Santiago, Chile. He went on to University of Concepción and after studying five years ("Licenciatura") he returned to Santiago to Dr. Hermann Niemeyer's laboratory because he had become interested in the regulatory properties of enzymes and their roles in metabolic pathways. His undergraduate thesis was on Glucose-phosphorylating Isoenzymes in the liver of avian, reptiles and amphibian and was directed by Dr. Tito Ureta. He obtained the Biochemist title at the University of Chile and has an academic career that spans nearly 46 years, from his first paper, a comparative study on liver hexokinases of vertebrates, until his last, in which is demonstrated that polyglucosan molecules induce mitochondrial impairment and

apoptosis in germ cells without affecting the integrity and functionality of Sertoli cells. He started his academic carrier at the Department of Biochemistry, Faculty of Medicine, University of Chile (1970) and after eight years he moved to the Institute of Biochemistry, Faculty of Sciences, at the Austral University of Chile (Associated Professor) where he has been until now (Distinguished Professor). In 1974, Professor Marino Martinez-Carrión invited him to spend three years at University of Notre Dame, Indiana, USA and during his time there - as Staff Faculty Fellow - acquired an interest in the mitochondrial and cytosolic aspartate transaminase isozymes, the subject of his research in this period, with a series of papers on the application of 19F-NMR to its kinetic and thermodynamics followed by a paper on the stereochemistry of the transamination. In 1978 his attention turned to Fructose 1,6-bisphosphatase (FBPase) isozymes, using this key gluconeogenic protein as a model for studies on structure-function relationships in a regulatory enzyme, and rapidly his laboratory became one of the leaders in the study of the mechanisms of regulation of FBPase which is considered a new target for the control of diabetes. At the same time he obtained his Doctoral Degree at the University of Chile (1985). His research group has made significant contributions in the understanding of mechanisms involving FBPase in the regulation of the metabolism of glucose not only during normal healthy processes but also during abnormal states which lead to the high glucose levels observed in type 2 diabetes and the L-lactic acid acidosis observed in autism. He has been involved in several PhD programs and mentored the thesis of many undergraduate and graduate students that now are doing research in academic and/or applied fields at national and international prestigious institutions. Despite a heavy teaching load and a large output of research papers, he found time to be involved with administration at University Austral of Chile, becoming: Director of School of Sciences (1980 – 1987), Director of Research (1988 – 1990), President of the Central Commission for Doctoral Studies (1992-1994), Chairman of the Biochemistry Institute (1994-2006), Member of the Central Commission for Academic Evaluation (1995-2001), Member of the Directive Board – “Junta Directiva” - (1999- 2002) and Academic Member of the Board – “Directorio” – (2009 – 2017). He was President of the Biochemistry and Molecular Biology Society of Chile (1999 – 2000) and also was member of: the Study Section Biology 3 – FONDECYT – (1997-2000), Technical Committee of Biochemistry (Comisión Nacional de Acreditación de Pregrado; Ministerio de Educación (2000- 2003)) and the Committee Biology 2 (Comisión Nacional de Acreditación de Postgrados; CONICYT-Ministerio de Educación (2000- 2005).

Symposium 6, Understanding the epitranscriptome.

Chairs: Dr. Alvaro Glavic, Universidad de Chile, Chile and Dr. Ricardo Soto-Rifo, Universidad de Chile, Chile

Dr. Stacy Horner received her BA in Biochemistry and Chemistry from Gustavus Adolphus College in St. Peter, MN in 2001. As an undergraduate, she had research experiences with Dr. J. Ellis Bell at Gustavus and Dr. Thomas R. Broker at the University of Alabama, Birmingham. She entered graduate school at Yale University in the Microbiology graduate program where she worked with Dr. Daniel DiMaio. Her graduate research focused on human papillomavirus (HPV) regulation of cellular growth control pathways and also on designing strategies to eliminate HPV DNA from cervical cancer cells. She received her Ph.D. in Microbiology from Yale in 2007.

Building on her interest of virus/host interactions, Dr. Horner joined the laboratory of Dr. Michael Gale Jr. at the University of Washington for her postdoctoral training in 2007. Her postdoctoral research focused on understanding innate immune regulation by hepatitis C virus (HCV), a global human pathogen. During this time, she identified the mitochondrial-associated ER membrane (MAM; a subdomain of the ER located adjacent to mitochondria) as a membrane platform that organizes innate immune signaling and also as the intracellular site of immune regulation by HCV. Dr. Horner's postdoctoral research was supported by the Irvington Institute Fellowship Program of the Cancer Research Institute.

Dr. Horner joined the faculty of the Molecular Genetics & Microbiology and Medicine departments at Duke University Medical Center in 2013. Her laboratory is interested in understanding the cell biology of antiviral innate immunity and how RNA viruses, including hepatitis C virus, evade innate immunity. Overall, her research uses a interdisciplinary approach, combining techniques from cell biology, virology, biochemistry, and systems biology to reveal the viral and host strategies that coordinate and regulate innate immunity, with the ultimate goal of developing new immunomodulatory strategies for virus treatment and prevention.

Dr. Ricardo Soto-Rifo has been always interested in the molecular and cellular mechanisms controlling gene expression in Eukaryotes with a special emphasis in RNA viruses as study models. Biochemist from Universidad de Santiago de Chile, Dr. Soto-Rifo did his undergraduate thesis at the Animal Virology Laboratory (currently the Centre of Acuiculture Biotechnology) under the supervision of Dr. Ana María Sandino studying the mechanisms of translation initiation employed by the Infectious Pancreatic Necrosis Virus (IPNV). Then, he moved to Lyon, France where he obtained a Master in Sciences degree from Université Claude Bernard Lyon-1 in 2006 and then a Ph.D in Life Sciences from Ecole Normale Supérieure de Lyon (Université de Lyon) in 2010. He worked at the Human Virology Department (currently the International Center for Infectiology Research) under the supervision of Dr. Théophile Ohlmann on the translational control of the HIV-1 and HIV-2 genomic RNA. During his post-doctoral training at Dr. Ohlmann`s lab, Dr. Soto-Rifo worked on the remodeling and localization of the messenger ribonucleoprotein complexes (mRNPs) containing the HIV-1 genomic RNA by analyzing the role of the DEAD-box RNA helicase DDX3 in these processes. In 2013, he moved to the Virology Program, Biomedical Sciences Institute at Universidad de Chile Faculty of Medicine to start his own laboratory. Since, Dr. Soto-Rifo has established his research group, which is mainly focused in understand the mechanisms governing HIV and Respiratory Syncytial Virus (RSV) gene expression.

Dr. Alvaro Glavic is a Biochemist and PhD in Molecular, Cellular Biology and Neuroscience (University of Chile), with 20 years experience in developmental biology and genetics using Xenopus, Zebrafish and *Drosophila*. Alvaro did his undergraduate thesis in Biochemist in 1997 with Dr. Roberto Mayor at University of Chile studying the role of Iroquois genes in the formation of *Xenopus* nervous system. This work was published in EMBO J and awarded by the Chilean Society for Cellular Biology as the best undergraduate or master thesis in 1998. He obtained a CONICYT and the Fundación Andes scholarships to course his PhD in Molecular, Cellular Biology and Neuroscience. In 1998 he received

the Hermann Niemeyer Medal to the best PhD student awarded by the Chilean Society of Biochemistry and Molecular Biology. In 2000 he was visiting investigator at Sir John Gurdon´s lab at the Wellcome Trust Institute, UK. In 2002 he finished his doctoral thesis where he further explored the role of Iroquois complex in vertebrate development. In 2002 he obtained an EMBO long-term fellow to be trained in *Drosophila* genetics with Antonio Garcia-Bellido at Centro de Biología Molecular Severo Ochoa in Spain. After this period, he got a FONDECYT grant to finance a second postdoc and in 2005 he joined Faculty of Sciences (U de Chile) as Assistant Professor. His work was recognized in 2007 by the Academia de Ciencias de Chile and was invited to be part of the program "Cientificos de Frontera". His curiosity and line of research on tRNA modification and its role in multicellular organisms has attracted several talented students, which have received twice the Federico Leighton award for the best undergraduate and graduate theses in 2013 and 2015. Since 2014 Alvaro is Associate Professor at Faculty of Sciences and from 2016 he is director of a ANILLO grant to investigate the transcriptional, epigenetic, morphological and behavioral effects of developmental undernourishment in *Drosophila*.

Dr. Blerta Xhemalce received her Ph.D. at the Pasteur Institute in Paris, France and performed her postdoctoral training at the Gurdon Institute at the University of Cambridge in the United Kingdom. The focus of her research is to unravel how gene expression is regulated by epigenetic modifications of chromatin and RNAs. The ultimate goal of her lab is to discover novel enzymes, writers, or erasers of such modifications that are potential targets for therapeutic drugs that could alleviate human diseases including cancer. To achieve this goal the Xhemalce lab uses a diverse array of approaches, including cellular and molecular biology, biochemistry, and mass spectrometry. The Xhemalce lab is also committed to supporting its members to achieve their academic goals and to think outside the box.

Symposium 7, Symposium Cono-Sur: The role of the microbiome from multiple perspectives.

Chair: Juan A. Ugalde, uBiome.

Dr. Juan Ugalde is a computational microbiologist, specializing in the use of omics approaches to study microbial diversity in different ecosystems. Currently, he is Director of Bioinformatics in the microbiome company uBiome. He obtained his PhD in 2014, from the Scripps Institution of Oceanography, at the University of California, San Diego, studying the diversity of hypersaline microbial communities using metagenomics approaches. He returned to Chile in 2014, as an Assistant Professor at the Center for Genomics and Bioinformatics, Universidad Mayor. Juan's research uses genomics, bioinformatics, and data sciences approaches to understand the diversity, evolution, and adaption of microorganism to their environments. Among his work, he has worked in comparative genomic analysis of different microbial groups, including producers of natural products such as *Salinispora*, Chilean strains of *Staphylococcus aureus*, among other groups. The last few years he has been active in the field of microbiome studies, taking part in collaborations to understand how the urban microbiome, as well as taking part in several studies of the human microbiome.

Dr. Cristina Dorador is a microbial ecologist, who specializes in the microbial ecology of extremophiles and extreme environments. Currently she is an Associate Professor at the Universidad de Antofagasta, Chile. Cristina did her doctoral research in the Max Planck Institute for Limnology in Plön, Germany and was awarded her PhD in Microbiology from the University of Kiel, Germany (2007). She returned to Chile in 2008 and established the Laboratory of Microbial Complexity and Functional Ecology at the Universidad de Antofagasta. Cristina's research is based on the study of the diversity and function of microorganisms in natural environments, with a special focus in the adaptation of microorganisms to extreme conditions of Bacteria and Archaea in aquatic and terrestrial environments of north and southern Chile. Applied research in Cristina's group is based in the searching of bioactive compounds with antimicrobial and anticancer properties and skin protection (Atacama Cream) from bacteria from the Atacama Desert. Cristina is a Frontier Researcher of the Chilean Academy of Sciences, Young ISME Ambassador for Chile and represented Chile as young scientist in the book: "Young Scientists: a bright future for the Americas" published by IANAS (Interamerican Network of Academies of Sciences). She is the principal investigator on a series of national (Fondecyt; Fondef; PIA-CONICYT) and international (European Union) grants, and participates in national grant assessment panels (Fondecyt, INACH). Cristina is also a scientific assessor for scientific academies and for PAR Explora Antofagasta- CONICYT.

Dr. Gregorio Iraola is a computational microbiologist. His posgraduation studies started with a Master in Bioinformatics before obtaining a PhD in Biology focused on microbial genomics at the University of the Republic and the Institut Pasteur Montevideo in Uruguay. Since 2017 he is a staff Associate Researcher at the Bioinformatics Unit in the Institut Pasteur Montevideo. Also, since 2015 he has been a visitor scientist at the Wellcome Trust Sanger Institute and the Institut Pasteur Paris. From Uruguay, he leads several research lines aiming to develop and apply computational approaches for studying the microbial world. His work has been focused on understanding the evolution of viruses that affect livestock and pets using phylodynamics; and fundamentally on uncovering the evolutionary forces shaping the genomes of zoonotic bacteria like *Campylobacter*, *Leptospira* and *Mycobacterium*. Among his ongoing projects stands out a joint Latin American effort to study the population dynamics of *Clostridium difficile* using genomic epidemiology approaches. Recently, he became interested in complementing his work in pathogenomics with microbiome approaches, specifically by applying city-scale metagenomics to analyse antibiotic resistance dynamics in enterobacteria from urban environments. More recently, he got involved in science communication as a columnist aiming to bring microbiology and genomics closer to the society.

Dr. Valeria Márquez Miranda is currently team leader of the Drug Development group in the microbiome start-up company uBiome. She received her PhD in Biotechnology from Universidad Andrés Bello, for her work on the design and experimental testing of new nucleic-acid transfection systems based on dendrimers. This work was supported

by Fraunhofer Chile Research and a grant for PhD thesis in the Industry (PAI-CONICYT). After that, she worked as a postdoctoral fellow in a project from Universidad Andres Bello along with the US Air Force, entitled "*Neuromorphic Inspired Science to Maximize Big Data Dynamic Problem Solving for Future Intelligence, Surveillance, and Reconnaissance Operations"*. Currently, her work focuses on microbiota-mediated metabolism of drugs, dietary compounds and xenobiotics, aided by machine learning and cheminformatics. Other areas of interest are computational biophysics, molecular dynamics simulations, drug design, computer-assisted design of nanoparticles, and also cell biology and physicochemical characterization.

Dr. Eva Figuerola is a molecular microbiologist devoted to the study of environmental microorganisms. She earned her Ph.D. in Biological Chemistry in the University of Buenos Aires. Since her postdoc at INGEBI, she began working with soil microbial communities employing high throughput sequencing and bioinformatic analysis. She is currently Adjunct Researcher (II/V) of the National Research Council (CONICET). Her previous work leads to the discovery of some indicator species which can be monitored to track the management history of soils dedicated to agricultural production. Her studies on edaphic microbiome allowed determining that soy monoculture resulted in the homogenization of microbial communities among sites with different soil characteristics. This homogenization was attributed to the loss of endemic species and the simultaneous increase in the number of habitat generalists. Dr. Figuerola is also interested in harnessing environmental bacteria for biotechnology purposes, in this regard, she has a number of publications about microbial communities involved in wastewater treatment. More recently, her research group has begun to explore synthetic communities in order to gain understanding of microbial ecology with the aim to provide biotechnological applications.

Osvaldo Cori lecture

Multiples approaches to investigate the structure and function of a phycobilisome.

Bunster Marta [1]. [1]Depto. Bioquímica y Biología Molecular, Facultad de Ciencias Biológicas, Universidad de Concepción

The structure of a Phycobilisome is associated to its function of light harvesting and energy transfer(ET) towards the photoreaction center. Phycobilisome is a macro complex of phycobiliproteins and linker proteins. Each phycobilisome is formed by a CORE of Allophycocyanin from which radiate RODS formed by Phycocyanin and Phycoerythrin. A common feature of all phycobiliproteins is that they are formed by (aβ) heterodimers that oligomerize to trimers or hexamers originating ring structures that are piled up as in an antenna. Each phycobiliprotein contains chromophores bound to specific cysteine residues. The efficiency of the ET process is >95%, so the investigative question was: how these components are organized to justify this high efficiency?

This work describes the results obtained using experimental approaches such as molecular biology and biochemistry techniques, biophysical approaches such as X-ray crystallography, spectroscopy, electron microscopy and cryo-microscopy , as well as molecular simulations *in silico*. Electron microscopy provided evidences for a three cylinders core of Allophycocyanin, 5 to 6 rods of Phycoerythrin and Phycocyanin in the PBS. The three dimensional structures of all the phycobiliproteins were determined by X ray diffraction, and their association to form rods and the core was approached by *in silico* and *in vitro* studies. Variation of subunits and the presence of linkers were also approached by transcriptomics, biochemical techniques, spectroscopy, mass spectrometry associated to crosslinking to map interactions.

All this information will be presented in a model for the structure and function of the phycobilisome of *Gracilaria chilensis*.

Universidad de Concepción, VRID_ENLACE 216.037.021-7, FONDECYT 113. 0256

At present she is full professor at the Biochemistry and Molecular Biology Department in the Faculty of Biological Sciences of the Universidad de Concepción. Obtained the Biochemistry diploma on April 1974 from the Universidad de Concepción/Universidad de Chile and a Doctor of Sciences degree at the Universidad de Concepción in 1981. She has been Director and co-founder of the Magister in Biochemistry and Bioinformatics, Director of the Department of Biochemistry and Molecular Biology, and has been part of the Doctor of Biological Sciences since its creation. She has guided numerous undergraduate and graduate thesis. She has been member of the Sociedad Chilena de Química, Sociedad de Biología de Chile, Sociedad de Bioquímica y Biología Molecular de Chile, Biophysical Society, Member, Secretary and founder of the Iberoamerican Society of Bioinformatics. SOIBIO, Member of International Society of Computational Biology and Bioinformatics and Member of Latinoamerican Society of Crystallography of recent creation. After obtaining the Biochemistry degree, and a brief stay at the University of Chile, she obtained an academic position at the Biophysics section of the Department of Physiology of the Instituto de Ciencias Médico Biológicas, today the Faculty of Biological Sciences, to teach biophysics to biochemists and biology teachers. Simultaneously she enrolled at the nascent Doctor of Sciences Program of the University of Concepción with a DAAD scholarship working in controlled release anticancer and anti-depression drugs using biodegradable polymer matrices at the Polymer Labs at University of Concepción (Dr. Eckhart Schmidt and Juan Bartulín 1976-1977) and University of Florida with the financial support from OEA (Dr. George B. Butler, 1978-1980). Full returned to the University in 1981, and in a partnership/ friendship with Hilda Cid, she was deeply involved in the area of molecular biophysics specially the investigation of the three dimensional structure of proteins from the theoretical point of view and the beginning of the now called, bioinformatics. At this moment a method to predict the secondary structure of proteins was developed, and continue

adding new evidences from that time and until now. More than 10 international courses were given in order to increase the critical mass of investigators in structure and function of proteins and specially Protein crystallography, coordinating biology, physics, mathematics and chemistry. From 1995 the biophysics methodologies were applied to the study of an efficient light harvesting system, the phycobilisome. In 2001, the first 3D structure of R-phycoerythrin determined by a chilean group was published. During those years, also, with a group of young and experienced researchers formed the Iberoamerican network of Bioinformatics that then would become the Iberoamerican Society of Bioinformatics. The purpose of this society was and is to provide bioinformatic education and resources for the members of the society. From 2005 and on, she had the opportunity to work with an absolutely fantastic group of students at different levels that share a dream to mime the photosynthetic apparatus of algae to develop an energy harvesting system capable to provide clean energy at low cost. Following this purpose, “basic science” has been developed which has been published in many scientific journals.

Pre-course: Affinity measurements by capillary electrophoresis and force spectroscopy techniques

Norberto A. Guzman[1] and Christian A.M. Wilson[2],[1]Princeton Biochemicals, Inc., Princeton, New Jersey, U.S.A.,[2]Faculty of Chemical and Pharmaceutical Sciences, University of Chile, Santiago, Chile

The Meaning of "Affinity" in Chemistry and Biology.

In chemistry, affinity is defined as an attractive force between substances or particles that causes them to enter into and remain in combination. The most interesting part of this definition is the notion of a force, or attraction, between elements.

Conversely, from a standpoint of view of biology affinity is a relation between biological groups involving resemblance in structural plan and indicating a common origin. This definition relates to the understanding of the binding of substances to other substances or to receptors in physiological and pathological processes.

As biologists, we are aware of specific biological interactions in practically every field of study. Specific biological reactions occur in some of the most important life processes, such as the interactions of enzymes with their corresponding substrates and inhibitors, of hormones with their corresponding receptors, of antibodies with antigens, cell-cell interactions, and many other significant chemical and biological interactions.

Affinity Capillary Electrophoresis.

Norberto A. Guzman

The term "affinity capillary electrophoresis" is a broad concept used to define the separation of substances that participate in specific or nonspecific affinity interactions during capillary electrophoresis. The interacting molecules may be present in solution (free-solution IACE) or immobilized on a solid support or surface (immobilized IACE). Free-solution IACE is primarily referred to the study of molecular affinity interactions in solution and measurements of binding constants.

Capillary Electrophoresis (CE) and Immunoaffinity Capillary Electrophoresis (IACE) are miniaturized analytical techniques used primarily for the identification and characterization of a wide range of small molecules, biopolymers, biological particles, and for the determination of affinity interactions. Capillary electrophoresis is defined as a family of electrokinetic separation techniques performed in submillimiter diameter capillaries (conventional capillary electrophoresis) and micro- and nanofluidic channels (microchip capillary electrophoresis). Applications of CE have been used in many fields, primarily in pharmaceuticals, diagnostics, forensics, environmental, food-beverage industries, and other areas. There are many advantages of CE when compared with traditional analytical separation technologies, including higher number of theoretical plates in liquid-phase separations, a high peak capacity, faster analysis time, a variety of background electrolytes, a choice of separation modes, the use of low volumes of samples and reagents, a reduction in the generation of toxic organic waste, and relatively lower operating cost. However, a major disadvantage of the CE technology is the low concentration limits of detection (CLOD). The main reasons for this problem are the limited sample-volume capacity of the capillary and the short optical pathlength of the capillary, which limit the sensitivity of the detector. In attempts to overcome the poor CLOD, investigators have developed a number of methods to improve sensitivity levels of detections of analytes. In this presentation, I will describe applications referring to the on-line preconcentration or sample enrichment of one or more analytes of interest by

using an analyte concentrator-microreactor (ACM) device. The inner channel of the ACM device is a uniform confined space containing a matrix with immobilized affinity ligands. The highly selective affinity ligands can be antibodies, antibody fragments, aptamers, lectins, enzymes, receptors, phages, synthetic materials, and others. The coupling of IACE to a variety of detectors, including laser-induced fluorescence detector, mass spectrometry, and circular dichroism spectroscopy permit the enhancement of sensitivity and characterization of the analytes of interest. I will also present examples of free-solution IACE for the determination of affinity constants.

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Affinity Measurements Using Force Spectroscopy Techniques

Christian A.M. Wilson

Mechanical forces are generated inside the cell during such diverse molecular processes as transcription, replication, translation, protein unfolding, translocation of proteins across membranes, etc. Recent technological advances now allow the application and measurement of forces on biomolecules with extreme precision. In particular, the so-called “analytical optical and magnetic tweezers” instruments can manipulate single molecules, such as proteins and nucleic acids, while measuring their internal stress forces generated in the course of biological processes (Bustamante et al., 2015). The effect of force on protein structure and associated changes of protein function is a subject of current intensive research. Optical tweezers are a useful research tool for applying forces to single proteins and measuring the affinity between substrates (Ramirez et al., 2017). Some single molecule techniques that exert force on the protein are not able to measure small changes in distance at subnanometer resolution at low forces (below 1 to 5 pN), so it is difficult to correlate the elastic properties of the folded protein with ligand binding sometimes. Recently, a new technique called nanorheology allows measurement of elasticity in folded proteins. Nanorheology is a technique that exploits sub-Angstrom resolution to study the mechanical properties of the folded state of proteins by applying low force with 20 nanometer gold nanoparticles to the proteins in bulk. This viscoelastic transition is a universal mechanical property of the folded state, and it is relevant for the large conformational changes, which often accompany substrate binding in proteins (Casanova-Morales et al., 2018). FONDECYT-1181361, PCIPII20150073.

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PABMB lecture

Functions and Mechanisms of Flavivirus RNA Structures

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The Flavivirus genus include a large number of emerging and re-emerging human pathogens that cycle between mosquitos and humans including dengue, Zika and yellow fever. These viruses contain a single stranded RNA genome with a great deal of information in RNA structures that function as signals to enhance, suppress or promote viral replication. Natural sequence variability in these RNA structures are determinants for viral epidemiological fitness, pathogenesis, host adaptation and transmission between mosquitos and humans. An intriguing feature of the 3' untranslated region (UTR) of flavivirus genomes is the evolutionary conservation of sequence repeats and duplicated RNA structures. In the case of dengue, the 3'UTR contains two almost identical stem loop structures (SLI and SLII) and two similar dumbbell elements (DB1 and DB2). We have previously defined that the SLs facilitate host switching between mosquito and human cells. More recently, we found that the DB elements play opposite functions during infection and are under different selective pressures in the two hosts. Mechanistic analysis indicate that the DB elements modulate viral genome conformation and RNA replication. Our results support a model in which a functional diversification of duplicated RNA elements in the viral 3'UTR is driven by host specific requirements. This study provides new ideas for understanding molecular aspects of evolution of RNA viruses that jump between different species.

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Dr. Andrea Gamarnik is a molecular virologist. She earned her PhD degree in Biochemistry, in the University of Buenos Aires. After a postdoctoral training at UCSF, she returned to Argentina in 2002 where she stablished the first laboratory of Molecular Virology at the Institute Leloir, Buenos Aires. Since then, her laboratory became a reference in dengue virus basic biology and made seminal contributions for understanding flavivirus RNA replication. She is currently a Principal Investigator of the National Research Council (CONICET) and the Director of the Instituto de Investigaciones Bioquímicas de Buenos Aires-CONICET at the Institute Leloir. Her work focuses on understanding the function of viral RNA structures and defining how thee structures modulate viral processes. In this regard, her group identify the promoter for dengue virus RNA replication and uncovered the mechanism of viral RNA synthesis, which was then extrapolated to an extensive group of viruses. In addition, her studies on functional viral RNA structures provided a framework to analyze viral RNA genomes as dynamic molecules. More recently, she became interested in studying adaptation of viral RNAs in mosquito and humans, and proposed new models of viral RNA specialization in different hosts. The achievements of Dr. Gamarnik in virology have been widely recognized internationally. She was HHMI International Research Scholar in the Infectious Disease Program (2005-2011), became a member of the American Academy of Microbiology in 2014 and was recipient of numerous awards such as the L'Oreal-UNESCO 2016 "For Women in Science" in representation of Latin America.

Severo Ochoa lecture

Precision Medicine and K-RAS mutant tumors: Deconstructing K-Ras signalling in lung and pancreatic cancer

Barbacid Mariano [1]. [1]Molecular Oncology Program, Centro Nacional de Investigaciones Oncológicas (CNIO), Madrid, Spain.

KRAS oncogenes are responsible for the development of at least one fourth of all human tumors including lung and pancreatic adenocarcinomas, two tumors types with some of the worse prognosis. Unfortunately, development of suitable therapies to treat these tumors has remained elusive for the last thirty years and patients are still treated with old chemotherapy drugs. To address this important health issue, we decided to use genetically engineered **mouse tumor models that closely recapitulate the natural history of these tumor types in order to deconstruct, by genetic means, oncogenic** K-Ras signaling with the ultimate goal to identify molecular targets whose inhibition will result in therapeutic activity against advanced lung and pancreatic tumors. First, we have designed a new generation of mouse tumor models in which we can separate, both temporally and spatially, tumor induction from target inhibition. These new mouse tumor models make use of the yeast frt-FLp(o) recombinase system to induce cancer-driving mutations by inducing genomic recombination within their endogenous KRas and Trp53 cancer genes in either lung neumocytes or in their pancreatic acinar cells. In addition, these mice carry a transgene that encodes the bacterial CreERT2 inducible recombinase driven by the human Ubiquitin promoter which allows its expression in most, if not all, adult cells and tissues. Finally, these strains are used to introduce conditional knock-out or knock-in alleles of those molecular targets whose therapeutic potential we want to validate. Exposure of mice already bearing advanced tumors (as determined by imaging techniques) to a tamoxifen-containing diet results in the activation of inducible CreERT2 recombinase which allows us to systemically ablate expression of the target (knock-out alleles) or express an inactive isoform (knock-in alleles). This strategy makes it possible not only to evaluate the therapeutic consequences of ablating/inactivating selected targets, but equally important to determine the potentially toxic effects derived from its systemic elimination or inactivation.

We have used this sophisticated experimental strategy to interrogate the therapeutic as well as potentially toxic consequences of ablating or inactivating each of the members of the MAPKinase cascade, including the Raf, Mek and Erk kinases, as well as key effectors of the PI3Kca. pathway including the PI3K p110alpha and mTOR. We have also evaluated additional upstream and downstream signaling elements, such as the EGF Receptor and the Cyclin-dependent kinases (Cdks) responsible for driving the cell cycle. This systematic approach has revealed that most of the K-Ras signaling effectors are not suitable therapeutic targets due to either lack of therapeutic activity, such as Cdk2, Cdk6 A-Raf or B-Raf, or to the induction of unacceptable toxicities such as the Mek1/2 and Erk1/2 kinases, PI3k p110alpha and Cdk1. Therefore, only c-Raf, EGFR and Cdk4 turned to be suitable therapeutic targets, based not only on their anti-tumor properties, but also on the well tolerated toxicities observed upon their systemic ablation/inactivation. We are now combining these targets to define more efficacious therapeutic strategies that could be eventually translated to the clinic.

Mariano Barbacid (Madrid, Spain 1949) studied biochemistry at the *Universidad Complutense* (1966-71) and got his Ph.D. degree from the same university in 1974. From 1974-1978 he trained as a postdoctoral fellow at the National Cancer Institute (NIH) in Bethesda, Maryland working on the molecular biology of murine retroviruses. In 1978 he started his own research group to try to unveil the molecular events responsible for the development of human tumours. His work led in the spring of 1982, to the isolation of the first human oncogene and the first mutation associated with the development of human cancer. These findings, also made independently by two other groups, have been seminal to establish the molecular bases of human cancer. During the following decade (1988-1998), he joined Bristol-Myers Squibb where he became Vice President of Oncology Drug Discovery. There he started the concept

of what is now known as Precision Medicine by developing inhibitors against FTase and cell cycle Cdks, among other molecular targtes. In 1998, he returned to Spain to build and direct the Spanish National Cancer Research Center (*Centro Nacional de Investigaciones Oncológicas,* CNIO). Under his leadership, the CNIO was ranked within the top 15 leading research centres among more than 3,000 research institutions worldwide by the Scimago Institutions Ranking. In 2011, he stepped down as director to concentrate on his own research on the identification and functional validation of therapeutic strategies to treat K-Ras/TP53 driven lung and pancreatic tumors.

In 2012, he was inducted to the US National Academy of Sciences as a Foreign Member and in 2014, he was elected Fellow of the American Association for Cancer Research. He holds three Honorary Degrees from the International University Menendez y Pelayo (1995), University of Cantabria (2011) and University of Barcelona (2014). His work has also been recognized by several international and domestic awards including the Steiner Prize (Bern, 1988), Ipsen Prize (Vienna, 1994), Brupbaher Cancer Research Prize (Zurich, 2005), the Medal of Honour of the International Agency for Cancer Research (Lyon, 2007) and the Burkitt Medal (Dublin, 2017). In 2011 he was awarded an Endowed Chair from the AXA Research Fund (Paris). He is one of the few European scientists to receive two Advanced Grants from the European Research Council (2009 and 2015). To date, Dr. Barbacid has authored 303 publications, including 225 original research articles in journals with impact factor. Currently, Dr. Barbacid's Hirsch "h" factor is 112 (Google Scholar) or 106 (Web of Science).

Tito Ureta Prize

Dr. Pablo Valenzuela earned a Biochemistry degree from Universidad de Chile (1965) and a Ph.D. degree in Chemistry at Northwestern University (1970). He did postdoctoral training at University of California, San Francisco and held a position as Professor in the Biochemistry Department of that institution. Despite his interest in developing biotechnology products, Valenzuela has been a champion for basic, curiosity driven research. He has published more than 140 papers, directed more than 20 Ph.D. theses and named as inventor in more than 60 patents. At different times, he has been professor at Universidad de Chile, Universidad Católica, Universidad Andrés Bello and Universidad San Sebastián where presently he is a member of the Junta Directiva. Pablo Valenzuela is responsible for the development of several biotechnology products in USA and Chile. In USA he developed more than 10 products in the area of blood banking diagnostics including key tests for hepatitis C, AIDS virus and hepatitis B virus; and several pharmaceutical products including the hepatitis B vaccine, human insulin, a plateled grow factor derived wound healing cream (Regranex) and beta interferon, all made in yeast. All together, these products have worldwide sales higher than 5 billions of dollars a year. In Chile, he has developed a commercial vaccine for salmoniculture and several products for human and blood bank diagnostics such as Chagas, Helicobacter, Rotavirus, Blood Groups, etc. These products are today commercialed in Chile and Latin America with sales of approximately 10 million dollars per year. Valenzuela is an active entrepreneur. Internationally, he has been the cofounder of several biotechnology companies including Chiron Corporation, Ventria Biosciences, Applied Imaging, Phytotox, Austral Biologicals and Praxis Biotech. In Chile, he has been involved in the founding of GrupoBios (with Arturo Yudelevich and José Codner), Andes Biotechnologies (with Luis Burzio and Arturo Yudelevich) and Fundación Ciencia & Vida (with Mario Rosemblatt and Bernardita Méndez). Through the creation of the Science & Business Park, which harbors 15 national and foreign start-ups. He serves as a board member/advisor of several start-ups such as Algenis, Phage Technologies, NovaMineralis, Merken Biotech, Ango Sciences and Ingalfarma. Among his awards are the Chilean National Award in Applied Sciences & Technology (2002), the University of Chile Rectoral Medal Award (2002), Membership of the Chilean Academy of Sciences (2004), the Orden de la Cruz del Sur Medal from the Chilean Government (2012), the California BayBio Life Time Sciences Achievements Awards (2012), the University of California Medal (2014) and the 2017 Entrepreneur of the Year from the Chilean Association of Venture Funds.

Symposia 1

Protein crystallography: from structure, function and beyond

Chairs: Víctor Castro-Fernandez and Victoria Guixé, Universidad de Chile, Chile

Biochemistry of Hearing

Sotomayor Marcos [1]. [1]Chemistry and Biochemistry, The Ohio State University

Cadherins form a large superfamily of proteins essential for morphogenesis, neuronal connectivity, and tissue integrity. Two atypical members of this superfamily, cadherin-23 and protocadherin-15, are also involved in hereditary deafness and blindness. In the inner ear, these two proteins interact to form the tip link, a fine filament that pulls open transduction channels to initiate a cascade of events leading to sensory perception. Here we present structural, computational, and biochemical experiments that reveal unique properties of the tip-link extracellular cadherin (EC) repeats. Our crystal structures, simulations, and binding assays show how the tip of protocadherin-15 and some of its variants interact with the cadherin-23 tip to form a calcium-dependent heterotetrameric bond of tunable strength. In addition, structures and simulations of the entire protocadherin-15 extracellular domain show how non-canonical inter-repeat linker regions and a membrane adjacent domain may alter tip links´ tertiary structure, parallel dimerization, and elasticity. Overall, our results provide a molecular view of tip-link mechanics in vitro and in silico, and identify the structural determinants of tip-link function in vertebrate hearing.

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Insight in the association between gamma subunit and R-phycoerythrin

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Phycobilisomes (PBS) are accessory light harvesting protein complexes formed mainly by phycobiliproteins (PBPs). The PBPs absorb light due to chromophores covanlently bound to specific cystein residues, which is being efficiently transferred to photoreaction centers. Besides phycobiliproteins, the PBS contains linker proteins responsible for assembly and stabilization of the whole complex and the tuning of energy transfer steps between chromophores. The linker gamma 33 ($\gamma^{33)}$ from *Gracilaria chilensis*, is a chromophorylated rod linker associated to $(\alpha\beta)_6$ hexamers of R-phycoerythrin.

Chemical cross-linking coupled to mass spectrometry, X-ray diffraction data together electron cryo-tomography (Cryo-ET) of R-phycoerythrin complex were integrated to build a 3D interaction model of R-phycoerytrin with gamma linker. Based on the integration of the experimental approaches, the γ33 subunit structure has 11 α helices, six of which are forming part of the binding pockets for the phycoerythrobilin at position 82 of the β subunits. The γ33 subunit interacts integrally with the R-phycoerythrin α and β subunits, mainly in three specific zones of each trimeric unit. In addition both ends of the protein are inserted into the hexameric cavity. The N-terminus had a long loop and two short helix, that folds back to the cavity with a short helix protruding slightly to outside of cavity and could insert into the neighboring hexamer.

The γ^{33} subunit, in addition to having a structural role in the stabilization of the hexameric complex, has a role as intermediary in the transfer of energy through the phycoerythrin hexamer.

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Structural study of a two-component signal transduction system activated by light in Brucella abortus

Klinke Sebastián [1], Fernández Ignacio[1,2], Sycz Gabriela[1,3], Paz Juan M[1], Otero Lisandro H[1], Rinaldi Jimena[1], Goldbaum Fernando A[1]. [1]Laboratorio de Inmunología y Microbiología Molecular, Fundación Instituto Leloir. [2]Unité de Virologie Structurale, Département de Virologie, Institut Pasteur Paris. [3]Laboratorio de Microbiología Molecular y Celular, Fundación Instituto Leloir

The pathogenic bacterium *Brucella abortus* codes for a cytoplasmic blue light-activated histidine kinase called LOV-HK, which is a key virulence factor that belongs to a two-component signal transduction system involved in the modulation of the general stress response in this microorganism [1], together with two response regulators called PhyR and LovR. With the goal of understanding at the atomic level the activation and signal transduction events of this system, we aimed to solve the three-dimensional structures of these proteins by means of X-ray crystallography. The following structures will be presented: (i) the core of the blue-light sensor FMN-binding LOV domain (at 1.64 Å resolution in the dark) [2], (ii) the LOV core domain plus an N-terminal capping helix at 2.34 Å resolution (N-LOV), (iii) the two-domain N-LOV-PAS structure at 2.74 Å resolution bearing the intermediate PAS domain, (iv) the isolated HK domain at 2.51 Å resolution solved by sulfur SAD in a challenging procedure [3,4], (v) the structure of the PhyR response regulator at 2.05 Å resolution, and (vi) the structure of the complete LOV-HK protein in its activated form at 3.25 Å resolution. All these protein structures, together with spectroscopic, activity and biophysical assays, allowed us for a better understanding of this crucial system for the pathogenicity of *Brucella*.

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Analyzing the structure of the ancestors of the ADP-dependent kinases family

Castro-Fernandez Victor [1], Herrera-Morande Alejandra[1], Gonzalez-Ordenes Felipe[1], Cea Pablo A[1], Vallejos Gabriel[1], Muñoz Sebastian M[1], Fuentes-Ugarte Nicolas[1], Guixé Victoria[1]. [1]Departamento de Biología, Facultad de Ciencias, Universidad de Chile, Santiago, CL.

Existent proteins are the outcome of both continuous mutation and a natural selection process, which is dictated by functional and structural constraints. Hence, to understand the properties and functions of current proteins, it is necessary to know their structures and their evolutionary histories.

Here, will be shown a structural and functional study in the ADP-dependent kinases family, where determinants changes for substrate specificity could be tracked during the evolution of this family; including the crystal structure of a bifunctional ancestor (2.58 Å) and its substrate specific mutant (2.60 Å) will be presented. Moreover, we have analyzed the salt resistance (halophilicity) of these kinases from the group of archaea of the *Methanosarcinales*, and we have found that the halophilic characteristic of some of these kinases comes from the ancestor of the group. The resurrection of the last common ancestor of ADP-PFK/GK from *Methanosarcinales* showed that the ancestral enzyme had an extremely high salt tolerance and thermal stability. Structure determination of the ancestral protein (2.86 Å) revealed unique traits such as an increase in the Lys and Glu content at the protein surface and yet no reduction to the volume of the hydrophobic core like the classic model of halophilic proteins from *Halobacteria*. Our results suggest that the halophilic character is an ancient trait in the evolution of this protein family and that proteins from *Methanosarcinales* have adapted to highly saline environments by a non-canonical strategy, different from that currently proposed for *Halobacteria*.

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Dr. Marcos Sotomayor. Dr. Marcos Sotomayor received his B.Sc. in Physics from Universidad de Chile in 2001 and his Ph.D. in Physics from the University of Illinois at Urbana-Champaign in 2007. As a graduate student with Dr. Klaus Schulten in the theoretical and computational biophysics group he did molecular dynamics simulations of proteins involved in mechanotransduction. His computational studies predicted the conductance of the ion channel MscS structure, as well as the elasticity of ankyrin and cadherin repeats. After finishing his Ph.D., he joined the laboratories of David P. Corey and Rachelle Gaudet to do experimental work as a postdoctoral researcher at Harvard University. There he solved the first X-ray crystal structure of a heterophilic cadherin complex essential for hearing and balance. During his postdoctoral tenure he was a Howard Hughes Medical Institute fellow of the Helen Hay Whitney foundation. Marcos received a prestigious NIH K99/R00 award and started at OSU in July of 2013. In 2015 he received a Distinguished Undergraduate Research Mentor award from the undergraduate research office at OSU and was selected as an Alfred P. Sloan Research Fellow in Neuroscience.

Dr. José Martinez-Oyanedel. Dr. Jose Martinez Oyanedel, structural biophysic has been involved in crystallographic analysis of proteins to establish the structure-function relationship. Has been involved in the development of protein crystallography in Chile, is author of several crystal structure deposited in the Protein Data Bank and publications on protein crystallography. Since 1991 is academic in the Departamento de Bioquimica y Biologia Molecular from Universidad de Concepción. In the last time the research has been direct to build a model of the phycobilisome from Gracilaria chilensis, solving the protein structure that are presents in this macromolecular structure.

Dr. Sebastián Klinke. Dr. Sebastián Klinke holds a PhD degree in Biological Chemistry from the University of Buenos Aires (2007) under the supervision of Prof. Fernando Goldbaum, and is Associate Researcher of the Argentinian Research Council (CONICET) at the Laboratory of Immunology and Molecular Microbiology, Leloir Institute, Buenos Aires. His thesis project focused on the structural study of lumazine synthase in the pathogenic bacterium Brucella abortus, applying X-ray crystallography as well as other biophysical and biochemical techniques. Lumazine synthase

is an enzyme involved in the biosynthesis of riboflavin (vitamin B2), which corresponds to a very promising target for the development of vaccines and antimicrobial compounds against this pathogen. Through his thesis work, the laboratory became a pioneer in Argentina in the application of macromolecular crystallography both in know-how and in instrumentation. In the last years his projects have been focused on the structural study of several Brucella virulence factors related to the biosynthesis and metabolism of riboflavin, which are interesting antibacterial targets, since Brucella is unable to acquire vitamin B2 from the external environment with efficiency and depends exclusively of its endogenous synthesis. Since 2013, Dr. Klinke is director of the Crystallography Node of the Argentinian Platform for Structural Biology and Metabolomics PLABEM. Within the Platform, the first three-dimensional protein structure obtained entirely in Argentina by X-ray diffraction was solved in 2014. As general achievements of his career, Dr. Klinke has published 21 articles in international peer-reviewed journals (h-index = 10), with over 90 presentations to congresses and more than 30 protein structures solved to date. Additionally, he holds academic positions in Argentinian and international scientific associations (Vice-president of the Argentinian Association of Crystallography and Member of the Deliberative Council of the Latin American Association of Crystallography, respectively). To finish, he has been recently involved in science outreach projects in Argentina aimed for primary school and high school students, organizing workshops, seminars and competitions related to crystallization and crystal growth with other colleagues throughout the country.

Dr. Victor Castro-Fernandez. Dr. Víctor Castro-Fernandez studied Biochemistry at the University of Concepción. His undergraduate thesis was directed by Dr. Elena Uribe, in which he worked in enzymology of ureahydrolases. In 2010 he started his PhD in Biological Science at the Faculty of Science of University of Chile under the direction of Dr. Victoria Guixé. During his PhD thesis, he implemented the methodology of ancestral protein reconstruction and worked on specificity of substrates of kinases. During his PhD he made several research stays in the group of Dr. Richard Garrat at University of Sao Paulo in Brazil, where he worked in protein crystallography. After finish his PhD thesis, he awarded a postdoctoral grant Fondecyt with the sponsorship of Dr. Jorge Babul at the University of Chile and his postdoctoral work focused on the evolution of protein stability through evolution and development of protein crystallography from Chile. In collaboration with Dr. Victoria Guixé they have studied the adaptation of proteins to extreme environments such as halophiles, psychrophiles and thermophiles. Since 2017 is academic of the Department of Biology, Faculty of Science of the University of Chile.

Symposium 2

Symposium Sbbq-Brazil: Bioactive compounds with potential health benefits,biotechnological approaches.

Chairs: Dr. Luis Morales-Quintana (Instituto de Ciencias Biomédicas, Universidad Autónoma de Chile) and Dr. Patricio Ramos (ICB, Universidad de Talca).

Flavonoids and their increasing value: different approaches to induce flavonoid pathway genes and accumulation of their metabolic products in crops to face climate change.

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Plants are able to generate a wide variety of secondary metabolites in response to stress and have been reported to exert positive biological activity in mammalian cells. The main metabolites are those produced by the phenylpropanoid pathway and special interest has been placed on flavonoids due to their high antioxidant properties among others. The production of flavonoids is strongly regulated by the transcriptional activity of genes as well as by the post-translational regulation of the encoded enzymes. In our lab, we have placed the efforts in to identify differences between metabolic and transcriptional profiles on fruits with the goal to identify target genes in order to propose it as candidate genes for breeding programs in commercial crops. Another approach is the structural conformation of key enzymes involved in the anthocyanins production to understand the regulation in the accumulation of those compounds in colored and colorless strawberry fruits as a bio-prospective species model. Mutations that are translated into affinity alterations by dihydroflavonol reductase (DFR) with different substrates to conduce the production of anthocyanins were identified in strawberries with differences in anthocyanin content. Finally, other approach is to modulate the differential accumulation of those polyphenolic compounds through the plant interaction with extremophile microorganism. We identified endophyte fungus from Antarctic native plants in which, the interaction promotes an increase in plant fitness and polyphenolic accumulation through the modulation of hormone content in plants exposed to environmental stress conditions.

We acknowledge the financial, authorizations and logistic support of the Chilean Antarctic Institute (INACH) and Núcleo Científico Multidisciplinario from Universidad de Talca.

Thermal decomposition of the cell wall constituents isolated from different stages of ripening of strawberry fruit

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Fruit softening during ripening is mainly a consequence of solubilization and depolymerization of cell wall components mediated by the action of a complex set of enzymes and proteins. In the present work, we performed a comparative study of the changes in physiological properties, cell wall-associated polysaccharide contents and thermogravimetry and derivative thermogravimetry study during different fruit developmental stages of strawberry (Fragaria x ananassa Duch. cultivar Camarosa). The Camarosa cultivar showed a decline in the fruit firmness values. In other hand, the thermogravimetric (TG) curves showed the cell wall polymer stability at temperatures around 200 °C and exothermic peaks characteristic of mass loss close to 250 °C which was higher as the fruit matured, showing a loss in the polymer fraction. Additionally, the TG analysis showed that the sample dry of large green (LG) stage have a mayor thermal stability probably by the higher inter-chain hydrogen bonding of the cell wall, in contrast, the ripe stage showed a lowest thermal stability. Finally, the results showed that exist a correlation between cell wall-modifying enzymes, physiological properties and firmness, which would explain the fruit softening process that reduces post-harvest life.

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Phage display system and protease inhibitors: important tool in the control of *Aedes aegypti* larvae.

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Aedes aegypti is the main arbovirus vector for humans among them the dengue virus has been transmitted to millions of people every year in tropical and subtropical areas. Dengue and other arboviruses control has been done by *Ae. aegypti* control using insecticides, however, the emergence of resistant mosquito strains has been a new challenge. Recently, our group selected HiTI mutants specific for digestive enzymes of *Ae. aegypti* using phage display system. The aim of this work was to produce HiTI mutants and Kunitz type inhibitor chimeric proteins containing the selected amino acid sequences in yeast and evaluate their larvicide potential. HiTI mutants selected for Aedes digestive enzymes named T6 (RGGAV) and T128 (WNEGL) presented inhibitory activity for larvae trypsin (IC 50 1.1 nM) and chymotrypsin (IC 50 11.6 nM), respectively. T23 (LLGGL) and T149 (GGVWR) mutants inhibited chymotrypsin-like (4.2 nM IC50 and 29.0 nM, respectively, and elastase type enzyme (both IC50 of 1.2 nM). The purified Kunitz type chimeric inhibitors (Boophilin and HiTI) named T6 / D1, T149 / D1 and T23 / D1 showed an effect on the viability of the larvae in concentrations of mM range. The larvicidal effect was synergistic when the chimeras were used simultaneously. Recently, TiPI1 mutants were selected for mosquito digestive enzymes. The perspective of this project is to solve the tridimensional structure of those mutants in complex with mosquito or bovine trypsin to be used as a model for rational molecule design to mosquito control.

SBBq; FAPESP; CNPq; INCT - Entomologia Molecular.

Dietary Anthocyanins in Metabolic Syndrome

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In 2017, the prevalence of Metabolic Syndrome (MetSyn) in adults was 32% in Chile, with a tendency to increase due to poor dietary choices and inadequate lifestyle. The recommendation of several international agencies is to consume at least five daily servings of fruits and vegetables to prevent MetSyn. To date, the evidence is still incomplete regarding the molecular mechanisms by which plant metabolites could prevent the signs of MetSyn. Anthocyanin have been studied during the last 20 years for their preventive effects in different models of MetSyn, both *in vivo* and *in vitro*. Although the clinical evidence is still scarce, current research suggests that formulations rich in anthocyanins improve insulin sensitivity in insulin-resistant obese patients. Certain type of anthocyanins, specifically the cyanidin glucosides and sambubiosides display anti-inflammatory and insulin-mimetic effects. These molecules also inhibit the intracellular lipid accumulation in hepatocytes and adipocytes. The proposed mechanisms include the transcriptional modulation of genes involved in the synthesis of triglycerides and cell cycle regulatory genes. Recent data suggest that the modification of intestinal microbiome could also play a major role in the protective effects of anthocyanins in MetSyn. The present work presents a global vision on the effects of anthocyanins against MetSyn and describe the results from our research group, which together summarize the most significant findings in relation to the molecular mechanisms of anthocyanins as preventive agents against of MetSyn and Diabetes.

Fondecyt N 11140915 Universidad de Santiago de Chile

Dr. Patricio Ramos studied Biochemistry at the University of Concepción and obtained his professional degree in 2003. He obtained his PhD in engineering in plant genetics from the University of Talca in 2010 and then he performed a post-doctoral training at the Institute of Biological Sciences (ICB) at University of Talca. In 2011 started an insertion in the academy program (PIA) and now he works at University of Talca in “The scientific multidisciplinary nucleus” and is part of the academic team of the ICB and PhD program. One of the main research lines is focusing in the study of phenylpropanoid metabolic pathway regulation and the relationship with hormonal signaling. Phenolic compounds, specifically flavonoids, display wide biological effects such as modulation of the interaction between plants and microorganisms, stress response, pigmentation as well as the hormonal transport regulation in several plant tissues. Homeostasis of those compounds within the subcellular compartment and balance between lignin and flavonoid is part of his scientific research interest. On the other hand, phenylpropanoid displays several health’s benefit to consumers, the study of biosynthesis and accumulation in fruits and other edible plant tissues are also part of his research line.

Dr. Luis Morales Quintana studied Engineering in Bioinformatic at the University of Talca and received his degree in 2009. He performed a PhD in Science with mention in plant genetic engineering from the University of Talca and received the degree at 2013. After that he worked as professor at the Institute of Biological Sciences of U. of Talca (2014-2017). He is currently associate professor of Biochemistry and Molecular biology at the Instituto de Ciencias Biomédicas of the Universidad Autónoma de Chile, Talca, Chile. His research main topic focuses in the study of molecular aspects in the formation and degradation of primary plant cell wall. The strategies used involve: structural bioinformatics, biochemical characterization, kinetics studies, and functional genomics. To describe genes, proteins, enzymes and how they modulate the response to different events occurring in the plant cell wall. It has also been approached the study of enzymes involved in the study of quality traits of fruits, specifically in biosynthesis of volatile compounds related with aroma in strawberry and mountain papaya fruits.
Dr. Luis Morales Quintana. Paulo A.S. Mourão obtained his MD (1975) and PhD (1975) at the Federal University of São Paulo. Postdoc at Baylor College of Medicine (USA) with a fellowship from the US NIH/ Fogarty International Research Fellow. Since 1981, he has been a Professor of Biochemistry at Federal University of Rio de Janeiro, Full Professor since 1992. He coordinates the “Connective Tissue Laboratory”, located at the University Hospital, in a project to integrate

basic and clinical areas of the institution. He is responsible for an innovative postgraduate program that combines the MD with the PhD. His research theme is glycobiology, especially aimed at the study of structure, biological activity and metabolism of sulfated polysaccharides, including pharmaceutical preparations of heparin and chondroitin sulfate. His research work has been funded with regular grants from national and international agencies such as the World Health Organization (WHO), Mizutani Foundation for Glycoscience, British Council, Natural Sciences and Engineering Research Council (Canada) and COFECUB (France). Former Fellow of the John Simon Guggenheim Memorial Foundation, he is a member of the Brazilian Academy of Sciences, the Academy of Sciences of Developing Countries, and the National Order of Scientific Merit. In 2003-04 he was president of the Brazilian Society of Biochemistry and Molecular Biology.

Dra. Aparecida Sadae Tanaka studied undergraduate Chemistry at the Universidade Estadual Paulista (UNESP) in Araraquara, São Paulo – Brazil. She obtained her Ph.D. in Sciences from the Universidade Federal de São Paulo in 1993, under the supervision of Claudio A. M. Sampaio. She did a postdoctoral in the Ludwig Maximilian University of Munich (LMU) in Germany (1993-1995). In 1997, she got a position of Adjunct Professor in the Department of Biochemistry in the Escola Paulista de Medicina (EPM) –UNIFESP. In 2006, she obtained the title of Associate Professor - "Livre Docente" in the same Department, were she is currently Full Professor. The focus of the Tanaka's Lab is biochemistry and molecular biology of diseases' vectors. The group already described several new molecules from insects and ticks belonging to proteases and protease inhibitors families. In the present, the group has been focused in the role of those molecules in the vector-parasite or mosquito-virus interactions; and in the development of tools to vector control.

Dr. Leonel Rojo, is an Associate Professor and Head of the Pharmacy Academic Program at Universidad de Santiago de Chile. He has developed research on bioactive molecules from botanical sources with applications in metabolic syndrome and skin regeneration. Prior to pursuing postdoctoral training in Biotechnology at Rutgers University (New Jersey, USA), He served as a visiting scientist at Albert Einstein College of Medicine in New York. Dr. Rojo developed several R&D projects as a member of the multidisciplinary team led by Dr. Ilya Raskin and Dr. Bertold Fridlender at Rutgers University. He also served as a consultant for Nutrasorb LLC, a spinoff biotech company of Rutgers University. Dr. Rojo is co-founder and scientific advisor of Neuroinnovation Ltda., a pioneer startup Company based in Chile specialized in developing and commercializing therapeutic technologies for Neurological diseases. He has been a visiting scientist at Kwantlen Polytechnic University in Vancouver, Canada, and the National Institute of Engineering and Technology (INETI) in Lisbon, Portugal. His work in Chile, USA and Europe has resulted in several scientific ISI publications, book chapters and patent applications. Dr. Rojo served as General Director a drug-development program funded by the Chilean government and as the coordinator of the GIBEX-Chile program.

Symposium 3

Preclinical models for studying pathogenesis and designing therapies for hematologic malignancies

Chair: Ruben Carrasco, Harvard University, USA

Targeted deletion of *miR-15a/16-1* in activated B-cells promotes the development of plasmacytomas and germinal center-derived lymphomas in mice

Carrasco Ruben D. [1] Oncologic Pathology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, US.

MicroRNAs (miRs) are a group of short non-coding RNAs that regulate gene expression by repressing mRNA translation or inducing its degradation. miRs can function as tumor suppressors or oncogenes and their aberrant expression has been implicated in various types of B-cell malignancies. Chr13q14, harboring the *miR-15a/16-1* cluster, is frequently deleted in B-cell malignancies as well as multiple myeloma (MM), a plasma cell neoplasm, underscoring important tumor suppressor functions of miR-15a/16 in B-cells and plasma cells. To examine the role of miR-15a/16 in normal B-cell activation and in the pathogenesis of mature B-cell neoplasms, we have generated mice with conditional deletion of *miR-15a/16-1* in activated, germinal center (GC), B-cells. We show that miR-15a and miR-16 are highly expressed in murine GC B-cells, and that deletion of the *miR-15a/16-1* cluster in GC B-cells results in upregulation of its target genes. This leads to expansion of GC B-cells and eventually the development of mature B-cell neoplasms resembling human follicular lymphoma, diffuse large B-cell lymphoma, and plasmacytoma (a MM-related plasma cell tumor that colonizes extramedullary sites). Moreover, we show that miR-15a and miR-16 are highly abundant in normal human plasma cells and GC B-cells, whereas are significantly decreased in human plasmacytoma and follicular lymphoma, affirming the clinicopathologic resemblance of the murine and human setting. Taken together, these data indicate that miR-15a/16 are important regulators of the GC B-cells homeostasis and that miR-15a/16 function as tumor suppressors in mature B-cell neoplasms, pointing to miR-15a/16 mimetics as promising agents for replacement therapy.

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Notch Signaling in T-Cell Acute Lymphoblastic Leukemia: Lessons from Mouse Models

Aster Jon [1](1) Pathology, Yes, Brigham and Women´s Hospital.

T-Cell Acute Lymphoblastic Leukemia (T-ALL) is an aggressive neoplasm that constitutes approximately 20% of childhood ALL and a higher fraction of adult ALL. Approximately 80% of children are cured with chemotherapy, but outlooks are poor for the remaining 20% of children and are generally less favorable in adults; thus, new therapies are needed. Over 60% of T-ALLs have gain-of-function mutations in Notch1, making Notch an attractive potential therapeutic target in this disease. Our group developed the first mouse model of Notch-induced T-ALL using a hematopoietic transduction/transplantation approach that produces T-ALLs closely resembling their human counterparts in 8-10 weeks. We have used this model to show that within hematolymphoid cells the oncogenic effects of Notch is restricted to T cell progenitors, and have used human and murine T-ALL cell lines to show that this “oncotropism” stems from T-lineage-specific enhancers that allow Notch to drive key oncogenes such as MYC. We have also shown that most murine transgenic models of T-ALL acquire cryptic RAG-mediated rearrangements in Notch1 that produce truncated strong gain of function Notch1 alleles, further highlighting the central role of Notch in T-ALL pathogenesis. As predicted by mouse models, responses of relapsed/refractory T-ALL to Notch inhibitors have been observed in human clinical trials, but at low frequency, possibly because “enhancer switching” relieves addiction to Notch. This talk will provide an overview of key past advances and remaining questions and hurdles that must be overcome for Notch-directed therapies to be successful in the clinic.

National Institutes of Health and Leukemia and Lymphoma Society

Modeling and Therapeutic Targeting of Blastic Plasmacytoid Dendritic Cell Neoplasm (BPDCN)

Lane Andrew A [1] Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, US.

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is an aggressive hematologic malignancy thought to result from neoplastic transformation of dendritic lineage cells. Median survival is less than 12 months from diagnosis and there are no approved therapies. Genetic studies from our lab and others have found somatic mutations in BPDCN that partially overlap with those in myeloid malignancies (e.g., in *TET2, ASXL1,* RNA splicing factors), but also uniquely mutated genes and mutation combinations not seen in other blood cancers. One research challenge is the lack of BPDCN models that accurately reflect disease biology. We created several distinct animal models, each of which has provided insights into BPDCN pathogenesis and new directions for therapy. We will discuss a bone marrow transduction/transplantation model of dendritic cell leukemia combining germline *Cdkn2a* loss with an activating mutation in GNB1, a beta subunit of heterotrimeric G proteins, that we discovered in a functional oncogene screen from primary BPDCN. We will describe how we used a Cas9 transgenic mouse to test combinations of mutations, including in TET2 and RNA splicing factors, for their ability to expand dendritic cell precursors and facilitate abnormal persistence during immune stimulation. Finally, we will outline generation of BPDCN patient-derived xenografts (PDXs) that propagate in immunodeficient mice, which provided a platform to discover vulnerabilities in the mitochondrial apoptosis pathway and to develop strategies overcoming resistance to targeted immunotherapy. Each of these preclinical models has increased our understanding of BPDCN biology and elucidated new therapeutic approaches, some of which have already entered clinical trials.

Ras pathway activation cooperates with *Ink4a/Arf* deletion during the development of B-ALL in mice

Sewastianik Tomasz [1,2], Jiang Meng [1,3], Sukhdeo Kumar [4,5], Patel Sanjay S.[6], Roberts Kathryn [7], Kang Yue [1], Alduaij Ahmad [8], Dennis Peter S.[1], Lawney Brian [9], Liu Ruiyang [1], Song Zeyuan [1], Xiong Jessie [10], Zhang Yunyu [11], Lemieux Madeleine E.[12], Pinkus Geraldine S.[6], Rich Jeremy N.[4], Weinstock David M.[11], Mullighan Charles G.[7], Sharpless Norman E.[10], Carrasco Ruben D.[1,6]. [1]Department of Oncologic Pathology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, US. [2]Department of Experimental Hematology, Institute of Hematology and Transfusion Medicine. [3]Department of Surgical Oncology, The Fourth Affiliated Hospital of Harbin Medical University. [4]Department of Stem Cell Biology and Regenerative Medicine, Cleveland Clinic, Cleveland, US (5) Department of Pathology, Case Western Reserve University. [6]Department of Pathology, Brigham & Women´s Hospital, Harvard Medical School, Boston, CL. [7]Department of Pathology, St Jude Children´s Research Hospital, Memphis, CL. [8]Pathology and Laboratory Medicine Institute, Cleveland Clinic Abu Dhabi, Abu Dhabi, AE. [9]Center for Computational Cancer Biology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, CL. [10]Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, CL. [11]Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, CL. [12]NA, Bioinfo, Plantagenet, CA

B-cell acute lymphoblastic leukemia (B-ALL) is a heterogeneous malignancy of B-cell-committed precursor cells that affects bone marrow and peripheral blood. Despite recent advances in treatment, B-ALL remains a significant clinical problem. Among the numerous recently uncovered genetic alterations in B-ALL, Ras pathway mutations and loss of the *INK4A/ARF* locus seem particularly important, since they are frequent in relapsed and poor-prognosis B-ALL cases. To comprehensively characterize the functional roles of these mutations and to develop an *in vivo*preclinical model of relapsed B-ALL, we generated conditional mutant mice overexpressing constitutively active mutant KrasG12D and/or harboring a knockout of a single *Ink4a/Arf* allele. Although constitutive activation of KrasG12D in B-cells induced significant transcriptional changes leading to enhanced proliferation, it gave rise to only a low-grade mature B-cell malignancy in our model resembling human extranodal marginal-zone lymphoma of mucosa-associated lymphoid tissue or lymphoplasmacytic lymphoma.Interestingly, *Ink4a/Arf* inactivation, apart from reducing the number of apoptotic B-cells, suppressed the signature upregulated by Kras signaling. Nevertheless, simultaneous Kras activation and *Ink4a/Arf* loss cooperated functionally to induce a highly aggressive B-ALL phenotype recapitulating gene expression programs in poor-prognosis subgroups of human B-ALL that harbor *BCR-ABL* and *CRLF2* rearrangements, and representing an attractive model to study kinase inhibitors as well as anti-CD19 chimeric antigen receptor T-cell therapies for B-ALL. Moreover, these data highlight the importance of functional cooperation between mutated Kras and *Ink4a/Arf* loss in murine B-ALL, and suggest that these changes may also have functional, prognostic, and therapeutic impact in human B-ALL.

Dr. Ruben Carrasco. Dr. Ruben Carrasco received an MD in 1989 and a PhD in Biochemistry in 1993 from the University of Chile. He then completed clinical training in Anatomic Pathology at the Massachusetts General Hospital, followed by a subspecialty fellowship in Hematopathology at the Brigham and Women's Hospital (BWH), Harvard Medical School (HMS), Boston, Massachusetts. During his postdoctoral work in the Department of Medical Oncology at the Dana-Farber Cancer Institute (DFCI) under Dr. Ronald DePinho, he developed an interest in oncogenomics and the genetic modeling of murine hematologic cancers with emphasis on multiple myeloma (MM), a cancer of plasma cells. He has continued to actively pursue this research interest to this day. He is currently a hematopathologist at BWH and a research investigator at DFCI. Over the years his lab has led, or collaborated with other groups on work that has led to several important and original findings in the field, including: i) characterization of MM genomes using genome-wide array comparative genomic hybridization (a-CGH), ii) generation of a novel murine transgenic model of MM using the X-box binding protein 1 (XBP-1), iii) demonstration that the B-cell lymphoma gene (BCL9) is an oncogenic promoter of MM progression, (iv) acquisition of compelling proof-of-concept support for an innovative pharmacologic strategy to inhibit oncogenic Wnt signaling in MM via targeted disruption of BCL9/b-catenin complex, and v) demonstration that Cyclophilin A (CyPA) is a downstream transcriptional target of the Wnt/b-catenin/BCL9 complex that is secreted by bone marrow endothelial cells and promotes MM progression through via binding to CD147. He has led multi-

investigator multi-institution NIH funded Program Project Grants. In 2015, he was named an Associate Professor in Pathology at BMW and HMS. He has published more than 90 articles in peer-reviewed journals, holds 4 U.S. patents, and has been an invited speaker at major international meetings devoted mainly to MM.

Dr. Jon Aster. Dr. Jon Aster obtained his MD/PhD in 1987 from the University of Michigan, and then did clinical training in Anatomic Pathology and hematopathology at Brigham and Women's Hospital. During his postdoctoral work in the Division of Molecular Oncology with Dr. Jeffrey Sklar, he developed an interest in the role of Notch signaling in cancer and hematopoiesis, areas of research that he has continued to pursue to the present. Over the years his lab has led or collaborated on work that has produced a number of firsts in the field, including: i) production of the first mouse model of Notch leukemia; ii) demonstrating that Notch signals can induce T cell development from bone marrow progenitors; iii) demonstrating that T-ALL cells depend on continuing Notch signaling for growth; iv) detecting and characterizing frequent Notch1 mutations in human and murine T-ALL; v) solving key Notch structures at high resolution, including the structures of Notch transcription complexes on DNA; vi) identification of Myc and mTOR as important downstream targets of leukemogenic Notch signaling; vii) development of the first selective Notch receptor inhibitors, antibodies directed against the negative regulatory domain; viii) report of genome-wide Notch1 binding patterns in cancer cell genomes; and viii) description of Notch1 loss-of-function mutations in human squamous cell carcinomas. His work describing Notch1 mutations in T-cell acute lymphoblastic leukemia is one of the most highly cited in the field (2265 citations). He has led multi-investigator multi-institution NIH funded Program Project Grants and Leukemia and Lymphoma Society sponsored Specialized Center of Research Grants. Since 2007, Aster is full Professor of Pathology at Brigham and Women's Hospital and Harvard Medical School and as of 2017 is the first incumbent Michael A. Gimbrone Chair in Pathology. Aster has published more than 190 manuscripts in peer-reviewed journals that have been cited more than 55,000 times and an *h*-factor of 104. He holds 3 patents. He has been an invited speaker at all major international meetings focused on Notch signaling in cancer to date (the Notch Gordon conference, the International Notch Meeting), and has organized several of these meetings. He leads the division of Hematopathology at Brigham and Women's Hospital, serves as the co-leader of the Lymphoma and Leukemia Program of the Dana Farber/Harvard Cancer Center, and is on the Executive Committee of the Cancer Center. He is a past member of the NIH Cancer and Molecular Pathology study section, and continues to serve as an ad hoc reviewer for the NIH. In 2017, Aster was elected to the Association of American Physicians. He also is the co-editor of the Pathologic Basis of Disease, the most widely used pathology text in the world.

Dr. Andrew Lane. Dr. Andrew Lane is a physician-scientist whose goal is to define novel targets in hematologic malignancies that lead to new therapies. He obtained his MD and PhD degrees from Washington University in 2006. His PhD thesis research with Dr. Timothy Ley studied the pathophysiology of acute promyelocytic leukemia (APL). He created new mouse models to understand why the PML-RARa oncogene specifically transforms early myeloid progenitors but no other cell types. He then completed his internal medicine training at Brigham and Women's Hospital / Harvard Medical School, and fellowships in hematology and medical oncology at Dana-Farber Cancer Institute. His postdoctoral research interrogated patient leukemia genetics and animal models to ask why Down syndrome is associated with increased risk of B-ALL. Using an shRNA screen in primary B cell progenitors, he identified the epigenetic regulator and nucleosome-binding protein HMGN1, encoded on chromosome 21q22, as a novel lymphoid leukemia oncogene. Now an assistant professor at Dana-Farber and Harvard Medical School leading his own laboratory group, he continues to work on AML and ALL to elucidate new therapeutic targets. He now also studies blastic plasmacytoid dendritic cell neoplasm (BPDCN), a rare leukemia/lymphoma of dendritic cells, with projects on BPDCN genetics, dendritic cell transformation mechanisms, and testing novel therapies in animal models and in clinical trials, including BCL-2 inhibition, CAR-T cells, and cell surface receptor-targeted immunotoxins. Dr. Lane is director of a new BPDCN Center at Dana-Farber, a clinical and translational research group that aims to accelerate basic biological understanding and promote rapid clinical evaluation of novel therapeutics in BPDCN.

Dr. Tomasz Sewastianik. Dr. Tomasz Sewastianik is a translational scientist with a focus on the molecular biology of normal and malignant lymphoid cells and the clinical exploitation of validated signaling, transcriptional, and metabolic pathways. He obtained his MSc in 2011 from Maria Curie-Sklodowska University in Lublin, Poland, under the auspices of the Nencki Institute of Experimental Biology, Polish Academy of Sciences in Warsaw, where he worked in the area of DNA damage response and T cells death associated with immune system deterioration. He then obtained a PhD in 2015 under Prof. Przemyslaw Juszczynski at the Maria Sklodowska-Curie Memorial Cancer Center – Institute of Oncology and at the Institute of Hematology and Transfusion Medicine in Warsaw, where he studied redox-dependent signaling pathways in diffuse large B-cell lymphoma (DLBCL) and identified the TXN-p300-FOXO1 circuit as the major mediator of oxidative stress response in DLBCL. He also worked on the inhibition of PIM kinases in acute myeloid leukemia and on daunorubicin-resistance in acute lymphoblastic leukemia cells. In 2015, he began postdoctoral training with Dr. Ruben Carrasco at Dana-Farber Cancer Institute, working on mouse models of cancer using, for example, animals with mutated MYD88 protein overexpression, miR-15a/16-1 deletion, and Kras oncogene mutation with concomitant deletion of the Ink4a/Arf tumor suppressor. He has published in peer-reviewed journals and has presented his findings at international meetings including, for example, American Society of Hematology Annual Meetings and the International Conference on Malignant Lymphoma in Lugano, Switzerland.

Symposium 4

Exosomes in cancer disease

Chair: Andrew Quest (Universidad de Chile & Advanced Center for Chronic Diseases, ACCDiS)

The potential of extracellular vesicles for medical and nanotechnological applications

Serrati Simona[2], Palazzo Antonio[2], **Krol Silke [1,2]**. [1]Laboratory for Nanomedicine, Milan, Italy, Fondazione IRCCS Istituto Neurologico "Carlo Besta". [2]Laboratory for translational nanotechnology, IRCCS Istituto Tumori.

Exosomes are nature's nanocarriers that transport biological information. Exosomes are ddefined as vesicles formed in the endosomal compartments (multivesicular endosomes) which then get secreted into the extracellular space to serve as nano-rafts carrying biological information between cells. It follows from the mechanism of exosome formation that the content of exosomes contains mainly cytosol derived molecules (different RNAs, proteins, enzymes and dsDNA). Hence, they play a central role in intercellular communication (2). Exosomes have been found to originate from various types of cells in the body, including stem cells and fully differentiated cells.

Their most important feature is that the extracellular leaflet of the plasma membrane is fully preserved as extracellular part of the exosomes which makes them a valuable tool for the diagnosis of diseases, such as cancer, and also, as innovative tools for drug delivery. The proteins attached to the lipid bilayer of exosomes originate from the plasma membrane which is preserved its original orientation. The potential of exosomes of creating stealth nanoparticles that are better tolerated by the immune system than the presently available synthetic drug delivery systems represent a promising new approach in nanomedicine.

Exosomal properties which are on one hand promising in terms of stealth drug delivery system bear the risk to play a crucial role in disease development and progression. Exosomes play a central role in the manifestation and progression of several diseases, as well as in drug resistance, therefore mapping their functions in intercellular communication is essential in understanding the pathomechanism of these medical problems.

Circulating Exosomes in Ovarian Cancer – Liquid Biopsies for Early Detection and Real-Time Monitoring of Cancer Progression

Sharma Shayna[3], Morgan Terry [1], Perrin Lewis C[2], Felipe Zuñiga[4], Hooper John[2], Salomon Carlos [3,4,5]. [1]Department of Pathology and Obstetrics, Medicine, Oregon Health & Science University, Portland, US. [2]Mater Research Institute, Medicine, University of Queensland, Brisbane, CL. [3]Centre for Clinical Research, Medicine, University of Queensland, Brisbane, AU. [4]Department of Clinical Biochemistry and Immunology, Faculty of Pharmacy, Universidad de Concepción, Concepcion, , CL. [5]Maternal-Fetal Medicine, Department of Obstetrics and Gynecology, Medicine, Ochsner Clinic Foundation, New Orleans, Louisiana, US.

Ovarian cancer (OvCa) usually has a poor prognosis because it predominantly presents as high stage disease. Exosomes are a specific subtype of secreted vesicles released from a wide range of cells, including healthy and cancer cells with the capacity to deliver bioactive molecules to target cells. Recently, we have suggested that the analysis of exosomes and their content may provide an approach to enrich tumor biomarker detection and address this clinical need. We isolated by differential and buoyant density centrifugation from plasma obtained from women at different stages of epithelial OvCa (n=77; n=22 for Stage I, n=7 for Stage II, n=42 for Stage III and n=6 for Stage IV) and age-matched women with benign ovarian adenoma (n=62). Using Liquid chromatography-mass spectrometry (LC-MS/MS) and a small ion library, we identified a total of over 300 statistically difference proteins and miRNAs were identified to change in expression across OvCa progression. Then, we built an algorithm using five exosomal miRNAs and proteins that are significantly different between benign and stage I. The classification efficiency (i.e., the proportion of cases correctly identified) by measuring exosomal biomarkers was assessed by ROC curve analysis. The area under the ROC curves (AUC) were 0.785 ± 0.091 ($p = 0.0106$) with positive and negative predictive value of 75% and 76%, respectively. We propose that the combined measurement of exosomal biomarkers might allow the early identification of women with OvCa; however, a larger trial is required to further validate the utility of this approach for population screening.

Lions Medical Research Foundation, Ovarian Cancer Research Foundation, National Health and Medical Research Council (NHMRC; 1114013), and Fondo Nacional de Desarrollo Científico y Tecnológico (FONDECYT 1170809).

Exosomal miRNAs in Gastric Cancer

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Gastric cancer (GC) is one of the deadliest malignancies worldwide and linked to infections by either *Helicobacter pylori* (*H. pylori)* or Epstein-Barr virus (EBV). Both pathogens modify the expression of coding (i.e SHP-1) and microRNAs (i.e. let-7, miR-155, and miR-200), resulting in increased inflammation as well as suppression of pro-inflammatory cytokines. microRNAs (miRs) are 20-200 nucleotides in length RNAs that do not code for proteins. miRs are highly conserved and regulate gene expression in multicellular organisms at the posttranscriptional level. In *H. pylori* infection, several miRNAs are upregulated such as miR-103, -223, -375, and -532. and the above-mentioned miRs. EBV encodes its own viral miRNAs, miR-BHRF1s, and miR-BARTs. This viral miRs are crucial for the maintenance of viral latency and evasion of the immune response, as well as inhibition of apoptosis of infected cells through suppression of host miRNA production. By extracellular vesicles, especially exosomes, both pathogens communicate with gastric epithelial cells. Exosomes have been shown not only deliver viral miRs, but also *H. pylori* virulence factor (cytotoxin-associated gene A). In this conference, we will focus on the role of exosomes as vehicles for miR delivery in *H. pylori*- and EBV-related stomach carcinogenesis

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Lactadherin Incorporated In To Exosomes Promotes Metastatic In Breast Cancer

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Background:
It is well known that the probability for breast cancer patients for developing secondary aggressive tumors nodules is highly probable after going through a tumor resective surgery. In addition, there are no systemic biomarkers for clinical use that can provide a prognosis to indicate the target tissue this type of metastasis, which in turn leads to a diagnosis where the only thing left is palliative therapies. For this reason the aim of our work is to study how tumor cells mediate communication via exosomes with healthy tissues that may trigger a predisposition for the establishment of tumor cells in these organs. Our data suggests that the metastatic breast cancer cell model, MDA-MB-231 is capable of transporting ***Lactadherin in exosomes*** which are capable of potentiating Invasion.

Methodology :
The Lactadherin was knocked-down in MDA-MB-231 cells so this led to cells that secreted exosomes without Lactadherin (Exo-siLacta). Tumorigenic capacity was evaluated in this cell line compared to a non-modified or control cell line (Exo-WT). The in vivo model was evaluated by using the *Niche Preparation Model* in which the animals were previously injected with Exo-WT and ExosiLacta exosomes. MDAMB231 cells were inoculated in mice and after 21 days the tumor mass was analyzed in all tissues.

Conclusion:
Lactadherin that was incorporated into exosomes are capable of potentiating metastasis and the blockade of these cadherin with siRNA and/or antibodies in exosomes leads to a stop in tumor metastasis.
Funding: Fondecyt 11140204(LLG), 1160139(CR).

Dr. Silke Krol. Dr. Silke Krol was trained in Chemistry at the Westfälische Wilhelms-University in Münster, Germany where she obtained her Master degree in Chemistry in 1997. This was followed by the PhD with the topic of her thesis on the biophysical characterization of hydrophobic pulmonary surfactant components. She received her PhD in 2000 and continued working as a postdoc until 2001. Then she worked first as a post-doctoral fellow (2001-2003) and then as a junior researcher (2003-2007) at the INFM (Istituto nazionale di fisica materia), Institute of Physics, University of Genoa, Genoa, Italy. She developed nanodrugs and protective nanocoatings for cells in an EU project entitled “Nanocapsules with functionalized surfaces. With this approach she was one of the pioneers in nanomedicine in Genoa. A second EU project used the protective cell coating to protect pancreatic islets for a Bioartificial Pancreas for Type I Diabetes Therapy. From 2007-2010 she established and headed the „NanoBio“lab@LA (NADA) (laboratory of nano analysis, drug delivery, and diagnostics) at CBM in Trieste, Italy, a small enterprise dedicated to technology transfer from bench to bedside. Here her research focused on developing anticancer drugs and vehicles that allow the delivery through the blood brain barrier. In 2010, she established and headed the laboratory for Nanomedicine at the National Institute for Neurology ”Carlo Besta”, Milan, Italy. As a principal investigator and advisor to the director of the Nanomedicine Centre, where research activities focus on the design of nanoparticles for imaging and therapy of neurodegenerative disease, epilepsy and cancer. In this contest, she developed a very strong interest in exosomes and their importance for theranostics and the metastasis of tumors. This work was extended and intensified in the field of liquid biopsy for early diagnosis of cancer in the Institute of Oncology “Giovanni Paolo II”, a research hospital in Bari, Italy where she established the laboratory of translational nanotechnology in 2016.

Dr. Carlos Salomon. I lead the Exosome Biology Laboratory based at The University of Queensland located at the Centre for Clinical Diagnostics (CCD) within UQ Centre for Clinical Research (UQCCR). My research interests include extracellular vesicles, ovarian cancer, pregnancy, preeclampsia, preterm birth and maternal obesity in pregnancy and

gestational diabetes mellitus. I have obtained an undergraduate degree, Bachelor in Biochemistry with Honours in Immunology in 2005 (University of Concepcion, Chile) and a Masters degree in Clinical Biochemistry and Immunology in 2008. I began my Ph.D. studies in 2008 (Faculty of Medicine, The Pontifical Catholic University of Chile), and my Ph.D. was awarded December 2012. I have completed training in the regulation of transport system, placental function and mass spectrometry at University of Barcelona (Spain), The University of Texas Health Science Center (USA) and The University of Queensland (Australia), respectively. I have awarded the Chancellor's Prize for Excellence in the Ph.D. Thesis (2013). I am the author of 77 journal publications (51 in EVs field and 43 as senior/corresponding author) and over 100 abstracts during the period of 2011-2017, many of which appear in high-ranking journals in the field (e.g., Oncotarget, Diabetes, JCEM, Placenta, and FASEB). Currently, I hold appointments at the University of Queensland (Brisbane, Australia), Ochsner Medical Center (New Orleans, USA) and Universidad de Concepcion (Concepcion, Chile). I am a principal investigator on several projects on extracellular vesicles based at the USA (NIH), Australia (NHMRC), U.K (Action Research) and Chile (Fondecyt). I have established and lead the EXOSOME BIOLOGY LABORATORY that conforms the ISO standards (ISO17025 and 13185) and in which human exosomes can be isolated, characterised, and their role elucidated to evaluate their clinical utility as biomarkers of disease and therapeutic interventions.

Dr. Alejandro Corvalán. Dr. Alejandro Corvalan got both MD and MSc from the University of Chile, Santiago, Chile and went on to train as a clinical and research fellow at the Mount Sinai Medical School New York, USA and then at Kagoshima University at Kagoshima, Japan. During this period he characterized the role of Epstein-Barr Virus (EBV) in gastric cancer, a novel etiological agent that took almost 20 years to be recognized. He moved on to a position as an Assistant Professor at the University of Chile in Santiago, Chile and then to the University of Texas MD Anderson Cancer Center in Houston, TX, USA. In 2010, he moved back as an Associate Professor at the Pontificia Universidad Catolica de Chile, Santiago where he turned to the study of epigenetic modifications in pathogenesis and as biomarkers of diseases. His group identified a novel gene Reprimo that functions as a tumor suppressor in gastric cancer cells whose epigenetic modifications, such as methylation of the promoter region, may act as a cell-free DNA biomarker for non-invasive diagnosis of gastric cancer. More recently, his group switched to the study of the role of non-coding genes (i.e. microRNAs) in precancer lesions of the stomach and showed that the microRNA-335 may act as a tumor suppressor gene and by inactivating metastatasis-promoting genes. Currently, his group is exploring how downregulation of the microRNA-335 in exosomes promotes metastasis. Alejandro Corvalan is currently director of Grupo Oncologico Chileno Cooperativo de Investigacion (GOCCHI) and Principal Investigator of the Advanced Center for Chronic Diseases (ACCDiS).

Dr. Lorena Lobos-Gonzalez. Dr. Lobos-Gonzalez trained as a Biochemist in the Pontificia Universidad Católica de Valparaiso. She got her Master in Biochemistry from the Universidad de Chile under the supervision of Dr. Amalia Sapag and then her PhD with Dr. Andrew Quest working at the same institution. In her PhD thesis she contributed to development a new *in vivo* surgery model that permitted studying the dual role of Caveolin-1 as a tumor suppressor and promoter of metastasis. Her studies were the first in the literature to show directly the dual role of Caveolin-1 in an *in vivo* model. During her PhD training period, Lorena did a research stage in England at St George's Hospital, University of London in the lab of Dr. Dorothy Bennet (PhD), where she studied the role of CAV1 in different tumor and melanoma cell lines. In 2012, Lorena was awarded a PIA project to work in the *Fundación Ciencia y Vida* as a postdoctoral fellow in the lab of The Dr Luis Burzio, whose interests focus on the development of novel therapeutic approaches for the treatment of different types of cancer based on the knockdown of noncoding mitochondrial RNAs. Thanks to these studies, Lorena obtained several important publications and, importantly, the data obtained in the *in vivo* studies in animals permitted moving on to testing the pharmacogenics in a phase I study in the USA, approved by the FDA. In 2014, Lorena was awarded a *Fondecyt de Inicio* (Young Investigator Award) to study the role of exosomes in promoting breast cancer metastasis and identifying the exosomal miRs and proteins involved.

Symposium 5

Scientific research trajectory and scientist training in Chile

Chairs: Roxana Pincheira and Leonardo Guzmán, Universidad de Concepción, Chile.

Scientific research trajectory and scientist training in Chile

Pincheira Roxana [1], Guzman José L[2] Bioquimica y Biología Molecular, Universidad de Concepción [(2)] Physiology, Universidad de Concepción, Concepcion, CL.

The last four decades have been times of many and intense changes in the development of biological knowledge. Modern society has been amazed with scientific achievements that have cured diseases, improved industrial processes, introduced new drugs and, perhaps most importantly, have displaced our frontier of knowledge of biological nature to extensions only existing in fantasy. In this context, the training of the new generations of scientists has had to adapt itself in the same way, leaving a permanent factor that is the impact of the work of mentors in young scientists. The academic career is not just about scientific work but also about motivation, teaching, mentoring and the generation of knowledge, which contribute to a social development.

This symposium is focused on the personal experience of four recognized Chilean professors, which worked for many years in the development of different scientific fields at national and international universities.We will learn about their dreams as university students and how they achieved a remarkable national and international scientific recognition. Our speakers left a path in both, knowledge and scientific training, in areas such as enzymology, metabolism, signal transduction and the development of new analytical methodologies. By listening to their experiences, we will learn about the history of Biochemistry and Molecular Biology in Chile, but also about the importance of motivation, which comes from vision, goal setting, and celebrating small successes.

Signal transduction studies in the development of fundamental biological sciences en Chile

Olate Aravena Juan [1] Universidad de Concepción.

With a career marked by his PhD degree under the tutelage of Dr. Jorge Allende and a post-doctorate with Dr. Lutz Birnbaumer (at the Baylor College of Medicine, Huston, USA) in projects pioneering and transcendental projects for the understanding of signal transduction systems, Dr. Juan Olate became a reference for the development of basic sciences in molecular biology in Chile, and a school for undergraduate, master and doctoral scientific training. His scientific work achieved a significant advance in the identification of molecular mechanisms of signal transduction mediated by G protein, adenylyl cyclase and synembrin (Ric-8), among others. At the same time, it incorporated a large number of cutting-edge techniques that contributed significantly to the development of biochemistry and molecular biology in the country, among others, gene cloning, double hybrid, DNA sequencing, protein expression and purification. In the same way, his contribution was decisive in collaboration with groups of related areas such as enzymology, molecular genetics and neuroscience, which is reflected in the large number of scientific publications that he has been able to record. At the same time his work became fundamental for the development of the PhD program in Cellular and Molecular Biology of the University of Concepción, for the Society of Biochemistry and Molecular Biology, and for basic biological sciences in general.

A scientific life through kinases

Guixé Victoria [1]Laboratorio de Bioquimica y Biologia Molecular, Departamento de Biologia, Facultad de Ciencias, Universidad de Chile.

It has been a long road to the place where I am now. The road was sometimes rough, painful but most of the times full of joy and satisfaction. I start studying Biology, but very soon I realize that Biochemistry will be my passion. The Ph.D. program opens my heart and my brain to enzymology and the study of enzymes. Today, I am still interested in enzymes, but now I incorporate the structural and evolutionary aspects of them.

I am grateful to my mentors who were the founders of Biochemistry in Chile and from whom I learn a lot, and not only about science. Science in Chile is not easy but was even more difficult for a woman in the times I start my career. However, the message is yes you can. During my scientific life, I have had the opportunity to work with many distinguished professors as well as with many honorable kinases, such as hexokinase, phosphofructokinase, and pyruvate kinase, and more recently with ADP-dependent kinases. Today we are one of the very few groups in Chile that perform enzymology at its highest level. Also, we have implemented new methodologies, like ancestral enzyme reconstruction and protein crystallography. All these achievements have been possible due to the very talented students that we were lucky to train. Finally, the take-home message for the young students is that science is a multidimensional enterprise and that activities like teaching and work for others, (like in the SBMM) are also our responsibility.Fondecyt 1150460

Norberto A. Guzman's Professional Life

Guzman Norberto A. [1] Princeton Biochemicals, Inc., Princeton, New Jersey, US.

No one doubts that an ordinary person "can reach the stars" if hard work is fueled by persistence, determination, motivation, and passion to make a dream become a colossal masterpiece. It is true that certain amount of luck, collaboration, and just being at the right place and at the right time can help pave the way for success. However, one must truly believe in their own ideas, take daily actions, and ignore or solve the many barriers that for sure will be encountered to accomplish those goals.

I graduated as a biochemist from the School of Pharmacy and Biochemistry at the University of Concepcion. Then, I obtained a Master Degree in Biochemistry and Cell and Molecular Biology at the Medical College of Georgia, Augusta, Georgia, followed by a Ph.D. Degree at a joint program in Biochemistry offered by the University of Medicine and Dentistry of New Jersey, and Rutgers, The State University of New Jersey. The program was overwhelming, but the knowledge I obtained was priceless.

Subsequent to obtaining my Ph.D., I worked at Mount Sinai School of Medicine in New York City in clinical biochemistry. Next, I joined Roche Diagnostic Systems and the biotechnology sector at Hofmann-La Roche Pharmaceuticals in Nutley, New Jersey. Then, I worked at Johnson and Johnson Pharmaceuticals in Raritan, New Jersey, and a food science corporation based in Japan.

Details of my professional academic, pharmaceutical, and entrepreneurial activities will be presented at my seminar, given emphasis to innovation and creativity.

http://scholar.google.com/citations?user=n1w9kO8AAAAJ&hl=en&oi=ao
http://patents.justia.com/inventor/norberto-a-guzman

The power of feedback between professors and disciples on research and teaching

Slebe Juan C. [1], Asenjo Joel L.[1], Concha Ilona I.[1] Bioquímica y Microbiología, Ciencias, Universidad Austral de Chile, Valdivia, CL.

The aim of this presentation is to summarise key studies from almost 50 years in science as student and professor and discuss their implication on enzyme regulation. I will try to restrict myself to the studies on fructose 1,6-bisphosphatase isoenzymes, but since life is a culmination of several serendipities, I will also talk about hexokinases and aspartate amino transferases. When I traveled from the University of Concepción to Santiago in 1968, to join Dr. Niemeyer´s laboratory, I remembered an old tradition: students usually spend a long time with their mentor to learn. Through this presentation I express my gratitude to the professors who taught me in the first 10 years of my academic training: Drs. Hermann Niemeyer, Tito Ureta and Marino Martínez Carrión; and also to students and colleagues with whom I have worked in my career. I will also try to liven up with some experiences of academic life. As in the geographical world, the explorers who survive and become successful are those who are well trained, who have enough courage and who can overcome difficulties with a good sense of humor. We find we are ready to be on the road when we get the approval from our mentors and every challenge we encounter in life is a fork in the journey. One has to choose which way to go, taking on the challenges and devoting yourself to a life of learning and achievements and this can be the inspiration to many.

(Acknowledgements: UACh; CONICYT; FONDECYT; FONDEQUIP; FONDEF; AECI; MECESUP).

Dr. Roxana Pincheira is Biochemist from the University of Concepcion. She performed her undergraduate thesis under direction of Dr. Isolde Rudolph (Neurochemistry), and then moved to Santiago and worked for two years as a Research Assistant in the Pontificia Universidad Catolica. During this period she worked under the supervision of Dr. Gonzalo Bustos (Neurochemistry) and Dr. Paulina Bull (Molecular Biology). She obtained her Doctoral Degree in Biomedical Sciences from the University of Chile (2000), working on the identification and characterization of the major subunit of eukaryotic initiation factor 3, and its involvement with cancer. Her PhD thesis was under the direction of Dr. Jian Ting Zhang from the University of Texas Medical Branch (UTMB) through a Joint Graduate Program between Universidad de Chile and UTMB. After graduation she worked as a postdoctoral fellow in the laboratory of Dr. David Donner (Protein Signaling and cancer) at Indiana University-Purdue University Indianapolis (IUPUI) and in the Surgery Oncology Laboratory (Neurotrophin signaling and oncogene-tumor suppressor network) at the University of San Francisco California (UCSF), where she was appointed as Assistant Researcher. Since 2010 she is working as an Associate Professor of the Biochemistry and Molecular Biology Department at Universidad de Concepcion. Dr. Pincheira's research is aimed at understanding the molecular basis of cancer; currently her group investigates the regulation and function of SALL2, a transcription factor associated with Coloboma and several types of cancer. The Pincheira's group has demonstrated that SALL2 plays a key role in the cellular response to stress, and in cell cycle regulation, which together supports a tumor suppressor role for SALL2. The knowledge of the molecular bases of cancer, and in the specific the understanding of SALL2 function under different genetic contexts, including its p53 - independent functions is crucial for the rationale of cancer treatments and the design of future antitumor drugs. Since 2011 Fondecyt has continuously funded her research. During 2011-2016 Dr. Pincheira was the Director of an institutional regional project aimed at advancing biomedical sciences in the Bio Bio Region. She is currently the Scientific Director of CREAV (Centro Regional de Estudios Avanzados por la Vida). Since 2012 she has been the President of the Bioethics committee from the Faculty of Biological Sciences. Dr. Pincheira has mentored several undergraduate thesis (Biochemistry, Bioengineering and Biology) and graduate thesis from Master and PhD programs at University of Concepcion. Finally, since 2010 she is an active member of the Chilean Biochemistry Society, and acted as the Bio Bio regional director during 2011-2012.

Dr. Juan Olate. Dr. Juan Olate's journey is a very interesting one. After finishing high school he entered to Aviation School in Santiago. There, he become passionate about flights and stayed for 5 years (1966-1970), obtaining the rank of Military Pilot after doing the courses in the Beechcraft T-34 "Mentor" and Cessna T-37 instructional aircraft. In a span of eight months (July 1970 - March 1971) he changed his military life for university life to embrace the career of Biochemistry at the University of Concepción (1971) having in mind to become a scientist. After graduating as a Biochemist (1977), he decided to take the academy path (teaching and research). He obtained a PhD in 1985 at the University of Chile (1981-1985), working under the mentoring of Dr. Jorge Allende (National Award of Natural Sciences, 1992). Between 1985-1987 he performed a post-doctorate at Baylor College Of Medicine, Texas Medical Center, Houston, USA (1985-1987) learning the nascent areas of Molecular Biology and Molecular Genetics. After his postdoctorate, Dr. Olate come back to the Universidad de Chile to the Biochemistry laboratory where he was previously trained to establish his first research laboratory group (1988-1993). Latter, he was contacted by the Dean of the Faculty of Biological Sciences from the University of Concepción who offers him the position of Associate Professor, with the task of establishing a Molecular Biology laboratory that would allow cloning, expressing and understanding the function of genes and that would serve at the same time as a formative unit for pre and post-graduate students of the biological research area. He accepted the offer and returned to the Universidad de Concepcion (1994). In this new and modern laboratory, using cutting-edge techniques, he continued for 21 years (1994-2015). Dr. Olate's research focused on the molecular mechanisms that allow communication between cells. During this period, he held several university administrative positions as Biochemistry Department Director, Director of PhD program in Molecular and Cellular Biology, President of the Biochemistry Society of Chile and was an active member of the study groups of CONICYT (1995-1997). In 2013, he was awarded the "Municipal Science Award", in recognition of his long scientific trajectory, and for his contribution in the Bio Bio region to the scientific knowledge about the function of genes and their relationship with pathologies, and for training and scientific knowledge dissemination. Over the years he mentored more than 30 professionals, 15 doctors, published more than 60 papers in several high impacts journals and presented at numerous international conferences. He also was investigator in five International Cooperation Projects (Human Frontier with Japan and USA, ECOS with France, 3 NIH with USA). In March of 2015, Dr. Olate decided to leave the academy, hung the pipettes and retired. He now is happily enjoying reading, gardening, astronomy and his new house near Termas de Chillán, in a small town located 82 km east of city of Chillán.

Dr. Victoria Guixé obtained the Biology degree from Facultad de Ciencias, Universidad de Chile in 1978. She performs her undergraduate thesis on "Muscle hexokinase: Compartmental Aspects and Cellular Localization" under Dr. Tito Ureta's direction. She continues her scientific training by performing Ph.D. in Biology at Facultad de Ciencias working on the kinetic mechanism and regulation of wild type and mutants forms of *E. coli* phosphofructokinases, under the direction of Dr. Jorge Babul. After finishing her Ph.D., Dr. Guixé moved to P. Universidad Católica de Chile, where she performed teaching activities and scientific research with Dr. Alejandro Venegas working on yeast pyruvate kinase. Then, she returned to the Facultad de Ciencias to join Dr. Ureta' s group. She actively participates in elucidating an indirect pathway for glycogen synthesis in frog oocytes and other key findings related to the *in vivo* operation of glycolysis and gluconeogenesis in this system. Her research had been focused on the importance of the *in vivo* enzyme regulatory properties using as a model study *E. coli* strains expressing phosphofructokinases with different regulatory characteristics. Currently, her research is aimed to understand how along evolution, enzymes from the archaeal family of ADP-dependent kinases have acquired a vast range of molecular adaptations to thrive in many extreme environments. She has performed research stays at Harvard Medical School, Universidad de Barcelona, and Columbia University. Over the years at Universidad de Chile she mentored numerous undergraduate and graduate students, published more than 50 papers in high impacts journals, book chapters and books, and presented at numerous international conferences. She has been actively involved in teaching as well as in administration duties. She has been President, Secretary and Treasurer of the Sociedad de Bioquímica y Biología Molecular de Chile, Director of the Ph.D. program in Biología Molecular Celular y Neurociencias from University of Chile, Director of Biology 3 study group from Fondecyt, external review for the academic test for admission to the University (PSU), among others. Because of her multidisciplinary work, and complete academic career, in 2009 Dr. Victoria Guixé, the women scientist and mother of two daughters received the "Woman Generation Siglo XXI Distinction of the University of Chile".

Dr. Leonardo Guzmán. Dr. Guzmán is currently the Director of the Department of Physiology of the Faculty of Biological Sciences of the University of Concepcion. His area of primary specialty was the signal transduction, to then derive in the analysis of the interactions of these molecular systems with the function of ion channels and drug design. Dr. Guzmán received his degree in biochemist in the University of Concepcion in 1998, after completing his undergraduate thesis in the Molecular Genetic Laboratory directed by Dr. Juan Olate, in the Department of Biochemistry and Molecular Biology of the University of Concepcion. Then he did his doctoral studies under the guidance of the same Dr. Olate. In his thesis, advances were made in the knowledge of molecular aspects of the signal transduction associated with the meiotic maturation process of the Xenopus laevis oocyte. Later, he joined the Neurophysiology Group led by Dr. Luis Aguayo for the realization of a postdoctoral project in the Physiology Department of the University of Concepcion. Here, he participated in the determination of molecular aspects of the regulation of the glycine receptor by the transduction protein Gbg. In parallel, Dr. Guzmán joined the academic plant of this department, and integrated the scientific and academic work of the faculty of biological sciences. In this way, he obtained a FONDECYT Initiation project in 2007. Then, he has been awarded whith two other regular FONDECYT projects and a FONDEF IDeA project. During the years 2012 to 2015 he was the Director of the Doctorate in Biological Sciences area Cell and Molecular Biology of the University of Concepcion, being also director of a MECESUP project for the improvement or update of different aspects of this postgraduate program. Its scientific contribution has focused on the design of small molecules that inhibit the potentiation of ethanol on the glycine receptor, carried out from the conceptual and bioinformatic to the demonstration in in vitro and in vivo models of animal behavior. On the other hand, it has developed a line of research in the study of drug nanocarriers and the molecular interactions that determine their functionality in biological systems. Dr. Guzmán is currently the Regional Director for the Chilean Pharmacology Society (SOFARCHI) and an active member of the Chilean Biochemistry Society and its scientific productivity includes the publication of 33 scientific articles, six of them as author of correspondence or first author, 2 patents and numerous conferences and posters in national and international symposiums. He has guided the thesis of 10 undergraduate students, mainly in Biochemistry and Bioengineering, 4 master students in Physiology and Biochemistry, and 3 PhD students in Cellular and Molecular Biology.

Dr. Norberto Guzman. Dr. Guzmán is currently Chief Scientific Officer at Princeton Biochemicals Inc., Princeton, New Jersey, U.S.A. Dr. Guzman's expertise is primarily in biomedicine and biotechnology with emphasis in protein biochemistry and immunochemistry. At present, his main research interest is in the understanding of the function of newly-formed and/or post-translational-modified proteins in inflammatory processes, and the finding of therapeutic agents, such as natural and synthetic proteins/peptides, aimed to alleviate chronic inflammatory diseases. For several years, Dr. Guzman has developed immunoaffinity-analytical separation instrumentation and methodologies for the quantification, identification and characterization of proteins and peptides of relevance to the clinical laboratory, pharmaceutical industry and foodnutraceutical industry (e.g., erythropoietin, antibodies, and collagen). He also has used multiple crosslinking methods to generate scaffold of collagen with other natural or synthetic polymers to generate collagen-based biomaterials for use in tissue engineering applications or microencapsulation technology. Dr. Guzman received a B.Sc. degree in biochemistry (clinical biochemistry) from a Joint Undergraduate Program of the University of Concepcion and the University of Chile, Santiago, Chile; a M.Sc. degree in biochemistry (cell and molecular biology) from the Medical College of Georgia, Augusta, Georgia, U.S.A.; and a Ph.D. degree in biochemistry (protein biochemistry) from a Joint Graduate Program of the University of Medicine and Dentistry of New Jersey-Robert Wood Johnson Medical School (formerly Rutgers Medical School) and Rutgers, The State University of New Jersey, New Brunswick, New Jersey, U.S.A. Dr. Guzman has worked for the last 30 years in academic medical institutions, diagnostic and pharmaceutical companies, including Mount Sinai School of Medicine, Roche Diagnostic Systems, Hoffman-La Roche, and Johnson & Johnson. He also has worked in a collagen food-nutraceutical industry. Dr. Guzman is the author or co-author of more than 130 scientific publications, including manuscripts, patents and book chapters. He has delivered over 300 oral presentations in Europe, the Americas, the Far East, and Australia. According to Google Scholar Citations, Dr. Guzman's publications have been cited more than 5200 times, having an h-index of 38, and an i10 index of 69. One publication alone has more than 1300 citations. Nine figures of his publications have appeared on the front cover of prestigious scientific journals and books. One presentation at Google Headquarters in New York City has been viewed more than 1900 times (https://www.youtube.com/watch?v=1QnTrcYWk-o). He is the editor of 2

two widely referenced books on the subject of capillary electrophoresis and collagen prolyl hydroxylase. Dr. Guzman holds numerous worldwide patents on capillary electrophoresis and microchip technology, and his accomplishments have been recognized by being the recipient of many national and international awards in science and technology innovation. Dr. Guzman is a member of several international scientific organizations. He serves on the editorial board of Electrophoresis (European journal), and the Journal of Liquid Chromatography and Related Technologies (American journal). Dr. Guzman is the founding editor of the Journal of Capillary Electrophoresis and Microchip Technology and one of the pioneers in this field. He is also the founder of the international symposia series known as LACE (Latin-American Capillary Electrophoresis).

Juan Carlos Slebe was born and educated - primary and secondary school - in Santiago, Chile. He went on to University of Concepción and after studying five years ("Licenciatura") he returned to Santiago to Dr. Hermann Niemeyer's laboratory because he had become interested in the regulatory properties of enzymes and their roles in metabolic pathways. His undergraduate thesis was on Glucose-phosphorylating Isoenzymes in the liver of avian, reptiles and amphibian and was directed by Dr. Tito Ureta. He obtained the Biochemist title at the University of Chile and has an academic career that spans nearly 46 years, from his first paper, a comparative study on liver hexokinases of vertebrates, until his last, in which is demonstrated that polyglucosan molecules induce mitochondrial impairment and apoptosis in germ cells without affecting the integrity and functionality of Sertoli cells. He started his academic carrier at the Department of Biochemistry, Faculty of Medicine, University of Chile (1970) and after eight years he moved to the Institute of Biochemistry, Faculty of Sciences, at the Austral University of Chile (Associated Professor) where he has been until now (Distinguished Professor). In 1974, Professor Marino Martinez-Carrión invited him to spend three years at University of Notre Dame, Indiana, USA and during his time there - as Staff Faculty Fellow - acquired an interest in the mitochondrial and cytosolic aspartate transaminase isozymes, the subject of his research in this period, with a series of papers on the application of 19F-NMR to its kinetic and thermodynamics followed by a paper on the stereochemistry of the transamination. In 1978 his attention turned to Fructose 1,6-bisphosphatase (FBPase) isozymes, using this key gluconeogenic protein as a model for studies on structure-function relationships in a regulatory enzyme, and rapidly his laboratory became one of the leaders in the study of the mechanisms of regulation of FBPase which is considered a new target for the control of diabetes. At the same time he obtained his Doctoral Degree at the University of Chile (1985). His research group has made significant contributions in the understanding of mechanisms involving FBPase in the regulation of the metabolism of glucose not only during normal healthy processes but also during abnormal states which lead to the high glucose levels observed in type 2 diabetes and the L-lactic acid acidosis observed in autism. He has been involved in several PhD programs and mentored the thesis of many undergraduate and graduate students that now are doing research in academic and/or applied fields at national and international prestigious institutions. Despite a heavy teaching load and a large output of research papers, he found time to be involved with administration at University Austral of Chile, becoming: Director of School of Sciences (1980 – 1987), Director of Research (1988 – 1990), President of the Central Commission for Doctoral Studies (1992-1994), Chairman of the Biochemistry Institute (1994-2006), Member of the Central Commission for Academic Evaluation (1995-2001), Member of the Directive Board – "Junta Directiva" - (1999- 2002) and Academic Member of the Board – "Directorio" – (2009 – 2017). He was President of the Biochemistry and Molecular Biology Society of Chile (1999 – 2000) and also was member of: the Study Section Biology 3 – FONDECYT – (1997-2000), Technical Committee of Biochemistry (Comisión Nacional de Acreditación de Pregrado; Ministerio de Educación (2000- 2003)) and the Committee Biology 2 (Comisión Nacional de Acreditación de Postgrados; CONICYT-Ministerio de Educación (2000- 2005).

Symposium 6

Understanding the epitranscriptome.
Chairs: Dr. Alvaro Glavic, Universidad de Chile Faculty of Sciences, Chile and
Dr. Ricardo Soto-Rifo, Universidad de Chile Faculty of Medicine, Chile

The RNA modification *N6*-methyladenosine regulates *Flaviviridae* virus infection

Horner Stacy M [1] Molecular Genetics and Microbiology, Duke University Medical Center, Durham, US.

RNA-based regulation of viral genomes is known to play a fundamental role in their lifecycles. We have recently identified the molecular mechanisms of how the dynamic RNA modification *N6*-methyladenosine (m^6A) regulates infection by hepatitis C virus (HCV), a positive-sense stranded RNA virus of the *Flaviviridae* family. Viruses within this family include both established global pathogens, such as HCV, and emerging viruses, such as Zika virus (ZIKV). These viruses cause a range of disease pathologies, including chronic liver disease, microcephaly, and high fever. We have found that m^6A marks the positive-sense RNA genome of several viruses in the *Flaviviridae* family, including HCV, ZIKV, dengue virus, yellow fever virus, and West Nile virus. In addition, we have found that m^6A regulates their replicative life cycles. Interestingly, *Flaviviridae*infection also induces broad changes in the m^6A "epitranscriptome" of host mRNAs. We are currently defining how m^6A deposition on specific transcripts is regulated during viral infection, what this means for the fate of the modified transcripts, and ultimately, how these processes regulate viral infection. Taken together, our work reveals that m^6A is a conserved regulatory mark on the RNA genomes of viruses with the *Flaviviridae* family, and it suggests that m^6A provides an additional layer of gene regulation to the virus-host interactions that regulate infection. Ultimately, a detailed understanding of these interactions at the m^6A interface will uncover novel strategies to develop antiviral therapies to target this RNA regulatory control that is exploited by RNA viruses for their replication.

Epitranscriptomic regulation of HIV-1 genomic RNA packaging

Soto-Rifo Ricardo [1] Laboratorio de Virología Molecular y Celular, Programa de Virología, ICBM, Facultad de Medicina, Universidad de Chile, Santiago, CL.

The HIV-1 genomic RNA (gRNA) plays two critical roles in the cytoplasm of infected cells by acting as the mRNA for the synthesis of the structural proteins Gag and Gag-Pol and the viral genome that is packaged into assembling viral particles. It was recently shown that the gRNA is decorated with N6-methyladenosine (m6A) residues mainly located at the 5´- and 3´-UTR. Recognition of methylated adenosines by the cytoplasmic m6A readers, YTHDF1-3, induces degradation of the incoming gRNA early during infection (i.e., when acting as the viral genome) but also increases gRNA levels and Gag synthesis at late stages of viral replication (i.e., when acting as mRNA) suggesting that both functions of the gRNA are differentially regulated by m6A. Here, we report that hypermethylation of the gRNA interferes with its incorporation into viral particles. Interestingly, m6A-seq analyses revealed that, compared to the intracellular gRNA, the virion-associated gRNA lacks m6A within the 5´-UTR suggesting that methylation/demethylation of this region regulates gRNA packaging. *In vitro* analyses revealed that hypermethylation of the 5´-UTR results in specific structural changes and reduced dimerization, two features involved in the regulation of gRNA packaging. Further analyses revealed that A198 and A242 are the methylated adenosines involved in the m6A-mediated regulation of gRNA packaging.

Together our data strongly suggest that, contrary to what was proposed 20 years ago, the HIV-1 gRNA is not indistinctly used as mRNA and genome since only those molecules lacking m6A residues at the 5´-UTR are selected by Gag to be incorporated into viral particles.

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Levels of t6A modification in tRNAs modulate translation initiation, TOR kinase activity and growth

Glavic Alvaro [1], Eggers Cristian[2], Contreras Esteban[1], De Crecy Lagard Valerie[3].[1]Departamento de Biología, Facultad de Ciencias, Universidad de Chile. [2]Max Planck Institute, Munster, DE. [3]Department of Microbiology and Cell Science, University of Florida, Florida, US.

N6-threonylcarbamoyl-adenosine (t6A) modification is made by the Threonylcarbamoyl transferase complex (TCTC complex) at position 37 in tRNAs that decode ANN codons, this includes the eukaryotic initiator tRNA, tRNAiMet. Yeasts lacking t6A synthesis, such as Tcs3p (Kae1p) or Tcs5p (Bud32p) mutants, display translation and growth defects. Their counterparts in Drosophila are also required for t6A synthesis and their deficiencies show severe translation problems wtih strong reductions in cell and animal size. Moreover, just the proportion of t6A-modified tRNAiMet behaves as a restrictive factor for growth. Accordingly altering the fraction of t6A-modified tRNAiMet, by expressing an unmodifiable tRNAiMet or changing the levels of Tcs3, regulates TOR activity and influences cell and animal growth in vivo. In addition, variations in t6A modulate translational initiation in a translation reporter construct based on one of the TCTC complex subunits. These findings reveal an unprecedented relationship between the proteome, the translation machinery and TOR kinase, where translation selectivity and efficiency, defined by the availability of t6A-modified tRNA, assist to define protein homeostasis and growth parameters in mutlicellular organisms.

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Role of RNA phospho-methylation in gene expression regulation and cancer

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The 5' ends of RNA molecules are particularly important for determining their fate. In addition to the canonical mRNA capping, a chemically simpler 5' end modification by O-methylation occurs directly on 5' phosphate ends, either on the gamma-phosphate of nascent tri-phosphorylated snRNAs, or on the alpha-phosphate of processed monophosphate RNAs, including precursor microRNAs and tRNAs. These methylations are carried out by the Bicoid Interacting 3 (BIN3) family of methyltransferases which are conserved from fission yeast to humans. During the Symposium, I will report our findings about the mammalian homologs of these important enzymes and discuss their roles in gene expression regulation and cancer.

Dr. Stacy Horner. Dr. Stacy Horner received her BA in Biochemistry and Chemistry from Gustavus Adolphus College in St. Peter, MN in 2001. As an undergraduate, she had research experiences with Dr. J. Ellis Bell at Gustavus and Dr. Thomas R. Broker at the University of Alabama, Birmingham. She entered graduate school at Yale University in the Microbiology graduate program where she worked with Dr. Daniel DiMaio. Her graduate research focused on human papillomavirus (HPV) regulation of cellular growth control pathways and also on designing strategies to eliminate HPV DNA from cervical cancer cells. She received her Ph.D. in Microbiology from Yale in 2007.

Building on her interest of virus/host interactions, Dr. Horner joined the laboratory of Dr. Michael Gale Jr. at the University of Washington for her postdoctoral training in 2007. Her postdoctoral research focused on understanding innate immune regulation by hepatitis C virus (HCV), a global human pathogen. During this time, she identified the mitochondrial-associated ER membrane (MAM; a subdomain of the ER located adjacent to mitochondria) as a membrane platform that organizes innate immune signaling and also as the intracellular site of immune regulation by HCV. Dr. Horner's postdoctoral research was supported by the Irvington Institute Fellowship Program of the Cancer Research Institute.

Dr. Horner joined the faculty of the Molecular Genetics & Microbiology and Medicine departments at Duke University Medical Center in 2013. Her laboratory is interested in understanding the cell biology of antiviral innate immunity and how RNA viruses, including hepatitis C virus, evade innate immunity. Overall, her research uses a interdisciplinary approach, combining techniques from cell biology, virology, biochemistry, and systems biology to reveal the viral and host strategies that coordinate and regulate innate immunity, with the ultimate goal of developing new immunomodulatory strategies for virus treatment and prevention.

Dr. Ricardo Soto-Rifo. Dr. Soto-Rifo has been always interested in the molecular and cellular mechanisms controlling gene expression in Eukaryotes with a special emphasis in RNA viruses as study models. Biochemist from Universidad de Santiago de Chile, Dr. Soto-Rifo did his undergraduate thesis at the Animal Virology Laboratory (currently the Centre of Acuiculture Biotechnology) under the supervision of Dr. Ana María Sandino studying the mechanisms of translation initiation employed by the Infectious Pancreatic Necrosis Virus (IPNV). Then, he moved to Lyon, France where he obtained a Master in Sciences degree from Université Claude Bernard Lyon-1 in 2006 and then a Ph.D in Life Sciences from Ecole Normale Supérieure de Lyon (Université de Lyon) in 2010. He worked at the Human Virology Department (currently the International Center for Infectiology Research) under the supervision of Dr. Théophile Ohlmann on the translational control of the HIV-1 and HIV-2 genomic RNA. During his post-doctoral training at Dr. Ohlmann`s lab, Dr. Soto-Rifo worked on the remodeling and localization of the messenger ribonucleoprotein complexes (mRNPs) containing the HIV-1 genomic RNA by analyzing the role of the DEAD-box RNA helicase DDX3 in these processes. In 2013, he moved to the Virology Program, Biomedical Sciences Institute at Universidad de Chile Faculty of Medicine to start his own laboratory. Since, Dr. Soto-Rifo has established his research group, which is mainly focused in understand the mechanisms governing HIV and Respiratory Syncytial Virus (RSV) gene expression.

Dr. Alvaro Glavic. Dr. Alvaro Glavic is a Biochemist and PhD in Molecular, Cellular Biology and Neuroscience (University of Chile), with 20 years experience in developmental biology and genetics using Xenopus, Zebrafish and *Drosophila*. Alvaro did his undergraduate thesis in Biochemist in 1997 with Dr. Roberto Mayor at University of Chile studying the role of Iroquois genes in the formation of *Xenopus* nervous system. This work was published in EMBO J and awarded by the Chilean Society for Cellular Biology as the best undergraduate or master thesis in 1998. He obtained a CONICYT and the Fundación Andes scholarships to course his PhD in Molecular, Cellular Biology and Neuroscience. In 1998 he received the Hermann Niemeyer Medal to the best PhD student awarded by the Chilean Society of Biochemistry and Molecular Biology. In 2000 he was visiting investigator at Sir John Gurdon´s lab at the Wellcome Trust Institute, UK. In 2002 he finished his doctoral thesis where he further explored the role of Iroquois complex in vertebrate development. In 2002 he obtained an EMBO long-term fellow to be trained in *Drosophila* genetics with Antonio Garcia-Bellido at Centro de Biología Molecular Severo Ochoa in Spain. After this period, he got a FONDECYT grant to finance a second postdoc and in 2005 he joined Faculty of Sciences (U de Chile) as Assistant Professor. His work was recognized in 2007 by the Academia de Ciencias de Chile and was invited to be part of the program “Cientificos de Frontera”. His curiosity and line of research on tRNA modification and its role in multicellular organisms has attracted several talented students, which have received twice the Federico Leighton award for the best undergraduate and graduate theses in 2013 and 2015. Since 2014 Alvaro is Associate Professor at Faculty of Sciences and from 2016 he is director of a ANILLO grant to investigate the transcriptional, epigenetic, morphological and behavioral effects of developmental undernourishment in *Drosophila*.

Dr. Blerta Xhemalce received her Ph.D. at the Pasteur Institute in Paris, France and performed her postdoctoral training at the Gurdon Institute at the University of Cambridge in the United Kingdom. The focus of her research is to unravel how gene expression is regulated by epigenetic modifications of chromatin and RNAs. The ultimate goal of her lab is to discover novel enzymes, writers, or erasers of such modifications that are potential targets for therapeutic drugs that could alleviate human diseases including cancer. To achieve this goal the Xhemalce lab uses a diverse array of approaches, including cellular and molecular biology, biochemistry, and mass spectrometry. The Xhemalce lab is also committed to supporting its members to achieve their academic goals and to think outside the box.

Symposium 7

Symposium Cono-Sur: The role of the microbiome from multiple perspectives.
Chair: Juan Ugalde, ubiome

Microbial complexity of polyextreme ecosystems

Cristina Dorador[1,5], Yoanna Eissler[2], Martha Hengst[3,5], Verónica Molina[4].[1]Laboratorio de Complejidad Microbiana y Ecología Funcional, Instituto Antofagasta & Departamento de Biotecnología, Universidad de Antofagasta, Antofagasta, Chile. [2]Centro de Investigación y Gestión de Recursos Naturales, Instituto de Química y Bioquímica, Facultad de Ciencias, Universidad de Valparaíso, Valparaíso, Chile. [3]Departamento de Ciencias Farmacéuticas, Universidad Católica del Norte, Antofagasta, Chile. [4]Departamento de Biología & Programa de Biodiversidad, Facultad de Ciencias Naturales y Exactas, Universidad de Playa Ancha, Valparaíso, Chile. [5]Centre for Biotechnology and Bioengineering (CeBiB), Chile.

Microbial ecosystems could be defined as complex systems considering the existence of entities (microbial species) in a hierarchy of interrelated organizational levels, including in this case, relationships between microbial species, forcing environment conditions, viruses, spatial and temporal variability and local chemistry. Microbial communities has been studied in aquatic ecosystems in northern Chile using mainly culture-independent methods, starting in the middle of 2000. Microbial communities are in general, dominated by Bacteria (Proteobacteria, Bacteroidetes, Firmicutes). Interestingly, different studies report the presence of unique microbial communities in each of the studied aquatic systems and the presence of multiple bacterial phyla. The development of next generation techniques (NGS) together with metagenomics and single-cell genomics approaches has open a new window of knowledge about microbial diversity and function in natural environments. Recent studies made in Salar de Huasco, a polyextreme ecosystem located at 3800 masl in the Chilean Altiplano, has detected a high microbial diversity responding to daily cycles of solar radiation, where in some samples, up to 60% of the bacterial phyla are members of the rare biosphere including Candidate Phyla Radiation (CPR) and other undescribed and uncultivated bacterial lineages. Network analysis exhibited a clear compartmentalization of bacterial groups according with each sample, as such every site and sample have a unique bacterial core. Recent results detected changes in viral abundances in a temporal scale in Salar de Huasco, revealing a strong variation in picoplankton and viral abundances during the study. Viral abundance ranged between 8.44 ×105 (site H0 spring, dry season) to 8.88 ×108 (site H0 pond, wet season) VLP/ml. Despite the high level of bacterial phyla at low relative abundance the mechanisms explaining such levels of diversification still unclear. Here, we propose that mechanisms of diversification (e.g. Horizontal gene transfer and diversity of CRISPR-Cas spacers) in extreme environments fluctuate according to the frequency and intensity of forcing environmental conditions.

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City-wide metagenomics uncover antibiotic resistance reservoirs in urban beach and sewage waters

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Tons of human feces are evacuated daily through the municipal sewage systems and could be used to get an unprecedented coarse-grain, population-level overview of the gut microbiota of millions of people in a single shot. The composition of the gastrointestinal microbiota has been associated with human health and disease, and recent studies demonstrated that sewage bacteria reflect the gut microbiota. Here, we used city-wide shotgun metagenomics to study the microbiota present in the sewage system and beaches of Montevideo, the capital city of Uruguay, focusing on the characterization of the environmental resistome. We found a higher abundance and diversity of antibiotic resistance genes (ARGs) in sewage than in beach samples, and these genes coded for many well-known antibiotic classes like betalactams. Interestingly, we found extensive presence of carbapenemases and extended-specrtrum betalactamases (like TEM or OXA) which are frequently found in nosocomial isolates in Montevideo. Moreover, ARGs found in the sewage are frequently found in bacterial plasmids from enterobacteria like *Klebsiella pneumoniae* or *Escherichia coli* which, among others, were identified as sewage biomarkers. This evidence an increased ARGs mobilization potential between sewage enterobacteria. Additionally, the presence of class I integrons was exclusively found in sewage samples, highlighting this environment as a reservoir of clinically relevant horizontal gene transfer platforms, which could contribute spreading antibiotic resistance to the community. In summary, our approach resulted useful to recover gastrointestinal pathogens coding for diverse antibiotic resistance mechanisms, supporting the future implementation of non-invasive, metagenomic surveillance to inform public health on the emergence of microbiological hazards at the population level. Agencia Nacional de Investigación e Innovación (ANII), Uruguay. MetaSUB, US.

An overview about xenobiotics metabolism mediated by the human gut microbiota. How your microbiome modify drugs or dietary compounds?

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Humans consume a large number of small compounds that are foreign to the body, the so-called xenobiotics, which include dietary components, environmental chemicals, and pharmaceuticals. The trillions of microbes that inhabit the human gastrointestinal tract encodes a broad diversity of enzymes, which can modify the structures of such compounds including lipids, proteins, polysaccharides and phytochemicals, altering their pharmacokinetics and pharmacodynamics. Those modifications might produce either beneficial or detrimental effects on the human health. As an example, at least 40 therapeutic drugs have been reported to be metabolized by gut microbes. The microbiome might have the potential to, at least partially, explain the interindividual variability in drug response and variability in drugs secondary effects. However, specific microbes and enzymes that mediate those reactions are yet not fully described. Thus, to go deeper on these reactions will allow us to identify both specific targets for manipulation and diagnostic markers that can be incorporated into clinical studies. In this presentation, we aim to provide an overview of the gut microbiota effects on dietary compounds and pharmaceuticals. We also provide some examples of our work about identifying bacteria producing detrimental metabolites (TMA) and also predicting xenobiotics metabolism mediated by microorganisms and enzymes, aided by machine learning and cheminformatics tools. This might allow in the future to generate a platform for personalized dietary recommendations, precision medicine, inform toxicology risk assessment, and improve drug discovery and development.

uBiome Inc.

Dr. Juan Ugalde is a computational microbiologist, specializing in the use of omics approaches to study microbial diversity in different ecosystems. Currently, he is Director of Bioinformatics in the microbiome company uBiome. He obtained his PhD in 2014, from the Scripps Institution of Oceanography, at the University of California, San Diego, studying the diversity of hypersaline microbial communities using metagenomics approaches. He returned to Chile in 2014, as an Assistant Professor at the Center for Genomics and Bioinformatics, Universidad Mayor. Juan's research uses genomics, bioinformatics, and data sciences approaches to understand the diversity, evolution, and adaption of microorganism to their environments. Among his work, he has worked in comparative genomic analysis of different microbial groups, including producers of natural products such as *Salinispora*, Chilean strains of *Staphylococcus aureus*, among other groups. The last few years he has been active in the field of microbiome studies, taking part in collaborations to understand how the urban microbiome, as well as taking part in several studies of the human microbiome.

Dr. Cristina Dorador is a microbial ecologist, who specializes in the microbial ecology of extremophiles and extreme environments. Currently she is an Associate Professor at the Universidad de Antofagasta, Chile. Cristina did her doctoral research in the Max Planck Institute for Limnology in Plön, Germany and was awarded her PhD in Microbiology from the University of Kiel, Germany (2007). She returned to Chile in 2008 and established the Laboratory of Microbial Complexity and Functional Ecology at the Universidad de Antofagasta. Cristina's research is based on the study of the diversity and function of microorganisms in natural environments, with a special focus in the adaptation of microorganisms to extreme conditions of Bacteria and Archaea in aquatic and terrestrial environments of north and southern Chile. Applied research in Cristina's group is based in the searching of bioactive compounds with antimicrobial and anticancer properties and skin protection (Atacama Cream) from bacteria from the Atacama Desert. Cristina is a Frontier Researcher of the Chilean Academy of Sciences, Young ISME Ambassador for Chile and represented Chile as young scientist in the book: "Young Scientists: a bright future for the Americas" published by IANAS (Interamerican Network of Academies of Sciences). She is the principal investigator on a series of national (Fondecyt; Fondef; PIA-CONICYT) and international (European Union) grants, and participates in national grant assessment panels (Fondecyt, INACH). Cristina is also a scientific assessor for scientific academies and for PAR Explora Antofagasta- CONICYT.

Dr. Gregorio Iraola is a computational microbiologist. His posgraduation studies started with a Master in Bioinformatics before obtaining a PhD in Biology focused on microbial genomics at the University of the Republic and the Institut Pasteur Montevideo in Uruguay. Since 2017 he is a staff Associate Researcher at the Bioinformatics Unit in the Institut Pasteur Montevideo. Also, since 2015 he has been a visitor scientist at the Wellcome Trust Sanger Institute and the Institut Pasteur Paris. From Uruguay, he leads several research lines aiming to develop and apply computational approaches for studying the microbial world. His work has been focused on understanding the evolution of viruses that affect livestock and pets using phylodynamics; and fundamentally on uncovering the evolutionary forces shaping the genomes of zoonotic bacteria like *Campylobacter*, *Leptospira* and *Mycobacterium*. Among his ongoing projects stands out a joint Latin American effort to study the population dynamics of *Clostridium difficile* using genomic epidemiology approaches. Recently, he became interested in complementing his work in pathogenomics with microbiome approaches, specifically by applying city-scale metagenomics to analyse antibiotic resistance dynamics in enterobacteria from urban environments. More recently, he got involved in science communication as a columnist aiming to bring microbiology and genomics closer to the society.

Dr. Valeria Márquez Miranda is currently team leader of the Drug Development group in the microbiome start-up company uBiome. She received her PhD in Biotechnology from Universidad Andrés Bello, for her work on the design and experimental testing of new nucleic-acid transfection systems based on dendrimers. This work was supported by Fraunhofer Chile Research and a grant for PhD thesis in the Industry (PAI-CONICYT). After that, she worked as a postdoctoral fellow in a project from Universidad Andres Bello along with the US Air Force, entitled "*Neuromorphic Inspired Science to Maximize Big Data Dynamic Problem Solving for Future Intelligence, Surveillance, and Reconnaissance Operations"*. Currently, her work focuses on microbiota-mediated metabolism of drugs, dietary compounds and xenobiotics, aided by machine learning and cheminformatics. Other areas of interest are computational biophysics, molecular dynamics simulations, drug design, computer-assisted design of nanoparticles, and also cell biology and physicochemical characterization.

Circulating exosomal miRNA signature in gestational diabetes mellitus influences glucose metabolism in placental cells

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There is increasing evidence that miRNA, which are enriched in small nanovesicles called exosomes, are important regulators of gene expression. In this study, we tested the hypothesis that circulating exosomes from women with gestational diabetes mellitus (GDM) carry a specific set of miRNAs which regulate genes associated with placental glucose metabolism. Exosomes were isolated from plasma obtained from normal glucose tolerant women (NGT; n=12) and women with GDM (n=12) pregnancies at delivery. Exosomal RNA was extracted and an Illumina TrueSeq Small RNA kit was used to construct a small RNA library. Gene target identification and gene ontology analysis for miRNAs was performed using the Ingenuity pathway analysis (IPA). The effect of exosomes on glucose metabolism in placental cells was assessed using a human glucose metabolism array. In plasma, a total of 44 miRNAs were upregulated in exosomes from women with GDM compared to NGT pregnant women ($p<0.005$). IPA showed that exosomal miRNAs isolated from women with GDM regulates the expression of placental genes associated with the glycolytic pathway including 6-phosphofructokinase and phosphopyruvate hydratase. Interestingly, exosomes from women with GDM increases the expression of placental genes associated with glycolysis and decrease the expression of genes associated with pentose phosphate pathway. After integration of the miRNA and mRNA data, we identified 74 differentially expressed exosomal miRNAs associated with the modulation of 10 potential target mRNAs in placental cells. This data suggests that circulating exosomes under diabetic conditions might modulate the placental metabolic state to enhance glycogen metabolism in GDM. This work is funded by Fondo Nacional de Desarrollo Científico y Tecnológico (FONDECYT 1170809)

New Members Session I

DNA wrapping as a major contributor to the stability of transcription initiation complexes

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DNA wrapping and bending are common processes in DNA-protein interactions, known to play a role in the initiation of transcription. DNA wrapping around RNA polymerase cannot be studied in detail with traditional biochemical techniques or Atomic Force Microscopy because it is difficult to separate the initial binding from the DNA wrapping. We used optical tweezers to induce mechanical unwrapping and re-wrapping of DNA in individual open promoter complexes (RPo) of *E. coli's* RNA polymerase interacting with the Lambda PR promoter. These appear as single cooperative transitions that occur near equilibrium under most experimental conditions tested. The length of DNA involved in wrapping measured with the optical tweezers is coherent with a linear projection from our previous reports from AFM imaging and with new reports from FRET measurements and from electron microscopy. We show that DNA wrapping is a spontaneous process with a net change in free energy of ~ -13.3 kcal/mol, nearly that of the total change in free energy of RPo complex formation. This amount is modified by the ionic strength of the medium, or by adding the allosteric transcription regulator ppGpp. By introducing mutations upstream the promoter, we demonstrate that DNA wrapping is influenced in energy, dynamics and extension by DNA sequence but does not require a specific binding motif.

Cell-specific epigenomic features in the adaptive immune system uncover DNA regulatory elements

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DNA methylation regulates transcription by changing the binding affinity of chromatin remodeling complexes and transcription factors through the addition of a methyl group to cytosine residues. This covalent DNA modification can be reversed via a replication-dependent or a replication-independent mechanism. The latter, termed active DNA demethylation, features the oxidation of 5-methylcytosine (5mC) to 5-hydroxymethylcytosine (5hmC), which might regulate transcription but whose role has not been fully understood, partly due to technical limitations in its detection. We mapped for the first time the genome-wide distribution of 5mC and 5hmC at single-base resolution using oxidative bisulfite sequencing in primary, quiescent, mouse CD4+ T and B lymphocytes, to avoid confounding effects from cell proliferation and mixed cell populations. In addition, we profiled the whole-genome distribution of a variety of histone marks and the total transcriptome in these cell types. Comparative epigenomics and transcriptomics analyses reveal contrasting epigenetic states between cell types in terms of overall levels and distribution, which are conserved in mice and humans. Our study proves the importance of whole-genome epigenomics and transcriptomics to gain new insights into mechanisms of epigenetic regulation that operate in specific cell types and characterize genes with key roles in important physiological processes such as adaptive immunity.

Work supported by the research grant CONICYT - FONDECYT 1171004 and by funds from the European Commission EUFP7 BLUEPRINT grant HEALTH-F5-2011-282510.

Cell Migration in Physiology and Disease: New Regulators and Connections with the Endocytic Machinery

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Cell migration in wound healing: Identification of Histatin1 as a novel factor that promotes endothelial cell migration and angiogenesis. Saliva is an oral fluid, rich in peptides and factors that promote wound healing by increasing the migration of oral epithelial cells. Among these factors, Histatin1 is a histidinerich, antimicrobial peptide that contributes to the reepithelialization of wounds. Nevertheless, the relevance of Histatin1 in other crucial events for wound healing, such as angiogenesis, remain unknown. Bearing this in mind, our recent studies were focused on elucidating the role of Histatin1 in endothelial cell function and the underlying signaling pathways. In the first part of the talk, we show evidence that Histatin1 promotes endothelial cell adhesion, migration, and vascular morphogenesis *in vitro* and *in vivo*, as well as the underlying signaling pathways. Here, we point out Histatin-1 as a peptide with potential to the treatment of impaired wound healing.

Cell migration in disease: Role of the endocytic machinery in hypoxiadriven cell migration and metastasis. Increased cell migration is a common feature of tumor cells, although the mechanisms underlying such deregulation remain poorly understood. In the second part of the talk, we provide evidence to the relevance of the endocytic machinery in contributing to enhanced tumor cell migration and metastasis. Specifically, the small GTPase Rab5 is a central regulator of early endosomes that promotes focal adhesion disassembly, actin reorganization, tumor cell migration and metastasis. Intriguingly, spatiotemporal activation of Rab5 is accelerated in hypoxic conditions, whereas Rab5 is critical for hypoxiainduced metastasis.

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Potential use of a hydroalcoholic extract from *Senecio* nutans Sch. Bip. (Asteraceae) in the treatment of hypertension: Chronotropic and negative inotropic effect in mice

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Introduction:
Senecio nutans is an endemic species of the Andes Cordillera, popularly known as Chachacoma. It is widely used amongst mountain communities for folk medicine purposes, particularly altitude sickness and hypertension treatment. The aim of this study is to evaluate the hypotensive and antihypertensive effects of *S.* nutans extract and pure isolated compounds.

Methods:
Blood pressure and ECG measurements were simultaneously carried out on the mice (6-8 weeks, n=20). Langendorff isolated heart system, isolated right atrium, and papillary muscle of the left ventricle of rat were studied. Values are means ± S.E.M., compared by ANOVA. All experiments in this study were conducted following the ARRIVE guidelines.

Results:
S. nutans (40 mg/Kg) induced a 30% and 12% significant ($p<0.05$) reduction of the mean arterial pressure (MAP) in normotensive and hypertensive mice respectively. This decrease was caused by a decrease in heart rate (HR) in normotensive (25%) and hypertensive model (31%). It also decreased the sinus rhythm in the isolated right atrium of rat. Compared with Losartan, a known anti-hypertensive, *S.* nutans caused a dose-dependent negative inotropic effect (dP/dtmax). While Losartan, decreased the MAP by 30% but had no effect on heart rate. Seven pure compounds were isolated from HAE *S.* nutans, but only two pure compounds were responsible for the vasodilation in rat aorta: 4-hydroxy-3-(3-methyl-2-butenyl)acetophenone and 5-acetyl-6-hydroxy-2-isopropenyl-2,3-dihydrobenzofurane.

Conclusion:
These suggest an important clinical function in hypertension therapy, as *S.* nutans could decrease the blood pressure in hypertensive mice by decreasing the HR and contractility, leading to a reduction in myocardial oxygen demand.

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Molecular role of the genetic pathway Lin28/*let-7* in the thyroid hormone homeostasis

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The molecular mechanisms that coordinate cellular programs, such as proliferation and differentiation, with hormones in vivo are not understood. Classic genetic studies in C. elegans allowed the identification of heterochronic genes, a network that regulates the timing of larval transitions. Among these genes, the RNA binding protein Lin28 and the microRNA let-7 are highly conserved in animals. Lin28 inhibits the maturation of let-7 through its two distinct cold shock and zinc-knuckle domains. In addition, Lin28 regulates the translation of several genes through its C-terminal domain. To study the regulation of Lin28 and the molecular link between Lin28/let-7 and hormones we are using cell culture and amphibian metamorphosis as experimental models.

Amphibian metamorphosis is regulated by thyroid hormones (TH). We previously showed that the heterochronic gene Lin28 is downregulated during metamorphosis and the ubiquitous overexpression of Lin28 delays Xenopus metamorphosis. Our aim is to determine the molecular targets downstream of Lin28. Proteome analysis showed that the TH-transporter Albumin is downregulated after Lin28 overexpression. Importantly, a truncated form of Lin28 that is not able to regulate translation also delayed metamorphosis. These results suggest that Lin28 control the timing of metamorphosis through *let-7*. To study if food availability regulates Lin28 expression, we performed starvation experiments during pre-metamorphosis. The presence of food for two days downregulates Lin28 expression compared to starved controls. We propose that food availability, the genetic pathway Lin28/*let-7* and TH axis are integrated at the molecular level.

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Role of protein chaperone Grp94 on breast cancer cells invasiveness

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Introduction:
Grp94 (glucose-regulated protein of 94 kDa) participates in the detection of misfolded proteins in the endoplasmic reticulum (ER), sending them to the proteasome for their degradation [1]. In addition, the levels of Grp94 are higher in tumor cells and correlate with the advanced stage and poor survival of cancer patients [2,3].

Aim. To investigate first the effects of tumor microenvironment (i.e. hypoxia, glucose depletion, acidosis) on the regulation of Grp94 expression. Secondly, to assess the putative role of Grp94 in the acquisition of an aggressive phenotype by tumor cells.

Results:
Hypoxia did not change Grp94 expression in the human tumor cell lines MCF-7 (breast cancer) and HepG2 (liver cancer). Glucose deprivation significantly increased Grp94 protein levels. Subsequently, we focused in the putative role of Grp94 in the acquisition of an aggressive phenotype by cancer cells. Using a more aggressive cancer cell model (MDA-MB-231 breast tumor cells), we found out that Grp94 knockdown using siRNA decreased the invasive capacity of cancer cells. Moreover, cells with decreased Grp94 levels displayed an enhanced sensitivity of tumor cells to doxorubicin, a standard drug in the treatment of breast cancer.

Conclusion:
Our results suggest that the expression of Grp94 is linked to tumor aggressiveness. Therefore, targeting Grp94 could be an effective way to inhibit tumor growth improving chemotherapy outcome.

[1] I. Kim, et al, Nat Rev Drug Discov 7 (2008) 1013-30.
[2] N. Dejeans, et alFree Rad Biol Med 52 (2012) 993-1002.
[3] B.X. Wu, et al Adv Cancer Res 129 (2016) 165-90.

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New Members Session II

Cisplatin-resistant ovarian cancer cells transfer chemoresistance through mTOR-dependent release of extracellular vesicles

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Introduction:
Different studies support the hypothesis that extracellular vesicles (EVs) could modify other cells to promote chemoresistance. Cisplatin, a standard drug used in cancer treatment, could activate signaling pathways and trigger changes in the release and cargo of EVs. One of the pathways activated by cisplatin in cancer cells is mTOR, a pathway involved in cell survival. In this context, we propose that cisplatin induces release of EVs from cisplatin-resistance cancer cells with survival properties, and the release of these types of EVs is mediated by the activation of mTOR.

Methods:
First, we isolated EVs by ultracentrifugation from chemoresistant A2780cis ovarian cancer cells treated or not with cisplatin and rapamycin, followed by characterization by nanotracking particle analysis, transmission electron microscopy, and western blot. Second, we cultured the different EVs with sensitive A2780 ovarian cancer cells, and evaluated properties involved in chemoresistance such as cell viability, and stemness.

Results:
EVs derived from A2780cis in response to cisplatin showed similar distribution size, morphology and markers of EVs than EVs derived from A2780cis without treatment. Cisplatin induces more secretion of EVs in A2780cis, and these EVs decrease the cell death, and induce cancer stem cells properties in A2780 cells. Interestingly, the release of the pro-survival EVs is mediated by mTOR activation.

Conclusion:
EVs derived from cisplatin-resistant ovarian cancer cells are modified in response to cisplatin to induce transfer of chemoresistance, and this modification is mediated by mTOR.

Fondecyt Iniciación 11150624

Role of Cytoskeleton Remodeling at the B Cell Synapse

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Engagement of the B Cell Receptor (BCR) by surface-tethered antigens (Ag) leads to formation of a synapse that promotes Ag uptake and presentation onto MHCII molecules. Here, we highlight the membrane trafficking events and associated cytoskeleton remodeling required for efficient Ag extraction and processing at the B cell synapse. We show that MHCII-containing lysosomes are recruited at the synapse and locally undergo exocytosis, a process that relies on the SNARE protein Vamp-7. Lysosome secretion allows the extracellular release of proteases, whose activities promote the extraction of the immobilized Ag. We further show that local reorganization of cortical actin by type I Myosins, which link the cortex to the plasma membrane, is required for lysosome exocytosis and Ag extraction. Remarkably, while the short-tail Myosin IC is recruited at the synapse and facilitates vesicle secretion and Ag uptake, the long-tail Myosin IE negatively regulates both processes. These results suggest that the two class I Myosins play antagonistic roles in the local reorganization of cortical actin for vesicle secretion and Ag uptake. On the other hand, microtubules cytoskeleton was associated to changes in nucleus morphology leaving a place where BCR-Ag complex and MHCII-containing lysosomes are localized. The B cell synapse therefore emerges as a highly specialized site where tightly regulated exocytic and endocytic events take place thanks to the local cytoskeleton remodeling.

Fondecyt de Iniciación 11171024

Nucleosomes stabilize ssRNA-dsDNA triple helices in human cells

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The chromatin epigenetic landscape and its associated gene expression program is modified by the interaction with non-coding RNAs (ncRNAs). Previous studies described the ncRNA-chromatin interaction through triplexes as a mode of functional and sequence-specific targeting of ncRNA to chromatin in order to regulate gene expression. However the molecular determinants for triplex formation on chromatin are unclear. Here we analyzed the triplex-nucleosome formation *in vitro*, and found that nucleosomes stabilize ssRNA+dsDNA triplexes specifically at the nucleosomal entry/exit site through the histone H3 tail. We determined the positioning of nucleosomes and triplex targeting sites (TTS) genome-wide and show that TTS-nucleosome arrangements allowing the triplex formation are enriched on active and accessible chromatin. We further designed a method to determine the triplex formation on human cells based on the triplex DNase I protection, and reveal that TTS protection depends on RNA, crosslinking, and nucleosome position. Together, the results show the critical role of nucleosomes strongly supporting the triplex formation *in vivo* as a mechanism for ncRNA targeting to chromatin.

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Astrocytic Syndecan-4 strengthens the effect of alpha$_v$beta$_3$ integrin on Thy-1-induced neurite shortening

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In a pro-inflammatory context, reactive astrocytes undergo changes in surface protein expression that impede axon regeneration in the brain. alpha$_v$beta$_3$ integrin is upregulated in reactive astrocytes and interacts with neuronal Thy-1, suppressing neurite outgrowth and inducing retraction of existing neurites. However, blocking alpha$_v$beta$_3$ only partially prevents these events suggesting the participation of other molecules. We proposed that Syndecan-4 binds to Thy-1 and acts as a co-ligand to strengthen integrin-mediated effects on neurites. Using neurons seeded over astrocytes and Syndecan-4 silencing, we tested the effect of Syndecan-4 in astrocyte-dependent suppression of neurite outgrowth. We also tested the effect of Syndecan-4 on neurite retraction induced by the integrin, using differentiated neurons incubated with a combination of the recombinant proteins alpha$_v$beta$_3$-Fc and Syndecan-4-Fc. Syndecan-4 silencing precluded astrocyte-mediated inhibition of neurite outgrowth, and this effect was more pronounced when beta$_3$ integrin was also blocked. Furthermore, alpha$_v$beta$_3$-promoted neurite shortening was faster when co-incubated with Syndecan-4-Fc. Using the Fc-tagged proteins and optical tweezers, direct interaction between Thy-1 and Syndecan-4 was demonstrated and we quantified the free-energy landscape of the unbinding processes. The unbinding kinetic parameters indicated that Thy-1/alpha$_v$beta$_3$ binding is more stable than the Thy-1/Syndecan-4 interaction, and that Syndecan-4 enhances binding parameters of Thy-1/alpha$_v$beta$_3$ by decreasing the off-rate constant at zero force.These findings indicate that Syndecan-4 strengthens the effect of the integrin on Thy-1-induced neurite shortening by stabilizing the interaction Thy-1/alpha$_v$beta$_3$ integrin. Thus, the interaction of both astrocytic molecules with Thy-1 likely participates in generating the non-permissive environment for axon regeneration attributable to reactive astrocytes.

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Effect of the forces involved in the conformational changes associated to the ligand binding and catalysis in Adenylate kinase

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Enzymatic function and catalysis depend upon a fine balance between structural rigidity and flexibility. To be catalytically active, proteins must adopt a three dimensional structure, reaching to their most stable folded state. On this ground, force spectroscopy rises as an important tool, used to control the folding and unfolding of single proteins by force, and following the trajectory of the molecule by distance. This methodology allows an in depth characterization of protein folding process and catalysis, where kinetic and thermodynamic parameters can be determined to characterize these events. Adenylate kinase (AK) catalyses the reversible Mg^{2+}-dependent phosphoryl transfer reaction ATP + AMP ↔ 2ADP, and structurally it has three domains: the CORE, the ATP Lid, and the AMP binding domain. We used AK from *Aquifex aeolicus* as our model to study the cracking phenomena (local unfolding/refolding event). *In silico* pulling force studies using Steered Molecular Dynamics (SMD) showed that the ATP lid is the first region to unfold with a distance about 5.3nm between the pulling sites. *In singulo* pulling performed by optical tweezers (OT) showed that wild-type AK unfolds completely around 20pN, exhibiting a $DG_{unfolding}$ of 11kcal/mol, showing an unfolding intermediate of 5nm that could correspond to an ATP Lid unfolding intermediate. Complementary, an unfolding promoting AK mutant (Gly mutations) was pulled by OT, unfolding completely around 10pN, with a $DG_{unfolding}$ of 6kcal/mol, showing no intermediate, suggesting that AK should be partially unfolded before being pulled. SMD and OT results suggest that AK unfolding goes via a cracking mechanism.

Fondecyt 3160645

A Halo-TEV genetic cassette for spatial and mechanical phenotyping of native proteins

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Over the last two decades, single-molecule experiments using recombinant molecules have generated transformative hypotheses on how biological tissues generate and sense mechanical force. However, lack of suitable anchoring and purification technologies has precluded testing these hypotheses on native molecules, limiting our understanding on how protein mechanics determines tissue function. Here, we overcome these limitations by engineering a novel class of knock-in mouse models that carry a Halo-TEV in-frame insertion into a target mechanical gene. The Halo-TEV cassette includes a Halo-tag module enabling both mechanical anchoring in single-molecule experiments and covalent labelling and localization, and a TEV site for directed polypeptide severing. We test the Halo-TEV cassette to probe the native mechanical function of the muscle protein titin, the main determinant of the passive elasticity of myocytes. Using single-molecule magnetic tweezers, we observe that unfolding and folding transitions of native titin domains readily occur over the range of physiological forces between 1 and 12 pN, and that adaptation of titin to changing mechanical loads occurs in the millisecond time scale. Both results support an active role of titin in muscle contraction in coordination with actomyosin motors.

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Threading is the limiting step during the folding mechanism of a trefoil knotted protein

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Knotted proteins constitute a group of topologically complex proteins. It has been suggested that threading of the polypeptide chain is the limiting step during folding of these proteins. However, there is no experimental evidence that supports this statement, moreover there is no a full thermodynamic and kinetic description for a natural knotted protein. To address this problem, we studied the folding mechanism of MJ0366 by using optical tweezers. Specifically, four pulling geometries were designed to either tight the knot or to untie it.

When the knot was tightened in the unfolded state, MJ0366 displays single unfolding/refolding transitions stabilized by ~13 kcal/mol. At constant-force MJ0366 fluctuates between two states with a refolding constant at zero force (k^0_R) of 10^7 s^{-1}. This suggest that with this pulling geometry MJ0366 has a two-state folding mechanism whose refolding is extremely fast.

Alternatively, when MJ0366 was untied by keeping the C-terminal free to thread, we observed single unfolding transitions with extensions consistent for fully unfolded/unknotted proteins. To determine folding kinetics, we calculated the unfolding rates from Dudko's analysis and folding rates from refolding probability as a function of force. The value of ΔG is ~3 kcal/mol and k^0_R is 10^{-1} s^{-1}. Notably, when only the N-terminus is allowed to thread the backbone, the protein is unable to reach the native state.

Our results indicate that MJ0366 folds by threading the C-terminus and that this process is the limiting step during folding with an energy cost of 10 kcal/mol.

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ORAL SESSION 1

Molecular Cell Biology and Biomedicine

Post-translational modifications of IRES trans acting factors (ITAFs) hnRNP A1 and HuR impact on the activity of the HIV-1 IRES

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The human immunodeficiency virus type 1 (HIV-1) genomic mRNA harbors an internal ribosome entry site within it 5' untranslated region (HIV-1 IRES). The activity of the HIV-1 IRES is modulated by IRES transacting factors (ITAFs). The heterogeneous nuclear ribonucleoprotein A1 (hnRNP A1) and the human antigen R (HuR) are known ITAFs for the HIV-1 IRES, were the first stimulates, while the second inhibits, its activity. In this study we evaluated how hnRNPA1 and HuR post-translational modifications, phosphorylations and methylations, impact on their ability to modulate the activity of the HIV-1 IRES. Results show that the hnRNPA1-S199D (phosphomimetic) and -R218K (methylation) mutants exhibit a decreased ability to stimulate the activity of the HIV-1 IRES. For HuR, the triple phosphorylation mutant S88/S100/T118, as well as the S221 phosphorylation mutant, conserve their inhibitory function over the HIV-1 IRES. However, the HuR S202A mutant gains the ability to stimulate HIV-1 IRES mediated translation initiation. Thus, we show that ITAFs post-translational modifications are important for the proteins ability to modulate translational activity of the HIV-1 IRES.

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Polypyrimidine tract-binding protein isoforms differentially impact on Dengue virus mRNA translation

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Dengue virus (DENV) is an enveloped, positive sense, single-stranded RNA virus belonging to *Flaviviridae* family. The DENV mRNAs has a 5'm7GpppN (cap) and lacks a 3'poly(A) tail. The viral mRNA exhibits highly structured 5'- and 3'- untranslated regions (UTR) that physically anneal to mediate RNA cyclization. Both 5' and 3'UTRs participate in viral mRNA translation initiation which is mainly through a cap-dependent mechanism. Several cellular RNA binding proteins (RBP), are known to be required for DENV mRNA translation. The Polypyrimidine-tract binding protein (PTB), an ubiquitous nuclear-cytoplasm shuttling protein, is a host factors that is required for DENV mRNA translation. As a result of alternative splicing three isoforms of PTB are expressed, namely PTB1, PTB2 and PTB4. Interestingly the ratio between the different PTB isoforms varies in different cell types and the different PTB isoforms have distinct impact on the rate of translation of their target mRNAs. In this study we evaluated the activity of the different PTB isoform on translation of the DENV mRNA using a virus like mRNA as a model system. Results show that the PTB1, PTB2 and PTB4 impact differently on DENV mRNA translation. Furthermore we show that the PTB1/PTB4, PTB1/PTB2, and PTB4/PTB2 ratios in cells regulate DENV protein synthesis. Thus, we show that PTB isoforms differentially modulate DENV mRNA translation.

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Tellurite promotes Stress Granules assembly in response to oxidative stress and DNA damage

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Tellurite (Te) is a highly toxic compound for many organisms. Its presence in the environment has increased due to industrial manufacturing processes and has been associated with adverse effects on public health. Te induces the phosphorylation of eIF2α, DNA damage and oxidative stress, however, molecular mechanisms associated with the cellular response to Te-induced stress are poorly understood. The aim of this study was to test whether Te induce the Stress Granules (SGs) assembly in U2OS cells. Cells were exposed to different concentrations of Te, followed by immunostaining for SGs markers. To evaluate whether phosphorylation of eIF2α could be related to the response to oxidative stress and DNA damage induced by Te, the cells were treated with Te or with H_2O_2, as a control, followed by staining for reactive oxygen species (ROS) and γH2AX (markers of oxidative stress and damage to DNA, respectively). We demonstrate that Te promotes the assembly of *bona fide* cytoplasmic SGs. Unexpectedly, Te also induces the assembly of nuclear SGs. We observed that Te-induced nuclear SGs colocalize with γH2AX *foci*, however, although H_2O_2 also induce DNA damage, no nuclear SGs were observed.

Here, we described that Tellurite promotes the assembly of cytoplasmic and nuclear SGs in response to oxidative stress and DNA damage. Together, our results reveal a new aspect of stress response mediated by Stress Granules.

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hnRNPU, hnRNPK, hnRNPA1, and HuR are modulators of HIV-1, HTLV-1 and MMTV IRES-mediated translation initiation

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The genomic mRNA of the human immunodeficiency virus type 1 (HIV-1), the human T-cell lymphotropic virus type 1 (HTLV-1), and the mouse mammary tumor virus (MMTV) can initiate translation using an internal ribosome entry site (IRES). Retroviral IRESs require cellular proteins, IRES trans-acting factors (ITAFs), for their function. Using a GRNA-affinity chromatography coupled with mass spectrometry the RNA binding proteins hnRNPK, hnRNPU, hnRNPA1 were isolated in association with the 5'UTR of these retroviral mRNAs. In this study we evaluated whether these proteins could impact on translation mediated by the HIV-1, HTLV-1 and MMTV IRESs. Results show that hnRNPK, hnRNPU and hnRNPA1 when independently over-expressed stimulate translation driven by the HIV-1, HTLV-1 and MMTV IRESs. Translation mediated by the HIV-1, HTLV-1 and MMTV IRESs is further enhanced when hnRNPU, hnRNPK, and hnRNPA1 are co-expressed confirming that, these RNA binding proteins act as ITAFs for these retroviral IRESs. In addition we also evaluated the role of HuR, a protein previously described as a repressor of the HIV-1 IRES. Results show that HuR also inhibits activity of the HTLV-1 IRES, but has no impact on translation mediated by the MMTV-IRES. Furthermore, HuR hinders the stimulatory effect excreted by hnRNPK and hnRNPA1 over the HIV-1 IRES. Together, these results suggest that hnRNPU, hnRNPK, hnRNPA1, and HuR act as positive or negative modulators of HIV-1, HTLV-1, and MMTV IRES-mediated translation.

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An anti-N monoclonal antibody as a new therapy for the Respiratory Syncytial Virus

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Human Respiratory Syncytial Virus (hRSV) is the main cause of acute lower respiratory tract infection in susceptible individuals, such as young children and elderly around the world. The immune response observed during the infection is a Th2 profile, which is inefficient to induce viral clearance. Although hRSV is a major public health burden, there are no licensed vaccines and the only available therapy is palivizumab, a humanized monoclonal antibody against the fusion (F) protein. During life, reinfections with hRSV are common. Along these lines, our group described that the N protein could be involved in this process, due to its capacity to impair the immunological synapsis between dendritic cells (DCs) and T cells. Based on this observation, we have developed a monoclonal antibody that binds with high affinity to the N protein, both purified or expressed in infected cells. Also, we tested its therapeutic capacity on a murine model of hRSV infection, observing a decrease in cellular infiltration and viral loads in lungs of infected animals. The above results suggest that this antibody helps control the inflammation and viral spreading triggered by this pathogen. These results suggest that a new therapy using a monoclonal anti-N antibody could be considered to control infection caused by the hRSV.

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Lifesaver molecules for C. elegans neurons produced by bacterial diet

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Nutrients sources are directly related to development and behavior of all living organisms. Understanding the mechanisms by which dietary molecules interact with intestinal and neuronal functions is a new approach to describe the development of neurodegenerative diseases and behavior illness. In our laboratory, we discovered that when the nematode bacterivore *C. elegans*, *mec-4d* mutant, were fed with *E. coli* K12 HT115 neuronal death was prevented by 50%, compared to *E. coli* B OP50 diet. This animal model mec-4d is based on a constantly opened sodium channel that promotes axonal damage of touch response neurons in a trackable manner.

In this study, we described the neuroprotective effect provided by bacterial diet and identified the responsible metabolites. First, we predicted compounds by differential metabolic pathways among both bacteria strains using genomic and transcriptomic analysis, and secondly, we validated with bacteria mutants, pharmacological supplementation, and metabolomic analysis. We found that *E. coli* HT115 overexpressed 60 genes absent in *E. coli* B OP50, including glutamate decarboxylase (*gadA*, *gadB*), which produced gamma-aminobutyric acid from L-glutamic acid. When *mec-4d* worms were fed with *E. coli* HT115 mutants for GABA production the neuroprotective effect was diminished in 40% ($p=0.0001$). Moreover, wild-type axons were recovered in 30% in *mec-4d* worms by dietary GABA supplementation ($p=0.04$) or genetic complementation of *gadA* ($p=0.018$). According to those result, we proposed the role of dietary *E. coli* GABA producing bacteria in neuroprotection process, including its accessibility through the intestine and activation of molecular signaling to prevent axonal damage.

ORAL SESION 2

Plant Biology and Microbiology

Characterization of components, antioxidant activity and possible therapeutic use of Microsorum scolopendria obtained in Easter Island

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Microsorum scolopendria is a fern of wild growth on Easter Island. In alternative medicine is used for different purposes, being part of some treatments in diseases such as breast cancer. Coumarin (1,2-benzopyrone) is one of the active compounds that gives biological activity to the species. Studies show that coumarin has anti-inflammatory and antibacterial activity.

The objective of this work was to characterize the biochemical components of the leaf and rhizome by HPLC and correlate them with their biological properties in an in vitro model of epithelial damage generated by a condition of high glucose (AG), condition of post-prandial hyperglycemia, over the embryonic renal cell line, HEK -293. After the tests carried out IC50 of viability and cytotoxicity of different extracts of different ecotypes of Microsorum scolopendria in the cell line HEk-293 were obtained, decreasing the reactive oxygen species produced by a high glucose. These tests are conditioned with the antioxidant capacity obtained by different methods and with membrane perturbation tests performed.

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Vicerrectoria de Investigación PUCV Proyecto 037.728-28

Insights into the impact of iron on the Botrytis cinerea-plant interaction.

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Iron acquisition is essential for life. This metal is required in redox-dependent cellular processes within the cell. A highly abundant metal on the Earth crust, its bioavailability is limited. Since iron modulates plant defense and fungal virulence, a combined strategy is required to look at both organisms to adequately address its influence in the context of the interaction. Plants and fungi depend on analogous systems to fulfill their iron needs. Succinctly, both kinds of organisms can utilize iron-chelating agents known as siderophores. Besides, they can also utilize a strikingly similar iron acquisition system that depends on iron reduction/oxidation and later capture from the extracellular medium. Interestingly, the two major plant defense hormones influence plant iron acquisition. Thus, jasmonic acid, the key phytohormone involved in *B. cinerea* defense mechanisms reduces iron acquisition by transcriptional downregulation of related genes. Also, iron acquisition significantly modulates virulence attributes in most pathogens including fungi. However, little is known about how *B. cinerea* manages to obtain iron during the infection. To address this question, we generated a *B. cinerea* mutant strain devoided of a vital component of an iron acquisition system. The mutant exhibits a developmental phenotype that can be reverted with increasing Fe (III) concentrations indicating iron-dependent stress. Although the mutant displays significantly reduced whole-cell iron content, instead of displaying the expected reduced virulence phenotype, it consistently shows bigger lesions after 72 hpi in comparison with the wild-type *B. cinerea* strain. Interestingly, only iron-starved plants displayed the expected reduced virulence phenotype. We are currently performing distinct assays employing iron-starved and not-starved plants to obtain mechanistic insights.

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Study of the composition and mechanism of action of outer membrane vesicles of gram negative bacteria of the genus Vibrio

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Various bacterial diseases associated with fish have been reported in our country given the increase in the aquaculture industry. One of these diseases is vibriosis, a disease that causes hemorrhages and complete losses of the culture pools. Antibiotics are used as treatment, which must be reduced or eliminated according to current regulations. Therefore, new pharmacological targets must be found and in this study we used the constitutive production of outer membrane vesicles by gram-negative bacteria and the use of cationic peptides to attack the disease. We characterized three strains of bacteria of the genus Vibrio by SEM, Raman, SDS-Page, fluorescence and techniques associated with the study of membranes (Anisotropy and Generalized Polarization) components of OMVs. The areas involved in the interaction between host cells and bacteria are evaluated by fluorescence microscopy and specific marking. Cationic peptides are synthesized and the effect of these on the infection rate is evaluated.

Beca Doctorado Nacional 21180737 Conicyt

Regulatory networks underlying differential susceptibility to Botrytis cinerea in tomato plants grown under different nitrogen regimes

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Nitrogen (N) is one of the main limiting nutrients for plant growth and crop yield. Despite its role as a nutrient, N plays an important role acting as a signaling molecule that modulates gene expression of a wide range of plant processes. Indeed, N availability influences plant ability to cope with pathogen attacks. Since plant defense is complex biological process and energetically costly response mechanism, it is expected that the metabolic state of the plant plays a fundamental role in the outcome of the plant-pathogen interaction. In the case of *Botrytis cinerea*, the role of N on disease development in different plants appears to be variable and the molecular mechanism underlying this interaction are poorly understood. In this work, we analyzed the global gene expression response of *Solanum lycopersicum*against infection by the necrotrophic fungus *Botrytis cinerea*, under contrasting nitrate conditions. Our results indicate that defense responses to *B. cinerea*infection are affected by N availability, showing more susceptibility in nitrate-limiting conditions. Using a systems biology approach, we identified ethylene (ET) and jasmonic acid (JA) transcriptional regulatory networks implicated in plant response to the fungus infection under contrasting nitrate conditions. Moreover, we characterize expression patterns of genes for the biosynthesis, modification and signal transduction to infer the potential link between hormones and plant N status in plant–pathogen interactions. We integrated these results with susceptibility phenotypes of plants compromised in hormone synthesis and perception, to provide a model describing how nitrate influence the susceptibility of tomato to *B. cinerea*.

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Endocytic cellular trafficking, an unexpected contributor in the vacuolar configuration process in Arabidopsis thaliana

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Plant development involves cell growth and cell differentiation. At the subcellular level, the configuration of the vacuole is a driving force for cell growth. Root meristem cells grow progressively to reach to the transition root zone and finally the differentiated root zone. Along this root growth gradient, the vacuole expands progressively increasing the volume and consequently the amount of membrane to configure as a central vacuole. The vacuole primarily is fed of protein and lipid components by secretory trafficking and also by interaction with membranous compartments. In addition, the plasma membrane is delivered to the vacuole by endocytic trafficking, however its contribution to the vacuolar configuration process remains unexplored. Interestingly, increasing the rate of endocytic trafficking positively impact the vacuolar membrane complexity and promotes growth of the roots cells and roots. Our evidences showed that clathrin-mediated endocytosis has an important role in vacuole configuration along the root growth gradient in *Arabidopsis thaliana*. Particularly, we determine that clathrin-mediated trafficking is required for early stages of vacuolar configuration; most likely modulating the membrane flow to the vacuole. Overall our evidences show that the clathrin-mediated endocytosis is required for vacuolar expansion and strongly point to the plasma membrane as an important contributor of the membrane flow for vacuole configuration.

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Molecular response of peach fruit under exogenous application of cytokinin during maturity reveals a novel set cytokinin-response genes

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Peach (*Prunus persica* L. Batsch) is a climacteric export fruit with high economic and commercial value for Chile. During peach development, there are physiological changes induced by a strict phytohormonal control that can alter the final quality of the fruit. Physiological evidence in fruit trees suggests that exogenous application of phytohormone cytokinin could delay the maturation process in the fruit. However, the molecular mechanisms involved in cytokinineffect on peach are barely known. To address this question, we exogenously applied cytokinin to peach fruit in both field (TDZ) and laboratory (*trans*-zeatin) settings at maturation stage. Later, by using bi-directional blast analysis we selected ripening-related genes that were potentially regulated by cytokinin in peaches. We then performed bioinformatic and gene expression analyses in order to gain insight into these novel set of genes. Through this approach, we identified 18 genes that express differentially under cytokinine treatment, 17 of which exhibited *cis*-responsive elements to cytokinin in their regulatory region. Among them, we identified “polygalacturonase”, “auxin-responsive protein IAA”, “expansine” and “gibberellin 2-beta-dioxygenase 4”, related to the maturation of the peach fruit. Thus, by performing cytokinine treatments to peach fruit under laboratory and field work, we identified a set of novel cytokinin-responsive genes in peach fruit related to maturation in peach fruits.

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Oral Session 3

Protein Structure and Inmunology

Characterization of the Domain Swapping dimer of Forkhead Domain of FoxP1 using Optical Tweezers

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Domain Swapping (DS) is a mechanism in which monomers exchange structural elements to form oligomers. For FoxP, it has been shown that it's domain-swapping mechanism occurs via a monomeric intermediate. Nevertheless, there is no information about the kinetics of the domain swapping-process. To address this question, we study the DS mechanism of FoxP1 at single molecule level using optical tweezers. To do this, we generated a fusion protein joining two FoxP1 chains (FoxPsc) and its folding mechanism was characterized by pulling from its N and C terminal at constant velocity. Mechanical unfolding/refolding cycles showed three unfolding transitions followed by three sequential refolding transitions. The first unfolding transition occurs at low forces (~9 pN) and show a contour length (lc) of ~18 nm. Both following transitions appear at higher forces (~13 and ~18 pN) with a lc of ~28 nm which agrees with the expected for the unfolding of each domain of FoxPsc. These data suggest that the low force transition accounts for the unwinding of the domain-swapped structure, and the following transitions corresponds to the unfolding of each FoxP domains. Using the Dudko approximation, we calculate the rates for the unwinding and the folding of the FoxPsc domains. The unwinding rate is one order of magnitude faster than the unfolding of the domains. Additionally, the re-association of the swapped structure is 3 orders of magnitude slower than the refolding of the domains. Hence, the re-association of the swapped structure is the rate limiting step in the domain-swapping mechanism of FoxP.

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Specific Amino Acid Replacements Allow Calcium-Selective TRP Channels To Evolve Fast Inactivation

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TRPV5 and TRPV6 are inwardly rectifying calcium-selective ion channels, considered as gatekeepers of epithelial calcium transport and key elements for calcium homeostasis. In mammals, TRPV6 is a key player in intestinal calcium absorption, while TRPV5, participates in fine-tuning during calcium reabsorption at the distal tubule in the kidney. To achieve this goal, TRPV5 lacks the calcium-dependent fast inactivation, characteristic of TRPV6 channels. We show that the phenotype of rapid inactivation phase observed in TRPV6 channels originates when these channels were duplicated in the genome of different species. Our phylogenetic reconstruction suggests that this feature emerge recursively on each event of gene duplication, creating a traceable sequence signature. Electrophysiological data suggest that this sequence signature is an important element to fully define the inactivation phenotype exhibited by these channels. Molecular Dynamics Simulations suggest that the differences in the inactivation phenotype can be explained by differences in calcium ion coordination and in the tridimensional conformation of the pocket formed by the Helix-Loop-Helix domain, the intracellular connector between transmembrane segments S2-S3 and the TRP helix. We propose an evolutionary-functional-structural correlation of this fast inactivation phase in TRPV5 and TRPV6 ion channels.

Proteomic approach and in vitro evaluation of neurotoxicity by the action of a phospholipase A2 isolated from the snake venom of the Peruvian Amazonian Coral (Micrurus spixii)

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A new PLA2, with myotoxic activity, was purified from de venom of *Micrurus spixii*, with a high degree of purity and molecular homogeneity by two chromatographic steps: molecular exclusion chromatography G-75 (1 cm x 60 cm) and high performance liquid chromatography pressure reverse phase (RP-HPLC). The SDS-PAGE electrophoresis shows a molecular mass ~ 14 kDa, which was confirmed by mass spectrometry MALDI-TOF with a molecular mass of 14149,005 Da, showing a single polypeptide chain and a high sequence homology of its N-terminal with other PLA2, 70% with the PLA2 GL16-1 of *Laticaudata semifasciata,* 68% of the PLA2 pkP2 of *Laticaudata semifasciata* and 68% of the pancreas of *Sus scrofa* (pig).

Kinetic activity was evaluated in the presence of synthetic chromogenic substrate 4-nitro-3octanoiloxi benzoic acid (NOAB), which describes a sigmoidal curve at different concentrations; the enzyme shows stability at different temperatures (25 to 45 ° C), pH (5 to 10) and it´s calcium dependent faced to divalent ions. This new K49 PLA2 showed a potent myotoxic local effect (intramuscular way) and systemic too (tail vein) in mice, at a concentration of 20ug/ml compared to other snake of the same gender and high inflammatory activity at a concentration of 5ug/ml.
José Carlos Mariategui Research Institute – Peru

Evolutionary constraints determine threedimensional domain swapping of the forkhead domain of FoxP transcription factors

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The forkhead box (Fox) proteins are a widespread family of transcription factors whose DNA–binding domain exist canonically as a monomer in solution. Nevertheless, structures of FoxP2 and FoxP3, which are members of the P subfamily (FoxP1–4) showed dimeric structures via three–dimensional domain swapping (DS), a mechanism where the exchange of identical segments between subunits leads to intertwined dimers, stabilized by intermolecular interactions. In order to understand how DS emerged in the FoxP subfamily, we characterized FoxP members showing that their dimer–monomer equilibria is reached in hours, and in the case of FoxP3 an obligated dimer is observed. Despite their high sequence identity, the dissociation constant values (K_D) obtained are in micro (FoxP1, FoxP4) to milimolar range (FoxP2). To gain a detailed structural insight of FoxP members, we solved the X-ray structure of FoxP4; its comparison with other FoxP members showed that all of them share high structural similarity. We carried out a network analysis of molecular dynamics simulations of FoxP2 and FoxP3 members, representing amino acids by nodes and interactions by edges. Interestingly, dissection of protein networks in short sub-networks or communities resulted in six communities for FoxP3 and nine for FoxP2. Away from the hinge region, the FoxP3 network showed a prominent community between three helices, while in FoxP2 these helices were organized as independent communities. These results suggest that the stability of this region can be an important feature for the emergence of DS in this family.

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N-glycosylations of mollusk hemocyanins are essential to maintain their quaternary structure, and contribute to their immunogenic properties in mammals

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Mollusk hemocyanins from *Concholepas concholepas* (CCH), *Fisurella latimarginata* (FLH) and *Megathura crenulata* (KLH) are oligomeric glycoproteins (4-8 MDa), with complex didecameric quaternary structures and heterogeneous glycosylations, mainly mannose-rich N-glycans that reinforce the interaction between subunits. Hemocyanins are widely used as carriers, adjuvants, and non-specific immunostimulants in cancer because they bias towards Th1 immunity. These glycoproteins are incorporated by antigen presenting cells through glycan-recognizing C-type lectin receptors, such as Mannose Receptor (MR), Dectin-1 and Dectin-2, and stimulate proinflammatory cytokine secretion. However, the role of N-glycans on the structure and immunologic properties of hemocyanins have not been compressively demonstrated. Thus, we hypothesized that enzymatic N-deglycosylation of CCH, FLH and KLH disfavors their quaternary structure and immunogenic effects in mammals. Hemocyanins were enzymatically N-deglycosylated by treatment with PNGase F, and chemically deglycosylated by sodium periodate oxidation as control. Biochemical analyses by lectin array blot, circular dichroism and transmission electron microscopy showed structural modifications in N-deglycosylated hemocyanins, and the presence of residual fucose-rich glycans. ELISA analyses showed a decreased binding of deglycosylated hemocyanins to chimeric receptors MR-Fc, Dectin-1-Fc and Dectin-2-Fc. Analyses in J774.2 murine macrophages by flow cytometry and ELISA showed a decreased incorporation of N-deglycosylated hemocyanins, as well as an impaired production of TNF-α, IL-6 and IL-12p40. Finally, the humoral response of mice inoculated with native and N-deglycosylated hemocyanins showed a reduced antibody titer in groups immunized with N-deglycosylated hemocyanins. Altogether, these results suggest that N-glycosylations of CCH, FLH and KLH play a structural role and contribute to their immunogenic properties.

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TLR4, but not Dectin-1 or Dectin-2, participates in the proinflammatory effects induced by mollusk hemocyanins in antigen presenting cells of mammals

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Mollusk hemocyanins have biomedical uses as carrier/adjuvants and non-specific immunostimulants, because these glycoproteins trigger the production of proinflammatory cytokines by antigen presenting cells (APCs), driving immune responses towards a Th1 polarization. Hemocyanins are internalized by APCs through receptor-mediated endocytosis with the participation of Mannose Receptor (MR) and DC-SIGN, which recognize mannose-rich branched structures. However, the contribution of other innate immune receptors in the proinflammatory signaling pathway triggered by hemocyanins has not been described. Thus, we studied the role of Dectin-1, Dectin-2 and TLR4 in hemocyanin activation of APCs, using hemocyanins from *Megathura crenulata (*KLH), *Concholepas concholepas* (CCH) and *Fissurella latimarginata* (FLH). The results demonstrated that Dectin-1 and Dectin-2 bound *in vitro* to these hemocyanins. Nevertheless, NIH3T3 cell lines that overexpress Dectin-1 or Dectin-2, did not show greater uptake of hemocyanins. Moreover, when wild-type (WT) APCs were cultured with hemocyanins, phosphorylation of Syk kinase was not detected, although the inhibition of Syk kinase activity with piceatannol or BAY 61-3606, decreased the secretion of IL-6 and IL-12. Indeed, proinflammatory cytokine secretion and maturation of APCs induced by hemocyanins were independent of Dectin-1 and Dectin-2. On the other hand, APCs derived from the adaptor molecule Mal were partially activated by FLH, suggesting a role of TLRs in hemocyanin recognition to activate innate immune cells. Furthermore, IL-6 secretion induced by FLH was abolished in APCs derived from TLR4 KO. Collectively, these data support that TLR4 would be required for the hemocyanin proinflammatory response in APCs, and could collaborate with CLRs like MR or DC-SIGN.

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Oral Session 4

Computational Biology and Biomedicine

Emergence and Stabilization of a Folding Duality in the Transcription Factor RfaH

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Metamorphic proteins are an extreme example of native state conformational heterogeneity by switching between distinctive functional and structural configurations in biologically relevant timescales. A remarkable example is the transcription regulator RfaH, which becomes activated upon binding to the bacterial transcription machinery by completely refolding its C-terminal domain (CTD) from an α-hairpin tightly bound to the N-terminal domain (NTD) into a β-barrel. The emergence of this folding duality is coupled to its sequence-dependent activation as transcriptional regulator, differentiating RfaH from its widely conserved paralog NusG, whose RNAP recruitment does not require a DNA signal. Co-evolutionary interactions inferred from mean field direct coupling analysis for both paralogs reveal that RfaH CTD is largely enriched in interdomains contacts, most densely packed between residues 130-150. Local stability calculated from confinement molecular dynamics and hydrogen-deuterium exchange mass spectrometry shows that residues 129-141 within RfaH CTD strongly interact with the NTD, greatly stabilizing its autoinhibited state. Conversely, most of the remaining residues strongly stabilize the folding of RfaH β-barrel, whose overall local stability is similar to that from NusG. Taken together, these results show that the folding duality in RfaH took place by the emergence of deeply stabilizing interdomain contacts in the 130-145 region in its CTD. This would allow for RfaH autoinhibition to become the ground state, and yet retaining the key contacts involved in the β-barrel formation and stabilization upon interdomain dissociation. Our results provide the thermodynamic grounds under which sequence specificity could be achieved inside such a conserved family of transcriptional regulators.

Novel small molecules modulate TASK channel activity, decrease cell proliferation, and promote cell death on cancer cell lines

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Two-pore domain potassium (K2P) channels underlie the background K+ currents in mammalian cells. They can be segregated into six subfamilies based on their structure and functional properties. The acid- sensitive TASK-1 and TASK-3 channels belong to the TASK subfamily. TASK channels exhibit an altered expression in cancer. TASK-3 is an oncogenic potassium channel overexpressed in breast tumors. Despite their potential as therapeutic targets in cancer, there is little information on small-molecule drugs to target or avoid TASK channels blockage. Based on already published small-molecule drugs that block TASK channels such as A1899, bis-amidated aromatic compounds and other compounds sharing a common pharmacophore, we rationally designed and synthesized three new modulators of TASK channels: one activator and two blockers. Metric tests of cytotoxicity on tumor cell lines were performed to analyze the efficacy of the compounds in the decrease of cell proliferation. The three compounds have antiproliferative activity on different cancer cell lines.

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Molecular Dynamics Studies on the Corticotropin-Releasing Factor (CRF) system

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The corticotropin-releasing factor (CRF) system is a key mediator of the stress response and addictive behavior. The CRF system comprises four peptides: CRF, urocortins I–III; the CRF binding protein (CRF-BP) that binds CRF with high affinity, and two class B G-protein coupled receptors CRF1R and CRF2R. CRF-BP is a secreted protein without significant sequence homology to CRF receptors or to any other known class of protein. Recently, it has been described a potentiation role of CRF-BP over CRF signaling through CRF2R in addictive-related neuronal plasticity and behavior. In addition, it has been described that CRF-BP is capable to physically interact specifically with the α isoform of CRF2R and acts like an escort protein increasing the amount of the receptor in the plasma membrane. At present, there are no available structures for CRF-BP or for full-length CRFR receptors. Knowing and studying the structure of these proteins could be beneficial in order to characterize the CRF-BP/CRF2αR interaction. In this work, we report the modeling of CRF-BP and of full-length CRF2αR and CRF2βR based on the recently solved crystal structures of the transmembrane domains of the human glucagon receptor and human CRF1R, in addition with the resolved N-terminal extracellular domain of CRFRs. These models were further studied using molecular dynamics simulations and protein–protein docking. The results predicted a higher possibility of interaction of CRF-BP with CRF2αR than CRF2βR and yielded the possible residues conforming the interacting interface, providing a framework for further investigation of the CRF-BP/CRF2αR interaction.

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Revisiting the phosphoryl transfer mechanism in CDK2: A QM/MM study

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CDK2 (cyclin-dependent kinase 2) is an extensively studied kinase that is involved in the regulation of the cell cycle, which is the reason why CDKs, in general, have attracted much attention as therapeutic targets for cancer treatment. Previous computational studies including only one Mg^{+2} ion have pointed to a substrate-assisted mechanism in CDK2, where the proton of the hydroxyl nucleophilic group at substrate is transferred to one of the oxygen atoms of the ATP γ-phosphate. On the other hand, a most recent computational study shed light on the preference of a base-assisted mechanism, where the Asp127 residue acts as a base abstracting the proton. Some years ago, the first crystal structure of CDK2 with two Mg^{+2} ions was published. Based on that recent crystallographic data, we pursued new theoretical calculations to study the phosphoryl transfer reaction in detail. These comprise QM/MM (quantum mechanics/ molecular mechanics) calculations at the level DFTB3/Amberff99SB by means of the adaptive finite-temperature string method combined with a path-based approach implemented in the software Amber16. It was found that the base-assisted mechanism is favored and the free energy barrier agrees with the experimental kinetic information. This revisited mechanism, obtained from updated X-ray data and with up-to-date computational approaches, is dissociative featuring a metaphosphate-like intermediate with the proton transfer occurring once the phosphoryl transfer is almost completed. Following the proton transfer to Asp127, this residue acts as an acid protonating the transferred phosphate in a process that is almost barrierless, restoring in this way the original state of Asp127.

FONDECYT No. 1181253

Thermodynamics of nutrient exchange in arbuscular mycorrhizal symbiosis

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Arbuscular mycorrhizal (AM) symbiosis is a widespread interaction between fungi and plants, in which both partners exchange nutrients for reciprocal benefit, in particular sugars, phosphate and nitrogen sources. As the dynamics of this reciprocal transfer is not well understood, the general thermodynamic features of the nutrient exchange were evaluated in computational cell biology experiments. This approach allowed to obtain a thermodynamically justified, independent, and comprehensive view on the dynamics of nutrient exchange in AM symbiosis. The deduced model substantiates a previously proposed notion that plant and fungus compete with each other for the same resources, and that this competition lays the foundation for a robust cooperation. The approach suggests probable scenarios, namely that (i) phosphate is released by the fungus via proton-coupled phosphate transporters, (ii) the plant accumulates ammonium in the charged form (NH4+) and not -as proposed- in the neutral form (NH3), and (iii) sugar release via SWEETs is either an initial defence reaction of the plant or a permanent suboptimal condition. The thermodynamic models can be generalized and adapted to other forms of mycorrhiza, and to parasitic fungus-plant interactions.

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The ectonucleotidase CD73 is a marker of profibrotic differentiation of renal epithelial cells

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BACKGROUND. The progression of diabetic nephropathy (DN) is linked to tubulointerstitial fibrosis conducted by TGF-β. Phenotypic transition of tubule epithelial cells in renal fibrosis depends on the crosstalk between TGF-β and adenosine (ADO) signaling. Our aim was to study the Cd73 gene regulation downstream TGF-β signaling and demonstrate its potential as a molecular marker of renal tubule injury. METHODS. Human urine samples from healthy, diabetic and DN subjects were tested for CD73 specific activity. Human renal epithelial tubule cells (HK2) were treated with TGF-β 10 ng/ml, ADO 10 mM , NECA 1 mM , IB-MECA 1 mM , MRS 1220 10nM and each with TGF-β for 48 h. CD73 induction was determined by RT-qPCR. Recruitment of transcription factors and changes in the histone code at the CD73 gene promoter were determined by ChIP-qPCR. Correlation between CD73 expression and HK-2 fibrotic trans-differentiation was assessed by light clear field microscopy, Immunofluorescence and Western blot. RESULTS. We found increased Cd73 activity in urinary sediments from DN patients compared to healthy and diabetic patients. CD73 expression increases in presence of TGF-β and sinergistically with the ADORA3 agonist IB-MECA. On TGF-β treated cells the active form of the Smad2/3 complex was positioned at the CD73 promoter proximal to the transcriptional start site along changes on the histone H3 code associated with transcriptional activation. Expression of CD73 correlated with changes in cell phenotype and increased profibrotic markers Fn-1 and α-SMA. CONCLUSION. The ectonucleotidase CD73 gene is a marker of the profibrotic TGF-b and ADORA3 signaling in epithelial tubule cells.

Proyecto Fondecyt Posdoctorado 3170812 Proyecto Fondecyt 1171340

Oral Session 5

Molecular Cell Biology and Signaling

Zinc supplementation alters nitric oxide (NO)-metallothionein (MT)- metallothionein transcription factor (MTF-1) pathways in chronic hypoxia in wistar rats, increasing right ventricular hypertrophy

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Introducción:
High altitude mining has been associatedwith erythrocyte alterations, pulmonary hypertension and right ventricular hypertrophy (RVH). The effect of simultaneously exposure to metals such as zinc, over hematological and cardiovascular system are not well known. The aim was evaluate the effect of zinc supplementation on erythrocytosis and RVH under hypobaric hypoxia and to association with MT, MTF1 and NO pathways.

Method:
Wistar rats were exposed to simulated hypoxia in a hypobaric chamber at 428 Torr (4800m) for 30 days, randomly allocated in 3 groups: Chronic (CH), n=16; Intermittent (CIH), hypoxia 2 days/2 days normoxia; n=16; Normoxia (NX; n=16). Each group was divided into two (n=8) receiving intraperitoneally, either a Zn sulphate solution at 1% or just saline, every 4 days. MT and MTF1 protein´s expression was assessed by Western Blot in lung. In pulmonary artery was measured the bioavailability of NO (DAF-2, confocal microscopy).

Results:
Hypoxic groups: decreased weight, a major decrease of plasma zinc in CH, a higher RVH in CH(zinc), both CH(Zinc) and CIH (Zinc)increased Hct and Hb without differences between them. Hypoxic groups´ lung presented protein overexpression of MT and MTF1, being higher in CH(zinc) group. In pulmonary artery, hypoxic groups decreased the bioavailability of NO.

Conclusión:
Simultaneously exposure to CH and zinc increases the effect on hematological and cardiovascular variables, probably due to protein overexpression of MT and MTF-1, and the action of NO.

Keywords:
Chronic intermittent hypoxia, chronic hypoxia, Zinc, NO, right ventricular hypertrophy and metallothionein.
FIC GORE TARAPACÁ BIP30477541-0 AND ARTURO PRAT UNIVERSITY.

Self-assembly of Cytoskeletal Filaments

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Self-assembly plays a central role in producing ordered supramolecular structures. The crucial questions are to identify the necessary features that a macromolecular monomer must have in order to form spontaneously a desired complex structure, and to understand why certain superstructures of biomacromolecules are preferentially formed out of many potential outcomes. In this talk we will discuss our work on the self-assembly of cytoskeletal filaments including microtubules and actin filaments using designed, coarse-grained building blocks and molecular dynamics simulations. The model monomer has either a wedge (for microtubules) or a bent-rod shape (for actin filaments) with binding sites on its lateral and vertical surface. Diagrams of the self-assembled structures from these monomers are calculated. Our results lead to fresh insights into the role of interaction strengths between building blocks in controlling the structure of the resulting assemblies. For microtubules, our work sheds new light on the connection between the chiral nature of the building blocks and the helical structure of the resulting tubules. For actin filaments, our model reveals the advantage of their double-stranded filamentous structure. Our ongoing work on the nanomechanics of microtubules and actin filaments using the coarse-grained building block models, and atomistic modeling of tubulin proteins, microtubule segments, and the interactions between multivalent ions (e.g., spermine) and microtubules will also be presented.

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Changes in cardiac MAPK protein and ROS in rats exposed to chronic intermittent hypobaric hypoxia

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Introduction:
Pulmonary hypertension leading to right ventricular hypertrophy (RVH) is an important consequence of Chronic Intermittent Hypobaric Hypoxia (CIH) and Chronic Hypobaric Hypoxia (CH) exposure. This is mainly attributed to a mechanical effect, but molecular pathways involved are not well known and reactive oxidative species (ROS) could play a major role. The aim was to determine hypertrophic status and oxidative balance in both ventricles in rats exposed to CIH.

Method:
Wistar rats were randomly separated into 3 types of exposure: CHH, n= 10, CIH; n=10), and normoxia (NX=10). Hypoxia was simulated in a hypobaric chamber at 428 Torr (4.600 m) for 30 days Right ventricle following parameters were measured: hypertrophy, lipid peroxidation (indirect method for oxidative stress measure), active expression of NADPH oxidase-NOX2, antioxidants bioavailability (SOD3) and redox-sensitive protein, p38MAPK and Akt.

Results:
Exposure to CIH caused a RVH along with an increase of NADPH oxidase-NOX2 expression, inducing ROS elevation in the right ventricle (to a lesser extent than CH) not compensated by the antioxidant system (SOD3). This, oxidative stress was found generated by the activation of p38MAPK, but not Akt protein.

Conclusion:
Oxidative stress found in CIH could contribute directly or indirectly through p38MAPK to the development of RVH. This response is remarkably different in both ventricles, since LV is not affected and would have relevant implication in future investigations and in clinical and pharmacological fields.

FIC GORE TARAPACÁ BIP30477541-0 and Arturo Prat University

Gastric cancer derived extracellular vesicles loaded with microRNA-335-5p and their role in tumor development

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Introduction:
MicroRNA-335-5p (miR-335) is dysregulated in various cancer types, including gastric cancer (GC). Recently, we reported the downregulation of miR-335 in advanced GC tissues relative to their paired non-tumor tissues. As we also demonstrated miR-335 downregulation in plasma samples from GC patients, we aimed to investigate its expression in extracellular vesicles (EVs) isolated from plasma. Moreover, we prepared GC-derived EVs loaded with miR-335 and investigated their effect after administration in subcutaneous and intraperitoneal GC mouse model.

Methods:
EVs were isolated from a cohort of 12 paired plasma patients' samples, from supernatants from metastatic-derived GC cell line HS746T, and from cells transfected with miR-335-mimic. Expression levels of miR-335 in plasma EVs, transfected cells and their EVs were analyzed by qPCR. Incorporation of EVs into cells was quantified by flow cytometry. For in vivo studies, GC cells were injected intraperitoneally or subcutaneously into immunosuppressed mice and miR-335-loaded EVs or control EVs were injected every 3-4 days intravenously.

Results:
Our patients cohort shows a tendency that plasma EVs isolated from GC patients contain less miR-335 when compared to healthy donors. In vivo studies show, that after intravenous injection of these EVs in a mouse model with GC cell tumors, the tumor formation is altered and these mice lack ascites in comparison to control mice.

Conclusion:
MiR-335 is present in EVs isolated from both plasma and GC cell culture supernatants. EVs enriched in miR-335 are uptaken by GC cells and upon intravenous injection can modulate tumor development in a mouse model.

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A common house or particular niches for CoREST transcriptional co-repressors in chromatin

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CoREST proteins are transcriptional co-repressors that regulate gene expression during development and in differentiated cells. They form stable protein complexes with the histone H3 lysine 4 demethylase LSD1 and histone deacetylases HDAC1 / 2 to efficiently coordinate the activities of these epigenetic modifiers in a biochemical entity. Our lab has described the existence of three CoREST proteins able to form complexes with subtle differential biochemical properties that lead to different transcriptional repressive capacities. However, very little is known about their association with chromatin. In this work, we hypothesized that CoREST1, CoREST2 and CoREST3 have different chromatin association profiles.To test this hypothesis, we settled up subnuclear fractionations, and a salt- and DNAse I - induced protein extractions from chromatin in HT22 cell line. In addition, we studied how chromatin condensation affects CoREST proteins binding using treatments like mitotic-phase arrest, HDAC inhibitors and RNAse A. Immunofluorescent assays show that CoREST proteins are not present in the pericentromeric heterochromatin as assessed by colocalization with heterochromatin protein 1α (HP1α). Although, CoREST1 and CoREST2 are segregated, both colocalize with DNA-dense regions. Accordingly, CoREST1 and CoREST2 elute in high-salt and DNAse I – resistant chromatin fractions. On the other hand, CoREST3 is mostly found in cytosolic and DNAse I sensitive fractions. Altogether our data indicate that the CoREST co-repressors occupy different niches in the nuclei of cells and chromatin.

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SENP6 restrict the uncontrolled growth of SUMO chains

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SUMO modification is mediated by an enzymatic cascade involving an E1 activating enzyme, an E2 conjugating enzyme and a small number of SUMO E3 ligases. SUMO processing, deconjugation and chain depolymerisation are catalysed by SUMO specific proteases known as SENPs. Thus the steady state of SUMO modification is maintained by factors influencing the rates of conjugation and deconjugation. To identify components mediating SUMO homeostasis we carried out an siRNA screen in cells expressing a fluorescent version of SUMO and monitored the formation of SUMO nuclear foci. The factor with the greatest influence on SUMO foci was SENP6, as its depletion lead to a dramatic increase in the number, size and intensity of SUMO foci. SENP6 appeared to play a unique role in SUMO homeostasis as depletion of other SUMO proteases did not substantially alter the number of SUMO foci. Cells depleted of SENP6 displayed increased numbers of DNA damage induced SUMO foci and were sensitised to agents inducing DNA replication stress. Analysis of SUMO components by mass spectrometry revealed that after SENP6 depletion uncontrolled polymerisation of SUMO into chains by SUMO E3 ligases nucleated the formation of SUMO foci. These localised accumulations of SUMO are likely to disrupt the controlled interactions of SUMO with proteins containing SUMO Interaction Motifs, that are largely responsible for the biological outputs of SUMO modification. This provides an explanation for the diverse phenotypes reported for SENP6 depletion.

PAI-CONICYT 79150075 Proyecto de Fondecyt Iniciación 11150532

Poster Session I

1) Role of membrane - initiated cortisol action over the glycolysis and gluconeogenesis related gene expression in two relevant farm fish.

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Cortisol is the main glucocorticoid hormone in fish involved in the regulation of metabolic adjudgments under a stress condition. The effects of cortisol are attributed to canonical/genomics mechanisms involving the interaction of the hormone with its intracellular glucocorticoid receptor and the subsequently modulation of target genes. However, cortisol also can interact with membrane components activating rapid signaling pathways with unknow contribution during the stress response. Therefore, in this work we evaluate the impact of both cortisol actions over the early regulation of key glucose metabolism related genes in two relevant farm fish, rainbow trout (*Onchorynchus mykiss*) and gilthead seabream (*Sparus aurata*). Juveniles rainbow trout and gilthead seabream were intraperitoneally administrated with cortisol, cortisol-BSA, and vehicle. Cortisol-BSA correspond to membrane impermeable analogous of cortisol exclusive inductor of non-canonical signaling pathways. After one hour of each treatment,cortisol and glucose plasma levels were measured and key glycolysis and gluconeogenesis-related gene expression were evaluated by RT-qPCR Plasma cortisol and glucose increased in cortisol and cortisol-BSA groups respect to vehicle, reaching physiological levels associated with an acute stress condition. RT-qPCR reveals that transcripts of gluconeogenesis-related genes: glucose 6 phosphatase (*g6pase*) as well as glycolytic related genes: glucokinase (*gk*), phosphoglycerate mutase 1 (*pgam1*), enolase 3 (*eno 3*) are differentially modulates under cortisol and cortisol-BSA administration in both fish species. These results reveal that membrane-initiated cortisol action contributes to modulates the early stress response in two relevant farm fish.
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3) SALL2 transcription factor promotes cell migration by regulating focal adhesion dynamic.

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SALL2 is a poorly characterized transcription factor member of the *Spalt* gene family, involved in neurogenesis, differentiation and cancer. Interestingly, *SALL2* deficiency has been associated with failure in the closure of the optic fissure and deficient neurite outgrowth, both defects suggest a relationship between SALL2 and cell migration. Cell migration is a multistep process involved in development, maintenance of multicellular organisms and cancer. To determine the role of SALL2 in cell migration, we used immortalized *Sall2*-deficient and wild type Mouse Embryo Fibroblasts (MEFs), and *short hairpin RNA (shRNA)-mediated* depletion of *Sall2* in MEFs. Wound healing assay, transwell migration assay, immunofluorescence, cell adhesion assays, Western blot and bioinformatics analysis were performed. Our data indicate that SALL2 positively regulates cell migration promoting highly polarized states and cell detachment, but does not affect lamellipodia or filopodium formation. In addition, SALL2 accelerates focal adhesion (FA) disassembly after nocodazole- wash out treatment and in a spreading- context; SALL2 promotes Focal Adhesion Kinase (*FAK*) autophosphorylation at Y397. RNA seq data analyses further support the role of SALL2 in cell migration and adhesion. Taken together, our data suggest that SALL2 promotes cell migration mainly through the modulation of focal adhesion dynamics. Deregulation on cell migration promotes several diseases such as, tumor formation and spread to others tissues. Therefore, the role of SALL2 in migration might have implications in cancer.

FONDECYT 1151031

5) Determination of the mechanochemical mechanism of the BiP protein in the translocation process *in multiplo*.

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Post-translational translocation (PT) of proteins through the endoplasmic reticulum (ER) is mediated by a channel protein called Sec61 and auxiliary motors proteins such as BiP. BiP is a member of the ATPase Hsp70 type chaperones family, and studies suggest that it would be involved in force application during the process of PT of extended polypeptides. The work exerted by BiP in the translocation of a protein is not clear and studies suggest that BiP could be involved in a "*ratchet*" passive mechanism and/or an active mechanism of direct pulling. To determine the mechanochemical mechanism exerted by BiP during PT, we designed a novel procedure to measure forces in bulk using chimeric proteins (with different unfolding forces) and microsomes (vesicles obtained by ER fragmentation) to perform functional assays of translocation *in vitro*. A new method of obtaining pure and active microsomes was developed, based on the disruption of the cells by glass beads followed by a sucrose gradient. By using a semi-quantitative Western blot analysis, we were able to estimate the concentration of BiP in the microsomes, obtaining a value around 2 mM. Finally, we prepared an enriched fraction of a chimeric-protein containing the Calmodulin molecule (composed of a signal-sequence, unfolded titin, and Calmodulin, with an unfolding force of 7 pN), as a translocation substrate. Thus, we obtained the components required to perform the translocation assays *in vitro*. These results demonstrate that the new procedure we developed represents a very simple, low cost and efficient system to measure force in translocation.

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7) Effect of poly (dA:dT) tracts on nucleosome remodeling activity of ATP-dependent chromatin remodeling complexes.

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Chromatin dynamics has a wide impact on regulation of different cellular processes involving protein-DNA interactions, such as transcription. For this reason, nucleosome positioning in different genomic regions has become a relevant issue to better understand these processes. In this context, it has been shown that many gene promoters have a stretch of unusually long linker DNA of around 150 bp, called nucleosome-depleted region (NDR). Many studies have been focused on understanding how these regions are formed, finding homopolymeric tracts of DNA, such as poly (dA:dT) tracts, at the center of many NDRs. However, it is currently considered that these sequences play a passive role on NDR formation. On the other hand, key remodeling factors, such as ATP-dependent chromatin remodeling complexes, have been considered to play a major role on NDR formation. In this context, the RSC complex (a SWI/SNF subfamily member) has been defined as a key factor on NDR formation. Interestingly, recent studies suggest a functional connection between RSC and poly (dA:dT) tracts, although it is still poorly understood. Taking into account these phenomena, we determined *in vitro* the influence of poly (dA:dT) tracts on nucleosome remodeling activity of RSC and ISW1a complexes (ISWI1a, an ISWI subfamily member). Using mononucleosomes containing poly (dA:dT) tracts and purified complexes, we performed remodeling assays. We found that poly (dA:dT) tracts can directly influence remodeling activity of these complexes. Additionally, we found that orientation of poly (dA:dT) tracts can differentially stimulate their remodeling activity.

CONICYT, FONDECYT/Regular 1180911. UdeC-Enlace 216.037.020-1.0.

9) A simple method for instructing protein structure for high school and university students using recycled material.

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To understand proteins, the student must use their imagination, or appropriate software to see the structures, but, always in a 2D plane. The use of 3D structures and 3D printers facilitates the study of proteins and their behavior with other proteins or ligands, but they are not easily available to all students and 3D printing is still very expensive. The aim of this presentation is to discuss an approach to construct 3D structures of proteins in a didactic and cheap way, using recycled material and thus allowing many students to have access to this fascinating world. I will show how to build a protein with a ribbon polymer. The materials to be used are: a ribbon of PET of 8x800 mm, a clamp tweezer, tape scotch and folding instructions of the crystal of interest. In summary, it will be illustrated how to construct a β sheet and an alpha helix. In the first case, as an example, a tape and a clamp are used. The clamp is placed in a vertical position with respect to the tape and is folded to the front, a width of the clamp is separated and folded back. These steps are repeated as many times as the number of amino acids present in the secondary structure of the protein. In both structures, the angle of folding must be 120°, emulating the angle of twist between amino acids. In this presentation I will show the way to build two different proteins: insulin and secretin.

Fondecyt 1141033; DID-UACh 2013-45

11) An inflammatory status in the brain causes behavioral alterations after infection by the human respiratory syncytial virus.

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The humanrespiratory syncytial virus (hRSV) is the major cause of hospitalizations in young children worldwide,including severe bronchiolitis and pneumonia. Recently, neurologic alterations have been associated with hRSV infection in children, which include seizures, central apnea and encephalopathy. Further, hRSV impairs behavioral and learning processes in animals probably due to either an altered production of pro-inflammatory cytokines or by the CNS cells infection. First, we evaluated if the hRSV infection promotes the immune cell transmigration into the CNS and we observed that neutrophils, resident macrophages and inflammatory monocytes are increased at day 3 post-infection, whereas B lymphocytes and CD8+ T cells are increased at 7 days post-infection, Then, we analyzed the pattern of cytokine expression by RT-qPCR and ELISA in the brain of mice intranasally challenged with of hRSV, observing a down regulation of CD200 and an elevated IL-6, TNFα, CCL2, and IL-4 expression levels.hRSV-infected murine astrocytes showed an increased production of nitric oxide (NO), GFAP, IL-6 and TNFα, suggesting an activation of astrocytes. Furthermore, similar results were found using hRSV and human astrocyte cultures for viral loads and GFAP levels. Moreover, hRSV infection caused acute and chronic behavior impairment. In these mice we found, an altered expression of cytokines such IL-4, IL-10 and CCL2, as well as increased GFAP levels in mice with a severe behavioral impairment due to hRSV infection. This work suggests that hRSV-infection can impair the proper CNS function due to local inflammation and that astrocytes can be targeted during this process.

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13) Characterization of SNX5 Trafficking During B Cell Activation.

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The interaction of the B cell receptor (BCR) with antigens (Ags) tethered at the surface of presenting cells gives rise to an immunological synapse (IS). During this process, B cells undergo extensive remodeling of their actin cytoskeleton and microtubule network, which polarizes towards the synaptic interface. Polarization of the microtubule-organizing center is a key step, which allows the local recruitment and secretion of lysosomes at the immune synapse to facilitate the extraction and processing of immobilized antigens. BCR-Ag complexes are internalized through clathrin-mediated endocytosis and must converge with lysosomes where antigen processing occurs. However, the mechanisms involved in the intracellular trafficking of BCR compartments are largely unknown. We focused on sorting nexins, which regulate vesicle trafficking can bind directly to the plasma membrane and vesicles, through their phox homology (PX) domain. In particular, we studied sorting nexin 5 (SNX5), which was identified in a semi-quantitative screening of proteins associated to the centrosome of activated B cells. To assess the localization of SNX5 in the intracellular trafficking of the BCR during activation, we used a B cell line (IIA1.6) activated with immobilized antigens on beads, and evaluated the distribution of SNX5 together with recycling endosomes, BCR and cytoskeleton markers by immunofluorescence. The results of this work show that in non-activated B cells, SNX5 is associated with the centrosome and BCR^{+} intracellular compartments. Upon activation SNX5 becomes polarized to IS, together with recycling endosomes. We anticipate that SNX5 coordinates intracellular BCR trafficking when forming an immune synapse.

This work was supported by FONDECYT Regular # 1180900, research grant to MIY and FONDECYT Iniciación # 11171024 research grant to JD.

15) Quillaic acid *from Quillaja Saponaria*: New cytotoxic agent for gastric cancer treatment.

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The gastric cancer (GC) is a health problem worldwide. In Chile, is the second cause of cancer death. Late diagnoses, lack of preventive treatments or ineffectiveness in chemotherapy are a problem to reverse of mortality. A promising approach is the use of phytochemicals as new antitumoral agents.

The inner bark of *Quillaja saponaria* contains more than 60 types of triterpenic saponins. Triterpenes have shown a several biological activities as: anti-inflammatory, antiviral and cytotoxic activity. This diversity result of the chemical variability of the hydrophilic chains bonded to the aglycone core -quillaic acid (QA)-.
The aim of this work was to study the biological capabilities of QA on GC cell lines. The cytotoxic effect and viability changes of QA was evaluated on *in vitro* model using SNU1 and KATOIII human gastric cancer cells by flow cytometry. The viability changes were analyzed using a 3-state model (AVD). Cells with optimal mitochondrial function and membrane integrity are defined as “alive” (A); with cell damage (alterations of several parameters) as “dead” (D) and with a specific damage in organelles as “vulnerable” (V) cell. As apoptotic parameters, was evaluated: release of cytochrome c and caspase activity.

In conclusion, QA from *Q. saponaria* has anti-proliferative activity on GC cells, inducing sequential damage on KATOIII (160 µM QA) and no-sequential on SNU-1 (20 µM QA) and inducing cell death by apoptosis mechanism. Our results confirm that QA is a prominent antitumoral agent; however, *in vivo* experimentation is required.

This work was funded by DI 037.227 (PUCV) and CONICYT N 21141206

17) Tracing the evolutionary history of protein stability in a thermophilic bacterial lineage.

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Evolution is the main driving force of divergence and adaptation in all living organisms, allowing life to thrive even under the most extreme conditions. One of the major goals of evolutionary biochemistry is to unravel how extremophile organisms have adapted their metabolic machinery to adverse physicochemical environments at a molecular level. To address this, we studied the evolution within thermophilic and mesophilic lineages of the 4-amino-5-hydroxymethyl-2-methylpyrimidine kinase (EC. 2.7.1.49), an enzyme exclusively found in bacterias, through a combined experimental and bioinformatic approach. Using ancestral sequence reconstruction, we resurrected the last common ancestor of the protein from a thermophilic clade (*Thermales*), a mesophilic clade (*Entherobacteria*) and the last common ancestor between them, and compared their properties with their extant counterparts. Thermal stability measurements trough circular dichroism revealed that there is a divergent trend, reflected as an increase in the melting temperature along the thermophilic branch, whereas a decrease is observed in the mesophilic branch. In order to get an atomistic detail of the structural differences emerged throughout the evolution of these enzymes, we performed molecular modelling and molecular dynamic simulations to assess the intramolecular interaction network in each protein, which showed that the changes in thermal stability are accompanied by variations in the conformational flexibility. Our results are concordant with the idea that *Thermales* were late colonizers of hot environments and illustrate the value of evolutionary information to understand how an industrially relevant property emerges in nature.

Fondecyt 3160332, 1150460 & 1181253

19) Adenosine-mediated signaling in proneural and mesenchymal cancer stem-like cells of patients with glioblastoma.

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High levels of extracellular adenosine in Glioblastoma Stem-like Cells (GBM) have been related to chemoresistance and cellular invasion, so the inhibition of the production and/or signaling of this nucleoside, has been proposed as a therapeutic target. It has been demonstrated that GSCs can respond differentially to treatments depending on whether they exhibit a proneural (PNG GSCs) or Mesenquimal (GSCs Mes) phenotype. However, clinical methods to differentiate and treat them have not been proposed. In this work, we have proposed the identification of GSCs PN and GSCs Mes by analyzing the expression of genes that are differentially expressed in each subtype by RT-qPCR. In addition, we have evaluated the degree of activation of purinergic signaling in GSCs PN and GSCs Mes through the quantification of extracellular adenosine using HPLC, and the expression of adenosine A2B (A2BAR) and A3 (A3AR) receptors by Western blot. Finally, we evaluated the effect of A2BAR and A3AR antagonists on the chemosensitivity of PN and Mes GSCs by MTS assays. We have observed that 6 genes are differentially expressed between GSCs PN and GSCs Mes. In addition, the Mes GSCs exhibited a greater production of extracellular adenosine, and higher expression of A2BAR and A3AR than their PN counterpart. In fact, the antagonism of these receptors chemosensibilized more to the Mes GSCs than to the PN GSCs when the cells were treated with temozolomide or doxorubicin, suggesting that adenosine-mediated signaling could be more active in Mes GSCs.
FONDEF VIU 16E0145 FONDECYT 1160777

21)**Characterization of the metal-dependent aggregation of a model catalytic amyloid peptide: implications for the development of novel active bionanomaterials.**

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Amyloids are polypeptides aggregates of highly regular structure involved in many neuropathologies. The amyloid architecture has a beta-sheet structural core that allows for a periodical solvent-exposure of functional groups from the constituent side chains, generating an ordered surface with a repetitive pattern. Previous studies have shown that many amyloids can interact with divalent metals forming amyloid-metal complexes. Moreover, rational design approaches of such complexes using small peptides have yielded reactive amyloids that exhibit catalytic activity. Our group recently developed a catalytically active amyloid-metal complex using a peptide (SDIDVFI) with a sequence derived from the active site of a DNA polymerase. The peptide self-assembly into amyloids is strictly metal-dependent and in presence of manganese ion (Mn^{2+}), the Mn^{2+}-amyloid complex displays an ATPase-like activity. In this study we show the effect that different divalent metals have on amyloid self-assembly and on the potential emergence of novel catalytic activities. Aggregation experiments were performed in presence of different divalent metals that are known to engage in coordination bonding and that are also typically found in the active sites of enzymes (Mg^{2+}, Mn^{2+}, Ca^{2+}, Zn^{2+}, Cu^{2+}, Ni^{2+}). The aggregation time-course experiments were followed by fluorescence of the amyloid-specific thioflavin-T probe whereas the ultra-structure of the fibers was characterized by transmission electron microscopy. Our data show that both the time-dependent aggregation of the peptide and the observed activities are highly modulated by the specific divalent metal used, indicating that the amyloid structure can provide a useful scaffold for the development of novel and diverse self-assembling bionanomaterials.

FONDECYT 11160554

23) NUAK1 regulates the mitochondrial bioenergetic function of colon cancer cells.

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NUAK1 is a kinase overexpressed in high malignant tumors of colon cancer, where it is associated with tumor progression, promoting processes like cell survival, proliferation and metastasis. NUAK1 has been associated with the maintenance of ATP levels in cancer cells, but the underlying mechanisms are unclear. Currently, cancer metabolism is a key subject of cancer research, therefore we were interested in knowing more about NUAK1 participation on bioenergetics regulation of colon cancer cells. We found that stable NUAK1 overexpression increases cellular ATP levels and mitochondrial function. Accordingly, shRNA-mediated NUAK1 depletion decreased cellular ATP levels and mitochondrial activity. Interestingly, NUAK1 only affected mitochondrial ATP, suggesting that NUAK1 play a role in the mitochondrial bioenergetics. We performed a MudPIT mass spectrometry analysis and we found ATP5A and ATP5B as possible interactors of NUAK1, both ATP synthase complex subunits. Because mitochondrial ATP production depends on ATP synthase function, we tested whether NUAK1 was functionally associated to this complex. NUAK1 expression was positive correlated with ATP5B expression and through co-immunoprecipitation assays we validated that NUAK1 interacts with ATP5A, in which interestingly we found a putative site of phosphorylation by NUAK1. ATP5A is translated in the cytosol and then imported to the mitochondria, so although we were unable to find NUAK1 inside the mitochondria, NUAK1 could be interacting with ATP5A in the citosol before mitochondrial ATP5A import. Altogether, we suggest that NUAK1 impacts mitochondrial activity of colon cancer cells by affecting ATPase complex activity, likely by regulating ATP5A import to the mitochondria.

FONDECYT 1160731

25) Measuring glucokinase activity at extreme salt concentrations.

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Glucokinase activity (GK) is generally measured with a coupled-enzyme assay using glucose-6-phosphate dehydrogenase as an auxiliary enzyme. Currently, the method available for measure GK activity can be used only at millimolar concentration of salt. However, halophilic enzymes perform catalysis near of salt saturation, being necessary search for new auxiliary enzymes to analyze catalytic properties of halophilic enzymes at extreme salt concentrations. In this work, we have used the ROK family ATP dependent glucokinase from *Halobiforma lacisalsi* (HlacROK-GK) and the glucose-6-phosphate dehydrogenase from *Haloferax volcanii* (HvGlc6PDH) as models. The sequence analysis of HlacROK-GK and HvGlc6PDH indicates a high content of acidic residues (Glu+Asp, 18.2 and 18.4%) and a low content of Lys (0.9 and 1.9%) with a consequent low isoelectric point of 4.18 and 4.59, respectively. Such characteristics are in agreement with the canonical strategy reported to be use by halobacteria protein to adapt to halophilic environments. Given the halophilic character of these proteins, the heterologous expression in *Escherichia coli* leads to mis-fold and inclusion bodies formation. Here we report the purification of HvGlc6PDH using a refolding strategy, kinetic parameters and analysis of enzyme activity at different salt concentrations. The highest activity was found with KCl and the optimal activity was reached over 1.66 M and kept constant until 3.52 M. This work will contribute to design an auxiliary assay for GK activity that could be used in biocatalytic processes requiring high ionic strength.

Fondecyt 1150460

27) Role of Hmo1 in SWI/SNF recruitment by transcription factors.

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ATP-dependent chromatin remodeling activity plays a relevant role in transcriptional regulation. Several protein complexes exerting this activity have been described, being the yeast SWI/SNF complex the founding member. These complexes can facilitate the access of DNA-interacting proteins to their cognate sequences. For a number of these complexes it has been previously observed by our laboratory that High Mobility Group (HMG) proteins can enhance their activity. Nhp6A, Nhp6B and Hmo1 are yeast HMG proteins present at high levels in the cell nucleus. In this scenario, we studied the relationship between SWI/SNF and these HMG proteins *in vivo*. We next studied the genome-wide binding patterns of Nhp6A/B, Hmo1 and the SWI/SNF complex, finding that most of gene promoters presenting high occupancy of this complex also display high enrichment of Nhp6 and Hmo1. Using deletion mutant strains we demonstrate that binding of SWI/SNF is significantly reduced at numerous genomic locations by deletion of *NHP6* and/or by deletion of *HMO1*. In addition, by comparing our genome-wide binding patterns of Hmo1 and SWI/SNF to genome-wide binding patterns of a large number of transcription factors, we have found that binding to gene regulatory regions of a number of these transcription factors only correlates with Hmo1 binding profile, while the binding pattern of other transcription factors correlates to both, SWI/SNF and Hmo1 binding profile. Within the target gene promoters of these transcription factors, our analyses will define those where Hmo1 is required for loading of SWI/SNF onto gene regulatory regions.

CONICYT, FONDECYT/Regular 1180911. UdeC-Enlace 216.037.020-1.0.

29) Changes in the activity level of the FaEG1 enzyme promoted by ABA hormonal treatments of Fragaria x ananassa fruit.

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Commercial strawberry (*Fragaria x ananassa*) is a berry fruit with excellent organoleptic properties, however its fast softening limits its commercialization. Fruit softening is related to cell wall degradation and several related enzymes have been studied in strawberries, including endoglucanases (EG). One *EG* gene has been identified in *F. x ananassa*, *FcEG1*. Phylogenetic analyses suggest that *FaEG1* belongs to α group of GH9 family with other proteins previously described with roles in elongation, ripening, and abscission. Additionally, *FcEG1* transcript increased during fruit growth and fruit softening. *FaEG1* gene expression seems to be regulated in plants by different factors including hormones. To test their responsiveness, fruit were treated with abscisic acid (ABA), and the expression of *FaEG1* isoforms was analyzed. RT-qPCR analysis revealed a significant variation in the expression of *FaEG1* gene after hormone treatment, showing an activator effect of ABA on *FaEG1* gene expression. *FaEG1* gene promoter was cloned and *in silico* analyzed to reveal putative *cis* elements. Different regulatory elements responding to hormones were found in each promoter sequence. Finally, the activity level of the treatment fruit showed higher levels than those not treated. The changes in expression in response to ABA hormone treatments are consistent with the activity levels and regulatory elements described in the promoter sequence of *FaEG1* gene.

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31) Expression of SIRT epigenetic modifiers and senescent-associated genes in hippocampal neurons and Cancer Cells.

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Cancer corresponds to one of the diseases with the highest mortality rate worldwide. This pathology is known to be heterogeneous, due to this, several causes that can generate it are known. One of them is deregulation in gene expression by epigenetic modifications. Among the genes involved in cancer are the senescent-associated genes p21, a cyclin-dependent kinase 1 inhibitor (CDK1) and p16, involved in the inhibition of CDK4 and CKD2 activity and the histone deacetylases sirtuins (SIRT): SIRT2, SIRT6 and SIRT7. In this research we characterized the expression levels of these genes and their proteins in different cells: primary hippocampal neurons in 7 (HN7) and 15 (HN15) days of *in vitro* culture, N2A neuroblastoma cells and A549 non-small cell lung cancer cells. These analyzes were performed by RT-PCR, qRT-PCR, immunocytochemistry and Western Blot. The results show that in hippocampal neurons p21, SIRT2 and SIRT6 increased their levels in HN15 with respect to HN7, while SIRT7 remained constant. On the other hand, neuroblastoma cells showed that SIRT7 has a higher expression when compared to HN7 neurons, contrary to SIRT6 and p21 that show low levels. Finally, in A549 pulmonary cancer cells higher p16 levels was observed compared to p21. In conclusion there is differences on the expression pattern of SIRT and p21 and p16 genes in normal and cancer cells, suggesting its possible differential association in the development of this pathology.

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33) Functional insights into human ADP-dependent Glucokinase: Kinetic and biochemical characterization.

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In some archaea, the glycolytic pathway presents unique features like the glucokinase (GK) and phosphofructokinase enzymes which uses ADP instead of ATP as phosphoryl donor. Recently, the presence of an ADP dependent GK from *H. sapiens* (hADPGK), located in the endoplasmic reticulum, has been reported. Comparison of its sequence with archaeal enzymes reveals the presence of an extra 53 amino acids segment located at the N-terminal. Moreover, the conserved motif of the glucose binding site of the eukaryotic enzyme NXCXD, shows a Cys residue instead of the Arg present in the enzymes from archaea. To evaluate the importance of this segment as well as the presence of a Cys residue at the active site, we generate a truncated protein (Δ53hADPGK), a C82N mutant and a complete hADPGK attached to a GB1 tag (GB1hADPGK). The truncated and the complete enzyme show similar specific activities and Km values for glucose and ADP at equimolar concentrations of Mg^{+2} and the nucleotide. An increase in the Mg^{+2} concentration produces a diminution in the Vmax, especially in the complete enzyme. The C82N mutant presents Km values for both substrates very similar to the ones determined for the Δ53hADPGK wild-type enzyme, but a 6 fold decrease in the Vmax, which suggest a role for this Cys residue as a catalytic one and not in substrate binding. The similar kinetic parameters for the truncate and the complete enzyme suggest that the extra N-terminal segment is probably involved in a regulatory role, perhaps in the Mg^{+2} inhibition

Fondecyt postdoctorado 3160373

35) Functional characterization of Hsp70 Immunoglobulin Binding Protein (BiP) and P163G mutant in order to analyze the allosteric disruption of SBD and NBD.

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The ATPase BiP is a chaperone belonging to the Hsp70 family that is involved in the regulation of important biological processes such as synthesis, folding and translocation of proteins in the endoplasmic reticulum. This chaperone has two domains communicated between each other that modulate the catalytic activity; a Nucleotide Binding Domain (NBD), in the N-terminal extreme, which binds and hydrolyzes nucleotides, and the Substrate Binding Domain (SBD) in the C-terminal extreme, which binds the extended conformation of proteins. Previously it has been shown that a protein from the same family, called DnaK from bacteria, has allosteric communication between the 2 domains via Proline 193. In this work, we studied the allosteric communication between SBD and NBD replacing a residue that plays an imperative role in the communication between them, just to uncouple this communication. We replaced Proline 163 (equivalent to the 193 from DnaK) for a Glycine in order to destabilize the allosterism in yeast BiP. We characterized the allosterism by catalytic activitymeasurements of BiP and its mutant using a coupled assay that leads to NADH oxidation. We determined the activity parameters of WT and mutant BiP in the presence and absence of an activating peptide substrate (HTFPAVL) showing that the mutant P163G was less active than the BiP WT, those results gave us a notion for the first time that the residue 163 could be involve in allosteric communication in BiP.

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37) Purification and crystallization essay of Escherichia coli agmatinase.

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Agmatinase catalyses the hydrolysis of agmatine to putrescine and urea. Agmatine, results from decarboxylation of arginine by arginine decarboxylase and is a precursor of putrescine and higher polyamines. Agmatine may have important roles in mammals, regulating several neurotransmitter-related functions. We have studied the amino acid residues that determinate the specificity of agmatinase, by mean of site directed mutagenesis. However, the high specificity for agmatine still is a mystery. Moreover, *E. coli* agmatinase is the only agmatinase characterized kinetically. Therefore, we propose to obtain the crystallographic structure of *E. coli* agmatinase. We purified recombinant *E. coli* agmatinase, by agarose-NTA- Ni2+ affinity chromatography obtaining a 90% of purity after this step. To obtain crystals of the purified protein, it was concentrated up to 10 mg/mL and we used the vapor diffusion method by hanging drop technique, using similar conditions reported previously for agmatinase from other species. Cristaline precipitate were obtained from three conditions, where the first contains 0.2M Ammonium acetate, 0.1M Sodium citrate tribasic dihydrate pH 5.6, 30% w / v PEG 4000, the second 0.1M Sodium acetate trihydrate pH 4.6 , 8% w / v PEG 4000, and the third 0.1M Sodium citrate tribasic dihydrate pH 5.6, 20% v / v 2-Propanol, 20% w / v PEG 4000. These results are the starting point to improve the conditions in order to obtain single crystals able to be diffracted and then solving the protein structure.

VRID-Enlace 217.037.022-1.

39) Characterization of the structural and dynamic features of NusG-bound bacterial transcription elongation complexes.

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NusG belongs to the only family of universally conserved transcription factors. Its main function is to increase RNA polymerase (RNAP) processivity and coupling its activity to translation. The crystallographic structure of NusG complexed with RNAP show how both proteins interact and suggested how the N-terminal (NTD) and C-terminal (CTD) domains of NusG change their conformations to tether transcription with translation. However, this transcription elongation complex (TEC) is incomplete because it was crystallized without DNA and RNA. Here, we performed a structural and dynamic characterization of NusG complexed with transcriptionally paused TEC to elucidate its regulation mechanism. RNAP was combined with oligonucleotides encompassing a pausing sequence, complexed with NusG and analyzed by hydrogen-deuterium exchange mass spectrometry. About two thirds of the NusG structure become protected upon complex formation, mainly located within the NTD, which binds to the central cleft in RNAP between the β and β´ subunits. CTD protection was observed in regions corresponding to strands β1, β2 and β5, whilst crystallographic studies proposed that these regions of the β-barrel were more exposed to facilitate binding to the ribosome. However, increased deuterium incorporation upon complex formation was observed in the β loop within the NTD, which participates in elongation, and β4 in the CTD, which binds to the ribosome. In conclusion, dynamics studies of NusG allow us to relate conformational changes when joining the TEC with its regulatory mechanism. Complementary experiments with the homologous virulence factor RfaH will allow us to elucidate the molecular mechanism of these proteins.

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41) Corrosion Resistance and Anti-biofilm Effect of Rock Rose Remedy: A Potential Preventive Measure in Implant Therapy.

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Staphylococci is the leading etiologic agent of implant-related infection. In presence of rock rose (*Helianthemum nummularium*) floral remedy, we evaluated the corrosion behavior of commercially pure titanium as well as quantified the *Staphylococcus aureus* biofilm formation. To analyze the corrosion resistance of pure titanium, electrochemical corrosion tests were performed. We submitted pure titanium samples into a physiological (pH 6.50) or pathogenic (pH 2.50) artificial saliva environment at 37oC. For the *in vitro* static biofilm assays, a multivirulent *Staphylococcus aureus* strain was used for assessment of biofilm formation over pure titanium disks in the absence/presence of rock rose floral. Triplicates were performed for both corrosion tests and biofilm experiments. P values were determined by two-way analysis of variance for pairwise comparisons (corrosion) and Student's t-test (biofilm assays). Results were considered significant when p-value < 0.05. Rock rose floral treatment reduced *Staphylococcus aureus* biofilm formation on titanium surface and promoted a higher titanium corrosion resistance in artificial saliva at low pH. We have shown that rock rose remedy can prevent bacteria adhesion over the pure titanium in a healthy oral environment (pH 6.50) and did not interfere in the titanium corrosion response.

Keywords: *Corrosion; Titanium; Staphylococcus aureus; Peri-Implantitis; Rock Rose; Floral*

CAPES / MEC - FUNDAÇÃO COORDENAÇÃO APERFEIÇOAMENTO DE PESSOAL DE NÍVEL SUPERIOR

43) **Endothelin converting enzyme-1c regulates malignity of oral squamous carcinoma cells.**

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Introduction:
Endothelin Converting Enzyme-1c (ECE1c) converts Big-Endothelin into Endothelin-1 (ET-1) and has been linked to colon and prostate cancer progression. Our recent findings show that a super-stable ECE1c mutant promotes cancer stem cells formation, as well as drug resistance and tumor growth of colon cancer cells. Moreover, recent data in literature suggest that ECE1c is overexpressed in oral squamous cell carcinoma, but its exact role in malignant progression remains to be determined. Here we studied the role of ECE1c in CAL27 oral squamous carcinoma cells.

Methodology:
Lentiviral bicistronic expression of mCherry and FLAG-tagged super-stable (ECE1c-SS) and wild-type (ECE1c-WT) forms were used to get CAL27 cell clones, which were sorted by flow cytometry. Protein stability was analyzed in presence of CHX with an anti-FLAG antibody. Messenger RNA levels of stemness genes were measured by RT-qPCR. Cell migration was evaluated by a wound healing assay, and viability by MTS and trypan blue assays.

Results:
ECE1c-SS displayed higher protein stability in CAL27 cells. ECE1c-SS expressing CAL27 clone cells produced higher mRNA levels of stemness genes, as well as higher rates of proliferation, viability and migration in comparison to WT and mock cells. **Conclusions.** Super-stable ECE1c overexpression promotes malignant characteristics, presumably by increasing levels of ET-1 in CAL27 oral squamous cell carcinoma cells.

FONDECYT grants 1161219 (FA), 11150624 (MVG), and 1160889 (JT).

45) Tracing halophilic traits within enzymes of the ADP-PFK/GK family from the Euryarchaeota phylum.

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Halophilic archaea thrive in environments with almost saturate salt concentrations, which has promoted the adaptation its molecular machinery. Within the *Euryarchaeota*, organisms from *Halobacteria* and some of *Methanosarcinales* have been shown to be halophiles. Proteins from *Halobacteria* have a canonical well-studied model for halophilic adaptation. Some of these traits include an increased content of acidic residues (Glu and Asp), with a lower content of Lys, leading to a negative charged molecular surface and isoelectric points around 4.2.

In order to established if ADP-dependents kinases from *Halobacteria* possess the mentioned canonical halophilic traits, we selected the sequence of ADP-PFK from *Halobiforma lacisalsi* to perform bioinformatic analyses that include sequence alignments and homology models. Trough these analyses, we determine the sequence of *H. lacisalsi* possess a high percentage of residues Glu and Asp (11.3 and 8.5%) and a 1% of Lys, the isoelectric point is 4.35 and it also has a negative electrostatic potential surface. However, we have described that ADP-dependents kinases from the order *Methanosarcinales* adapt to salt by a non-canonical evolutionary conserved strategy. A structural and biochemical analysis of the resurrected last common ancestor of ADP-PFK/GK from *Methanosarcinales* suggests the halophilic character is an ancient trait in the evolution of this protein family.

These results lead us to determine that ADP-dependent kinases from *Halobacteria* possess the classical signatures of halophilicity, while the ancestral protein of *Methanosarcinales* shows the non-canonical strategy, which open up new avenues for the search and development of novel salt tolerant biocatalysts.

Fondecyt 1150460

47) **Insights of sequence differences between the forkhead domain of FoxP1 and FoxP3 in their stability and dimerization properties.**

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Forkhead box P (FoxP) proteins (FoxP1– 4) are members of the human Fox transcription factors family, related with cell development, immunity and tissue homeostasis. Different to other Fox subfamilies, they adopt domain-swapped dimeric structures *in vitro* and *in vivo*, which have been associated with their regulatory cellular functions as genetic repressors. In this scenario, the DNA-binding domain (forkhead) is critical in those process due the direct participation in the exchanging of secondary structure between monomers to adopt the final quaternary structure. Despite the high sequence identity described between FoxP members (FoxP1–4), their dimerization properties (Kd) are dramatically different, varying from nM (FoxP3) to mM values (FoxP2). In that context, FoxP1 has showed intermediate thermodynamic properties with respect to the other members, encouraging us to use it as a protein model to describe the amino acid-specific changes in dimerization differences between FoxP members. Comparison between FoxP1 and FoxP3 showed three major residue changes located in helix H1 (Q15W), hinge loop (Y40F) and strand 2 (V69E), all regions described as highly flexible and relevant in domain-swapping in previous results. We explored the effect of these single mutations of FoxP1, focusing in the relationship between conformational dimeric stability and thermodynamic properties of association. Equilibrium unfolding experiments indicated that only the Q15W substitution decreased the conformational stability of the domain in a significant extent, whereas the Q15W and Y40F mutations altered the dissociation constant, indicating that changes in the dissociation behavior affect mainly the structural dynamics rather than protein stability.

FONDECYT 1170701

49) Can Alzheimer's beta-amyloid (1-42) be reactive in the amyloid-state? Characterization of a putative esterase activity of Zinc-complexed beta-amyloid (1-42).

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The accumulation of beta-amyloid (1-42) (Aβ) peptides into amyloid plaques is one of the pathological hallmarks of Alzheimers Disease (AD). These plaques are known to contain certain divalent metals such as copper (Cu^{2+}) and zinc (Zn^{2+}) and in vitro studies show binding of these ions to the peptide through coordination bonding with histidine residues located in the N-terminal. Recent studies with rationally-designed small peptides have shown that histidine-containing sequences can exhibit esterase activity in the amyloid state in presence of Zn^{2+}. In this work we show that the Aβ-Zn^{2+} complex can hydrolyse p-nitrophenyl-acetate (pNPA) into p-nitrophenol and acetate, suggesting a potential estarase activity. Ab was recombinantly produced in E. coli as a pure peptide without modifications using a previously reported purification method that allows for production of high quantities of peptide in a soluble form. The esterase activity of the peptide in the amyloid state is measured in TRIS 100 mM pH 7.5, Zn^{2+} 1 mM and pNPA 0.2 mM. Ab (20 uM) hydrolysed 0.5 nMs^{-1}, with a k_{cat} of $2.5x10^{-4}$ s^{-1}. The observation that the Ab-Zn^{2+} amyloid complex can exert hidrolytic reactivity such as the one reported here can have important implications as a novel toxicity mechanism in AD and other amyloid-related pathologies.

FONDECYT 11160554

51) Expression of EMT transcription factors is differentially induced by TGF-β and is related to breast cancer tumor subtypes.

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Metastasis is the main cause of death among women with breast cancer. Patients with triple negative breast cancer tumors develop distant metastases earlier compared to luminal tumors. Epithelial-mesenchymal transition (EMT), induced by TGFβ signaling pathways, is the main mechanism to promote metastasis, through the expression of transcription factors TWIST, SNAIL, SLUG and ZEB1. In this study we analyzed by immunohistochemistry the expression of four transcription factors as well as the active/inactive state of: TGFβ/SMAD, ERK/MAPK and PI3K/AKT pathways in 100 breast tumors. The same analysis was done by immunocytochemistry and western in breast cancer cell lines: HCC1937 (triple negative) and T47D (luminal) treated or not with TGFβ and/or TGFβ pathways inhibitors in order to determine which factors were activated in response to one particular pathway. At least one transcription factor was expressed in all triple negative tumors (n=20), and in 66% of luminal tumors. Luminal tumors showed an active PI3K/AKT pathway and ZEB1 expression (n=25). Triple negative tumors showed an active TGFβ/SMAD pathway with expression of any of the transcription factors. After TGF-β treatment, T47D cells showed activation of PI3K/AKT and ERK/MAPK pathways, and expression of SNAIL and SLUG, whereas HCC1937 cells showed activation of TGFβ/SMAD and ERK/MAPK, and expression of TWIST, SLUG and ZEB1. Inhibition of ERK/MAPK and PI3K/AKT in T47D cells showed a decrease of SLUG suggesting a role of these pathways in the expression of this EMT transcription factor. In conclusion, we found a differential activation of signaling pathways and transcription factor's expression, suggesting diverse EMT mechanisms.

CONICYT 63140118

53) **Cathepsin L promotes autophagy in cells subjected to metabolic stress.**

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Due to uncontrolled cell growth in pathological conditions such as cancer, tumor cells are not properly fed, which leads to a sustained metabolic stress. Evasion of apoptotic processes and/or autophagy promotion enables cells to survive these events. Some studies suggest that cathepsin L plays a fundamental role in cell survival. We studied the participation of cathepsin L in autophagy and apoptosis processes under metabolic stress conditions. In addition, we evaluated the effect of cathepsin L activity inhibition on the expression of Cathepsin D and B under these conditions. For this purpose, COLO320 colorectal cancer cell line was cultured in a glucose free medium or serum free medium; on the other hand, cathepsin L inhibition was carried out by means of specific inhibitor. We analyzed the function of cathepsin L on cell viability under the studied conditions, complemented with specific markers of apoptosis and autophagy, as well as with the analysis of genetic material integrity. For determination of the effects caused by stress in localization and expression of cathepsin L, immunofluorescence assays were employed. In parallel, to analyze changes in the expression of cathepsin D and B, PCR and western blotting analyses were performed. Cathepsin L activity was measured using a specific fluorogenic substrate and analysis of the active forms of cathepsin L by zymography. Our results show that cathepsin L is critical for cell survival colorectal cancer cell line under metabolic stress conditions. Additionally, the inhibition of cathepsin L activity altered the expression of cathepsin D and B.

FONDECYT 1160731

55) Π-sulfur interactions guide A1899 to the binding site in TASK-1 potassium channels.

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Two-pore domain potassium channels (K2P) allow the selective passage of K+ ions across the cell . These channels are dimers and each subunit contain two pore domains and four transmembrane segments. K2P channels such as TASK-1 and TASK-3 belong to the TASK subfamily and are sensitive to extracellular acidification. A1899 is a nanomolar antagonist that inhibits these channels and has been shown to have a 10-fold greater affinity for TASK-1 than for TASK-3. Alanine scanning mutagenesis has been used to explore the difference between TASK-1 and TASK-3 near the binding site and has been reported one single difference: in TASK-1 the residue 247 is a methionine, meanwhile in TASK-3 is a leucine. This residue is in the pathway of A1899 to the central channel cavity but does not participate in the binding site. We performed Random Acceleration Molecular Dynamics (RAMD) - a molecular dynamics technique that apply force to a ligand changing its direction randomly- to study all possible exit routes of A1899 from its binding site in TASK-1. In the wildtype channel (TASK1–WT) the sulfur of the side chain of methionine 247 maintains a pi-sulfide interaction with an aromatic ring present in A1899, during its passage towards the central cavity. This interaction is not present in the mutated channels (TASK1-M247L and TASK1-M247A) due to the absence of sulfur in the side chain of leucine and alanine.

Fondecyt 1140624 and Millennium Nucleus of Ion Channels-Associated Diseases (MiNICAD)

57)**The presence of m6A within the 5´UTR of the HIV-1 genomic RNA defines its usage as mRNA or as the packaged genome.**

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The HIV-1 genome is a positive sense RNA (gRNA), which is found as a dimer in the viral particle. During the late stages, the gRNA acts as an mRNA encoding Gag and Gag-Pol, and is also the genome packaged into the new viral particles. Although it is known that the 5´UTR is key in the regulation on the transition translation-packaging, the molecular mechanisms involved are not well understood. It was recently reported that HIV-1 gene expression is post-transcriptionally regulated by the presence of N6-methyladenosine (m^6A) along the gRNA. Here, we show that the hypermethylation of the gRNA through the overexpression of the METTL3/14 complex induces a strong decrease of the gRNA packaged into released viral particles. We also observed that this effect was dynamic since overexpression of the FTO (but not ALKBH5) induced an increase in the packaged gRNA. Interestingly, m6A-seq analyses revealed that the 5´UTR of the gRNA is methylated within the cell, but not in the viral particle, indicating that the absence of m6A within the 5´UTR is probably necessary for the packaging of the gRNA. We also identified A198 and the A242 as the potential methylated residues. We are currently investigating the impact of m6A within the 5´-UTR on the interaction with Gag as well as the dimerization of the gRNA and their structure in order to understand the molecular mechanism involved in this regulation.

Fondecyt 1160176; Anillo ACT-1408.

59) In vitro validation of microRNAs targeting EMT-transcription factors and their relation to lymph node metastasis.

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Metastasis is the leading cause of cancer-associated deaths, promoted by transcription factors SNAIL, SLUG, ZEB1 and TWIST trough the activation of epithelial-mesenchymal transition (EMT). MicroRNAs are small non-coding RNAs that regulate large sets of genes, emerging as candidate molecular biomarkers and novel therapeutic targets.The aim of this study is to identify microRNAs downregulated in breast tumors expressing EMT-transcription factors, and involved in lymph node metastasis. For this purpose, we used microRNA microarray data from 50 fresh frozen breast tumors, 28 from patients with lymph node metastasis. Transcription factor expression was detected by immunohistochemistry. Microarray data analysis revealed approximately 40 microRNAs downregulated in breast tumors with expression of EMT-transcription factors ($p<0,05$). Several microRNAs from this group were predicted *in silico* as regulators of SNAIL, SLUG, ZEB1 and TWIST. Six were selected for validation: miR-196a, miR-202, miR-210, miR-22, miR-331 and miR-34b. Luciferase reporter assays revealed that all tested microRNAs, except miR-210 and miR-34b, generated a dose-dependent decrease in luciferase activity through binding their predicted target 3'UTR, reaching a maximum decrease of 50%. miR-196a, miR-202 and miR-210 were also predicted to regulate the chemokine receptor CCR7, involved in targeted migration of lymphocytes to lymphoid organs. This target was validated by luciferase reporter assays. Co-transfection of the three microRNAs in MDA-MB-231 cell line decreased endogenous CCR7 expression. Finally, transfection of all validated microRNAs decreased migration of metastatic MDA-MB-231 cells, suggesting that downregulation of specific microRNAs, and upregulation of their targets, may induce a metastatic behavior of tumor cells, promoting lymph node metastasis.

CONICYT 21151349

61) Detection of protein-ligand binding site residues by a physicochemical and spatial uniqueness approach.

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Understanding protein-ligand interactions is important for function prediction of proteins and the design of new drugs. The prediction of binding sites has been performed with different methods where those requiring a template structure related to the query protein have shown the best results but have reduced the spectrum of proteins that can be analyzed. Here, we propose a method to detect binding site residues that is not template-based but relies on the uniqueness of the spatial arrangement of physicochemical properties of surface residues. We defined uniqueness as spatial the arrangement of residues that is found in a single protein only. We curated a non-redundant dataset of 98 protein-ligand complexes (test set) and a reference set of 100 unrelated proteins representing the plethora of proteins in the cellular medium. Then we matched protein surface patches from the test set with the reference set based on atom type and pairwise distances. A match is defined if the difference of distances is within a tolerance threshold. Only surface patches without a match in the reference set are considered unique. Then we ranked all residues by the number of unique patches they participated in. Finally, our preliminary results with the test set indicate an average area under the receiver operating characteristic curve (ROC-AUC) of 0.69 and the number of correctly predicted binding residues was significant for 46% of the proteins (hypergeometric test, α=0.05). This method could be useful for binding site prediction for proteins with novel 3D structure or unrelated sequence.

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63) Phosphorylation at threonine-9 of endothelin converting enzyme-1c modulates protein stability, viability and cell death of colon cancer cells.

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Introduction:
The Endothelin-1 (ET1) axis has a mitogenic potential, modulating signaling pathways that are involved in malignant colorectal cancer (CRC) progression. We recently showed that the expression of the endothelin converting enzyme-1c (ECE1c), the ET-1 activating enzyme, mutated to aspartic acid at Thr-9, Ser-18 and Ser-20, three CK2 putative sites, leads to its increased protein stability, but also promotes migration and invasion of DLD-1 colon cancer cells. However, only Ser-18 and Ser-20 were truly phosphorylated in vitro by MS analysis. Thus, we evaluated the role of a single phosphorylation at Thr-9 in ECE1c stability, as well as its effect on viability and cell death of DLD-1 cells.

Methodology:
Lentiviral bicistronic expression of mCherry and FLAG-tagged phosphomimetic (ECE1c-T9D) and non-phosphorylatable (ECE1c-T9A) mutants were used to get DLD-1 cell clones, which were sorted by flow cytometry. Protein stability was analyzed in presence of CHX with an anti-FLAG antibody. Viability was measured by MTS assay as well as cell death evaluated by both trypan blue and PARP cleavage in western blot.

Results:
Increased stability of ECE1c-T9D was observed with respect to the ECE1c-WT and -T9A forms. In presence of 5-FU, differences were observed in viability and cell death between the different forms.

Conclusions:
Phosphorylation at Thr-9 of ECE1c confers it a protective role against degradation, thereby promoting its stability and cell viability when overexpresed in CRC cells, similarly to that shown by the triple mutant ECE1c-DDD.

Acknowledgements. FONDECYT grants 11150624 (MVG), and 1160889 (JT).

65) **Composition of the upper respiratory tract microbiome of asthmatic children in a population of Santiago de Chile and comparison with another one in the United States.**

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It is estimated that there are around 155 million people with asthma in the world, causing 480,000 deaths annually and causes of asthma have yet to be determined with accuracy. We have collected 98 samples (nasal and oral) corresponding to 29 asthmatic children and 20 healthy children from Chile, we have also included 120 samples from asthmatic patients in the US. By sequencing the amplicon V4 16S rRNA using Illumina MiSeq, a total of 7,571,190 sequences were obtained (29,734 average, 25,671 median), after the quality analysis, 6,660,635 sequences were obtained for the analysis of taxonomic allocation. In the American samples, the genera *Moraxella*, *Staphylococcus* and *Corynebacterium* stand out. We have detected significant differences in the diversity between Chilean and American samples which indicates a greater wealth of taxa in the population American. The samples have a structure according to the type of sample and the health condition, that suggests a direct relationship between the composition of the microbiota with asthma and not the country of origin. Finally, we detected differences between the populations related to the core-microbiome, in the US the *Staphylococcus* genus dominates, on the contrary, in Chile dominates *Moraxella*, both groups in the core microbiome converge in the genera *Dolosigranulum* and *Corynebacterium*. This contribution in the study of the Chilean population is of vital importance for epidemiological studies and will contribute to the characterization of the microbiota of the upper respiratory tract in the southern hemisphere.

Ignacio Ramos (Proyecto Iniciación a la Investigación 2018, DAD, Universidad Andres Bello) / Eduardo Castro-Nallar (PAI 82140008 - CONICYT)

67) Calculation of accurate contact surface areas between atoms for the quantitative analysis of non-bonded molecular interactions.

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Intra- and intermolecular contact surfaces are routinely calculated for a large array of applications in bioinformatics, but are typically approximated as averaged buried surface areas. We implemented an extension of the original Shrake-Rupley algorithm to estimate accurate contact surface areas on an atomic level. Our extended algorithm is able to precisely calculate the contact area of an atom to all nearby atoms by directly calculating overlapping surface patches. We present a versatile software tool to calculate the solvent accessible surface area (SASA), buried surface area (BSA) and contact surface area (CSA) between atoms for different types of biomolecules, such as proteins, nucleic acids, carbohydrates and small organic molecules. Detailed results are provided in tab-separated values format for analysis and Protein Databank files for visualization. In a benchmark with a non-redundant set of 245 protein-DNA complexes we determined that BSA-based approximations of contact surfaces on average underestimated CSA by 15%. This software tool may be useful for surface-based intra- and intermolecular interaction analyses, and scoring functions. Availability and implementation: A web server, stand-alone binaries for Linux, MacOS and Windows, and C++ source code are freely available from http://schuellerlab.org/dr_sasa/.

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69) Effect of gold nanoparticles in Aβ42 amyloid formation.

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Amyloid structures are formed by amyloidogenic proteins, for example amyloid-β peptides (Aβ), which are directly related to Alzheimer´s disease. Several compounds have been developed in order to block the formation of amyloid structure, such as gold nanoparticles, which decrease the quantity and size of amyloid fibers. However, is unknown the effect of gold nanoparticles on the amyloid aggregation mechanism. We studied the effect of gold nanoparticles on theAβ42 aggregation kinetics by performing global fittings with models that considers several microscopic steps. In absence of nanoparticles the mechanism of formation of amyloid is described by a “multi-step secondary nucleation” mechanism which is not altered in presence of gold nanoparticles. Nevertheless, the presence of gold nanoparticles decreases the rate constant associated with the microscopic processes of elongation and secondary nucleation in two orders of magnitude. The elongation process describes the growth at the fibers ends while secondary nucleation describes the formation of new aggregation seeds at the fibers surface. Since, events of secondary nucleation are the main responsible for the generation of toxic species, gold nanoparticles can be used as therapeutic agents to control the progress of Alzheimer’s disease. This approach could be used to determine the action mechanism employed by several therapies developed to inhibit the formation of aggregates, and help to identify if these therapies aim to diminish the contribution of the main molecular process responsible for the toxicity.

Fondecyt 1151274, Fondecyt 1130425 and FONDAP 15130011

71) Chemoresistance through MRPs expression in Glioblastoma stem-like cells is elicited by low-affinity adenosine receptors under normoxia and hypoxia.

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Glioblastoma is a common nervous system primary tumor with one of the highest cancer death rates. Glioblastoma stem-like cells (GSCs) have been reported to be responsible for chemoresistance, and their hypoxic niches enhance the chemoresistant phenotype. We reported that adenosine contributes to chemoresistance in GSCs trough MRP1 expression mediated by activation of A_3 adenosine receptor in normoxia. Under hypoxia, MRP3 transporter expression increases. Currently, the role of adenosine in chemoresistance under hypoxia is poorly understood. Since adenosine increase under hypoxia, we propose that lowest affinity adenosine receptor A_2B may be involved in chemoresistance mechanisms through MRPs transporters expression. Here, we evaluated the role of low-affinity adenosine receptors on chemoresistance in GSCs under hypoxia. GSCs were cultured under normoxia (21% 0_2) and hypoxia (0.5% 0_2). GSCs were treated with the antagonists of low-affinity adenosine receptors (MRS1220 for A_3 and MRS1754 for A_2B) for 24 h under normoxia or hypoxia. Protein levels were evaluated by western blot and MRP activity was determined by CFDA accumulation assays. GSC viability was determined by MTS; cell cycle and apoptosis were determined by FACS. A_3 blockade decreased MRP1 and MRP3 expression under normoxia and hypoxia while A_2B blockade decreased MRP3 expression only under hypoxia. Moreover, A_3 blockade decreased MRP activity only under normoxia whereas A_2B blockade decreased MRP activity only under hypoxia. MTS and apoptosis assays showed significant chemosensitization after treatment with MRP3 drug substrates plus the A_2B antagonist under hypoxia. These results suggest different chemoresistance mechanisms mediated by oxygen dependent adenosine signaling.

Fondecyt 1160777 Beca Doctorado Nacional CONICYT Vicerectory for Research, Development and Artistic Creation, Universidad Austral de Chile

73) LabNettings as a tool for collaborative economy in science.

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Introduction:
The investment in R&D in Chile and Latam is limited (<1% GDP) compared to the rest of the world. If we add to this, the time spent waiting for reagents and equipment and the poor knowledge about the laboratories capacities, we end up with a problematic that could be solved through collaborative economy.

Methodology:
Creation of an online collaborative platform for laboratories, that can be used by lab chiefs, lab managers and investigators to manage their resources.

Results:
We reached 150 investigators (23% Lab Chiefs, 26% Lab Managers, 51% Investigators), from 8 different universities in Santiago and Concepción of Chile. 80% of the laboratories we interviewed throw away materials because of unused or expired resources. The main benefits they acknowledge are: collaboration, reduction of costs, organization and registration of equipment use. Thanks to this study we already have our first 10 laboratories to test the platform.

Conclusions:
Collaborative economies are necessaries in fields of science, in order to access more resources, take full advantage of it and expand collaboration. LabNettings solves this through an online platform where each laboratory can choose what to share or exchange in order to gain access to other people's resources, and so reducing their waste of time and money in research.

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75) Limits and potential of in silico target prediction by chemical similarity.

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Predicting the macromolecular targets of small molecules is important for drug discovery to flag off-targets and for drug repositioning. We have devised a target prediction method by representing small molecules with topological descriptors and predicting target proteins with a nearest neighbor estimator based on the Tanimoto coefficient of query molecules to annotated ligands of biological targets. We validated our approach with a dataset of 301,179 drug-protein interactions, comprised by 205,195 small molecules and 1691 targets, derived from ChEMBL22. Cross-validated results were analyzed by precision-recall analysis yielding excellent performance (average precision, AP AUC: 0.71; 90% chance of ranking the annotated target top-1). However, these results were biased by a large number of similar compounds, e.g. from series of analogs. We therefore devised a UCLUST-inspired clustering algorithm to remove redundancy. Performance dropped substantially (AP AUC: 0.35) on our non-redundant dataset with highly similar compounds removed (Tanimoto coefficient > 0.7). However, the annotated target was still ranked top-1 for 60% of all molecules. This indicates an unexploited potential for drug discovery despite the limits imposed by chemical similarity. We confirmed this potential by testing an adenosine A_{2B} receptor modulator and a c-Jun N-terminal kinase 3 inhibitor for inhibition of their predicted target: coagulation factor Xa. Both compounds were found to inhibit factor Xa in vitro.

This research was funded by FONDECYT Regular No 1161798

77) **Effect of differentiation of B lymphocytes induced by DNA damage on metabolic gene expression and mTOR pathway.**

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Introduction:
The process of differentiation of B lymphocytes into memory B cells and plasma cells that secrete specific antibodies, involves DNA double strand breaks. This event is associated with a change in the cellular metabolic profile, variations in their proliferative state and with progression of the cell cycle occurring under conditions of homeostasis, all of which are processes susceptible to deregulation that can cause lymphomagenesis. Due to the important role of the mTORC1 pathway in cell proliferation and metabolism, it is essential to study this pathway during the differentiation of B lymphocytes induced by DNA damage and its role in metabolism. Specifically, we studied this signaling pathway to detect the main downstream targets and also we evaluated the metabolic profile of these cells by analyzing the gene expression of several metabolic genes.

Material and methods:
Total proteins were extracted from Ramos cells treated with 20 µM Etoposide (Eto) and/or 50 nM Rapamycin. We immunodetected proteins involve in mTOR pathway. Gene expression was determined by RT-qPCR for specific metabolic genes.

Results:
We observed that DNA damage induced by Eto has an inhibitory action on the mTORC1 downstream targets in Ramos cells; the results were similar when we used Rapamycin. Interestingly, the inhibition of mTORC1 pathway modulated the expression of metabolic genes in this cell model.

Discussion:
Our results suggest that treatment with Eto has a similar effect to Rapamycin on the activation of mTOR signaling pathway and metabolic genes pattern

Fondecyt 1141067 and 1180957, DID SB2016-48-UACh

79) "Quantitative proteomic profile of toxigenic dinoflagellate Alexandrium catenella under the effect of nitrate variations".

Saldivia-Flandez Pablo F[1], Hernandez Mauricio A[2], Nourdin Guillermo A[1], Hertzberg Daniel E[3]. [1]Instituto de Bioquimica & Microbiologia, Facultad de Ciencias, Universidad Austral de Chile, Valdivia, CL. [2]Austral omics, Facultad de Ciencias, Universidad Austral de Chile, Valdivia, CL. [3]Instituto de Ciencias Clinicas Veterinarias, Facultad de Ciencias Veterinarias, Universidad Austral de Chile, Valdivia, CL.

Paralytic shellfish toxins (PSTs) are a group of neurotoxic alkaloids synthesized by dinoflagellates. This are highly nitrogenous, and it is been hypothesized that their biosynthesis would be related to nitrogen metabolism. The aim of this study was used a quantitative proteomic approach to estimate *Alexandrium catenella* expression profiles at 50, 100 and 150% of NO3 –.

Total proteins were extracted with Trizol. Subsequently, they were reduced, alkylated and digested with trypsin. Tryptic peptides were separated by LC-MS/MS. Protein identification was achieved using Sequest and X! Tandem as a validator. The database for identification used was made *in-house* from raw RNA-seq files of *Alexandrium catenella* (107,000 entries) available from NCBI. Quantification of identified proteins was done by spectral count and the significance was determined by t-test (p-value of 0.05). The functional annotation was done with Gene Ontology and KEGG.

We identified 1403 proteins, grouped in 600 clusters. Proteins involved in carbohydrate metabolism, nitrogen metabolism and biosynthesis of photosynthetic pigments showed a differentiated expression. The enzyme S-Adenosylmethionine synthetase was significantly in altered in high and low nitrate conditions. Several proteins related to PSTs biosynthesis were identified and some were significantly altered.

The variation of nitrate in the medium produces an alteration of the synthesis of PSTs that would generate a feedback in the nitrogen metabolism, being used for the biosynthesis of pigments and other nitrogenated compounds. Our study provides new findings about the biosynthesis of PSTs in dinoflagellates, being the only one using environmental strains.

This work has been financiated by CORFO project "Establishment of a baseline of the genomic, toxicological and temporal cycles of the red tide and toxic microalgae present on the coast of the Region of Los Ríos for public policy advance" (code 16BPE-62321).

81) Use of Taqman probes as a convenient assay to reveal the histories of ancient plant fibre textiles from the Pacific Islands.

Peña-Ahumada Barbara[1], Kuo Wen-Hsi [2], Chung Kuo-Fang[2], **Seelenfreund Daniela[1]**, Seelenfreund Andrea[3]. [1]Departamento de Bioquímica y Biología Molecular, Ciencias Químicas y Farmacéuticas, Universidad de Chile, Santiago, CL. [2]Research Museum and Herbarium (HAST), Biodiversity Research Center, Academia Sinica, Taipei, TW. [3]Escuela de Antropología, Facultad de Ciencias Sociales, Universidad Academia de Humanismo Cristiano, Santiago, CL. (Sponsored by FONDECYT Grants 1120175 And 1180052 To AS And Academia Sinica - Integrated Thematic Projects AS-107-TP-B18 To KFC.)

With the advent of modern molecular tools specimens and artifacts of biological origin, long stored in museum collections, have become open treasure chests. The genetic study of old textiles from Pacific islands made of plant fibres can reveal hidden histories about the past. We have analyzed barkcloth textiles made of paper mulberry (*Broussonetia papyrifera*) fibers from the XVIII and XIXth century with nuclear and chloroplast molecular markers. Because DNA obtained from these ancient textile samples is of low quality and highly degraded, we propose the use of TaqMan probes to detect informative SNPs and compare the obtained data with our data base of genomic DNA of *B. papyrifera* populations from the Pacific Islands. Taqman probes have been designed using SNPs detected with different molecular markers previously used by our group. We tested contemporary textile samples and two Taqman probes targeting specific chloroplast DNA sequences and a sex marker for *B. papyrifera* as a proof of concept. We confirmed the ability of this assay to correctly detect SNP information, reducing the time and cost of this analysis in comparison with the traditional PCR approach. Using the RadSeq data obtained from contemporary populations, it is therefore possible to design additional probes to test the most informative SNPs. In this work we present results obtained with these probes on contemporary material and propose their use on historical ethnographic textiles to contribute with valuable information in the study of human-mediated dispersal of paper mulberry, as a proxy of the settlement history of the Pacific.

FONDECYT grants 1120175 and 1180052 to AS; Academia Sinica - Integrated Thematic Projects AS-107-TP-B18 to KFC.

83) Recombinant BCG vaccines reduce pneumovirus-caused airway pathology by inducing protective cellular and humoral immunity.

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The Human Respiratory Syncytial Virus (hRSV) and the Human Metapneumovirus (hMPV) are two pneunoviruses and lead as causative agents of acute lower respiratory tract infections (ALRTIs) affecting young infants, the elderly and immunocompromised patients globally. Since these pathogens were first discovered, many approaches for the licensing of safe and effective vaccines have been explored being unsuccessful to date. We have previously described that immunization with recombinantstrains of *Mycobacterium bovis* Bacillus Calmette-Guérin (rBCG) expressing the hRSV nucleoprotein (rBCG-N) or the hMPV phosphoprotein (rBCG-P) induced immune protection against each respective virus. These vaccines efficiently promoted viral clearance without significant lung damage, mainly through the induction of a T helper 1 cellular immunity. Here we show that upon viral challenge, rBCG-immunized developed protective humoral immunity, characterized by production of antibodies specific for most hRSV and hMPV proteins. Further, isotype switching from IgG1 to IgG2a was observed in mice immunized with rBCG vaccines and correlated with an increased viral clearance, as compared to unimmunized animals. Finally, sera obtained from animals immunized with rBCG vaccines and infected with their respective viruses exhibited virus neutralizing capacity and protected *naïve* mice from viral replication and pulmonary disease. These results support the notion that the use of rBCG strains could be considered as an effective vaccination approach against other respiratory viruses with similar biology as hRSV and hMPV.

This work was supported by COMISIÓN NACIONAL DE INVESTIGACIÓN CIENTÍFICA Y TECNOLÍGICA (CONICYT) Nº21151028, CONICYT/FONDECYT POSTDOCTORADO No. 3160249 and the Millennium Institute on Immunology and Immunotherapy (P09/016-F)

85)**The upregulation of the Equilibrative Nucleoside Transporter 2 activity by insulin is Dependent on the Integrity of the Actin Cytoskeleton.**

Suárez Raibel[1], Jara Claudia[1], Barrientos Sebastian[1], Oyazún Carlos[1], San Martin Rody[1]. [1]Biochemistry and Microbiology Institute, Sciences, Universidad Austral de Chile, Valdivia, CL. (Sponsored by FONDECYT N° 1171340)

Introduction:
Extracellular homeostasis of adenosine is dependent on the uptake activity mediated by the equilibrative nucleoside transporters (ENTs) at the cell surface. Recently, it was reported that ENT2 is a target of insulin in renal cells and its activity was necessary to maintain basal extracellular levels of adenosine. Our objective was to study the mechanisms associated with the regulation of ENT2 activity and characterize the effect of diabetes.

Methods:
Rat glomeruli ex vivo from non-diabetic control rats and STZ-induced diabetic rats were used to evaluate ENT2 uptake activity, glomeruli were incubated with insulin 10nm, cytochalasin D 2µM (cytoskeleton disruptor) and LY294002 50µM (PI3K inhibitor). Kidney samples from the animal groups and human kidney biopsies were used to localize ENT2 protein.

Results:
The uptake activity of ENT2 was upregulated by insulin through PI3K signaling pathway in glomeruli from control rats. The effect of insulin was dependent on the integrity of actin cytoskeleton because the use of cytochalasin D blocked the uptake induction. The transport activity mediated by ENT2 and its localization at plasma membrane were found lower in glomeruli from diabetic rats. The immunohistochemical analysis of ENT2 distribution in kidney samples evidenced that in STZ-induced diabetes in animals and in biopsies from human DN the localization of ENT2 at the plasma membrane was lesser.

Conclusion:
The deficiency of insulin or insulin resistance may affect ENT2 activity which affect extracellular homeostasis of adenosine. The upregulation of ENT2 by insulin may be regulated through ENT2 translocation to plasma membrane.

Funding: FONDECYT N° 1171340

87) Common signatures of physiological aging and aging by neurodegeneration in Drosophila models.

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A major challenge is to understand which cues contribute to the appearance of the hallmarks of aging.Transcriptional alterations constitute one primary hallmark of aging. To gain insights into this matter we used *Drosophila* because it allows whole organism time course transcriptomics of a collection of individuals raised synchronically in an identical environment. We used healthy aged and Alzheimer models to gain insights into the common signatures of physiological aging or aging by neurodegeneration. We performed bioinformatics approaches in the transcriptomes of these flies to discover common gene networks (GNs) acting during aging. We validated high through-put and *in silico* data with molecular tools, and we correlated these data to behavioral changes. To discover new interactions among the differentially expressed transcripts in both models of aging we obtained gene co-expression modules which reveal new age and sex specific genetic interactions during the aging process. Among the differentially expressed transcripts in aging, we discovered a set of long non-coding RNAs (lncRNAs). We mapped these lncRNAs to the modules and characterized its nearest coding gene to infer their putative function. LncRNAs common to both aging by neurodegeneration and physiological aging are positionally conserved to the human genome and their nearest coding RNA is enriched in brain tissue pointing to a role of lncRNAs in the aging brain. These data help elucidate the cues that lead to the appearance of the hallmarks of aging and thus contribute to the understanding of how a "healthy aged phenotype" is achieved.

FONDECYT N11130203 -FONDECYT N1181645- FONDECYT N1171645- FONDECYT N11161020

89) **Dynamics of Nuclear Morphology in the B Cell Activation.**

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B lymphocytes are key players of the adaptive immune response. To become fully activated and produce high affinity antibodies, B cells must process antigens and present them as peptides to specific CD4+ T cells. Efficient antigen processing depends on intracellular trafficking coupled to cytoskeleton remodeling, where B cells must also tackle a major problem, their restrictive cytoplasmic space caused by the large size of their nucleus, which occupies almost the entire cell. How do B cells deal with this obstacle to coordinate intracellular trafficking? To answer this question, we aim to unravel how B cells modify their nuclear morphology during B cell activation. Nuclear morphology is controlled by structural proteins, which form the nuclear envelope. Among such proteins, Lamin-B, is a fibrous component of the nuclear envelope and thus sought to characterize the localization of this protein and correlate it with changes in nuclear morphology during B cell activation. Using immunofluorescence and cell imaging, we observed that in resting B cells, lamin-B is associated to the nucleus, which displayed a lobular morphology. Additionally, the nuclear shape of B cells, which was closely associated to the microtubule-organizing center (MTOC), was sensitive to microtubule de-polymerizing drugs. Moreover, upon activation B cells change their nuclear morphology increasing the intralobular space, which is redirected to the antigen contact site. Within this space, B cells accumulate lysosomes, suggesting that antigen processing is taking place. We conclude that nuclear morphology and its connection with cytoskeleton is a critical regulatory step for B cell activation.

fondecyt iniciación 11171024

91) **Expression analysis of a cellular gene fused to a parvoviral endogenous element in Cavia porcellus.**

Valencia Ignacio[1], Faunes Fernando[1], Gifford Robert[2], Arriagada Gloria[1]. [1]Departamento de Ciencias Biologicas, Universidad Andrés Bello. [2]Centre for Virus Research , Glasgow University, Glasgow, GB.

An Endogenous Viral Element (EVE) is a virus derived sequence present in the genome of contemporaneous species. EVEs are derived from all 7 classes of viral genomes. Some EVEs have maintained intact open reading frames (ORFs) and the proteins encoded in them have been co-opted by the host to fulfill a cellular function, others are expressed as functional RNAs while most are mutated or silenced. Parvovirus are single stranded DNA viruses, and several full genomes, genes and part of genes have been found in animal genomes. We and others have described parvoviral EVEs expressed in the liver of degu and elephants. We have found a new parvoviral EVE, named NS-Myo9, in the genome of *Cavia porcellus*. NS-Myo9 is predicted by the EST data base to be expressed as a fusion with 5 exons homologous to myosin 9 (XM_013153010.2). This new EVE has 40% identity to parvoviral NS protein, and 55.19% identity to the degu EVE that we previously described. This EVE has an intact ORF that encodes a protein with Rep-N superfamily and a SMC-N superfamily. Here we demonstrate that NS-Myo9 is indeed expressed as a fused RNA in Cavia porcellus, with the same splicing as predicted in the EST data base. We are currently cloning the NS-Myo9 coding sequence to analyze if it can be translated to protein. This is the first report of expression of an intact parvoviral EVE in fusion to cellular sequences.

Fondecyt 1180705

93) Computational study of xyloglucan (XG) adsorption on cellulose surfaces.

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Plant cell walls are a complex and dynamic supra-molecular assembly composed of crystalline cellulose microfibrils surrounded by an amorphous matrix of polysaccharides such as hemicellulose and pectins as well as inorganic molecules and proteins. The plant cell wall regulates growth and development, mechanical support, and cell shape and acts as a barrier against biotic and abiotic stresses.Regarding plant cell wall metabolism, disassembly is the main process that leads to fruit softening during ripening. Cell wall disassembly is related to loss of the xyloglucan-cellulose network and pectin solubilization. These processes increase cell wall porosity, which in turn enhance the access of proteins and enzymes to their substrates for degradation. We have investigated the effect of surface hydrophobicity and side-chain variation on xyloglucan adsorption onto cellulose microfibrils via molecular dynamics simulations (MDS). A molecular model of cellulose microfibril with (100), (010), (1–10), (110) and (200) crystal faces was built. We considered xyloglucan oligosaccharides (XG) with two repeating units, namely (XXXG)2 and (XXFG)2. We have evaluated the interaction of the two (XXXG)2, two (XXFG)2, and one XXXG with XXFG. Our work shows that (XXXG)2 binds more favorably to the cellulose microfibril in the hydrophobic surfaces than to the two substrate. The origin of this behavior is attributed to the topography of hydrophobic cellulose microfibril surface, which stabilizes (XXXG)2 in flat conformation.

This work was financed by FONDECYT #11150543

95) Wnt/β-catenin signaling induces genomic instability and the generation of RNA-DNA hybrids (R-loops).

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RNA-DNA hybrids or R-loops are structures that are naturally generated in cells during transcription and have been associated with genomic instability. Here we studied whether sustained activation of Wnt/β-catenin-dependent transcription has an effect on genomic instability through the formation of R-loops. Using single-cell electrophoresis assays and detection of H2AX phosphorylation (γ-H2AX) by immunofluorescence, we observed a significant increase in DNA breaks in human cell lines treated with the specific Wnt/β-catenin signaling activator CHIR-98014 (1-2 µM, 24-72 h). γ-H2AX immunofluorescence colocalized with active β-catenin foci within the nucleus. Notably, CHIR-98014 treatment produced a significant increase on R-loop formation, which was confirmed using the S9.6 antibody that specifically recognizes RNA-DNA hybrids in immunofluorescence and Dot Blot assays. Our results indicate that transcriptional stress induced by Wnt/β-catenin signaling produces genomic instability likely through R-loop formation.

Fondecyt Regular 1180848 to G.D.V.

97) Methylprednisolone treatment enhances early recovery following surgical decompression for degenerative cervical myelopathy without compromise to the systemic immune system.

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Introduction:
Degenerative cervical myelopathy (DCM) is caused by degenerative or congenital changes to the discs and soft tissues of the cervical spine, which leads to chronic compression of the spinal cord. The current treatment consists of surgical decompression, which while effective in most cases, can result in neuroinflammation and spinal cord reperfusion-injury, leading to perioperative neurological complications and suboptimal neurological recovery. In this study we assessed the efficacy of perioperative Methylprednisolone (MP) in enhancing neurological recovery and its effects on the inflammatory response following decompression.

Methodology:
DCM was induced in C57BL/6 mice. A biopolymer was implanted underneath the C5-C6 laminae to cause progressive compression of the cervical spinal cord. Decompressive surgery was undertaken at 12 weeks post initial biomaterial implantation. Animals received one dose of MP (30mg/kg) or vehicle 30 minutes before decompression and at 2 weeks after decompression. Acute analysis of secreted cytokines and spinal cord microvasculature was complemented with immunohistochemistry for glial and neuronal cell markers. Locomotor outcomes were measured using the CatWalk system. The composition of circulating white blood cells was analyzed by flow cytometry.

Results:
A single dose of MP before decompression significantly sped locomotor recovery and reduced the incidence of perioperative motor complications, without affecting the composition of circulating white blood cells. Histological assessment of the spinal cord showed significant neuronal preservation, and a modest reduction in parenchymal inflammation.

Conclusions:
Our data suggest that MP reduces perioperative neurological complications following decompressive surgery for DCM by protecting neurons from inflammation, without compromising the composition of circulating immune cells.

This work was supported by the 21st Century Research Grant from the Cervical Spine Research Society and the Krembil Research Institute post-doctoral fellowship awarded to PMV.

99) QS21 from Quillaja saponaria (Molina): a new prominent anticancer agent.

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Saponins are a class of triterpenes natural containing an aglycone portion with saccharide chains. The triterpenes are molecules with a great potential as anti-tumor because it can to alter diverse biological activities into de cell as: regulation of cell cycle, proliferation, anti-inflammatory and apoptosis.QS-21 is a saponin acylated 3, 28-bidesmodic glycoside of the aglycone quillac acid (QA). This saponin is purified by HPLC from *Quillaja saponaria* Molina, molecule used as a vaccine adjuvant for human and animal. Our aim was to test the cytotoxic of QS21 on human gastric cancer cells (SNU1 and KATOIII) by MTS and LDH assay. Furthermore, QS21-induced death was tested using a three-state cell death model [alive, vulnerable, and dead] and evaluation of apoptosis by Annexin V (AV). The cell death was established by flow cytometry analysis to determine the mitochondrial involvement in the death cell (Rhod123 and PI). 17,1 µM of QS21 showed a cytotoxicity effect on SNU-1 cells, being 1/9 of that which produces a half-maximal effect on KATO III (164 µM), without effect on GES-1 (human gastric normal epithelial cell line ($p< 0,0001$)). Also, QS21 generated mitochondrial dysfunction with release cytochrome C in both cell lines. Furthermore, a 80% of KATO III cell and 50% of SNU1 cell were AV positive.These results shown that QS21 induce the death cell by apoptosis. Accordingly, our results open a novel opportunity to treatment of gastric cancer or other type of cancer, using natural compounds extracted from a native species of Chile.

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101) **Circulating exosomal miRNA signature in pregnancies with gestational diabetes mellitus across gestatio.**

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Exosomes are small nanovesicles that carry bioactive molecules which can be delivered to others cells and modify their phenotype. We have established that the number of circulating exosomes is higher in women with gestational diabetes mellitus (GDM); however, the exosomal miRNA profile in GDM across gestation has not been established yet. The aim of this study was to establish the circulating exosomal miRNA profile in women with normal glucose tolerance (NGT) and GDM women in a prospective cohort of patients at three time points during pregnancy. Exosomal RNA was sequenced using an Illumina NextSeq 500 platform. Linear mixed modelling was performed on the normalized miRNAs across gestation for normal and GDM pregnancies, using the lme4 package in R. Statistically significant differences in miRNA expression between NGT and GDM women was determined using likelihood ratio tests. In the first trimester of pregnancy, 92% of exosomal miRNAs were significantly elevated in plasma of women with GDM when compared to NGT women. In the second trimester of pregnancy, the expression of these miRNA decreased in the GDM women with no significance difference in the exosomal miRNA profile between GDM and NGT women. Gene ontology analysis revealed that miRNAs which changed expression across gestation for GDM pregnancies are involved in the regulation of insulin. We have identified a range of exosomal miRNAs which change expression across gestation for GDM and normal pregnancies. Gene ontology analysis revealed that these miRNAs are involved in the regulation of insulin, playing significant role in the pathophysiology of GDM.

This work is funded by Fondo Nacional de Desarrollo Científico y Tecnológico (FONDECYT 1170809)

POSTER SESSION II

2) A new and most complete structure of Octarellin V.1 obtained by capillary counter-diffusion crystallization method.

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Octarellins are artificial proteins of more than 200 amino acids, designed to fold as a $(\beta\alpha)_8$ protein. The most stable version, Octarellin V.1, has been co-crystallized with αRep protein, an artificial crystallization helper, by vapor diffusion through the hanging drop technique. The 70% of the tertiary structure of the Octarellin V.1 protein was solved. The present work was aimed to obtain better crystals which may help to obtain a most complete structure of Octarellin V.1. To accomplish this, the recombinant artificial proteins Octarellin V.1 and αRep were expressed and purified individually from *E. coli*. The protein complex was isolated by size exclusion chromatography. To obtain different and better crystals, we implemented a new crystallization technique: counter-diffusion in a capillary. The complex αRep-Octarellin V.1 was concentrated up to 12 mg/mL and a capillary of 0.3 x 50 mm was filled with it. The capillary was exposed to a crystallization cocktail and several crystals appeared after a couple of weeks. The whole crystallization hardware (1 x 6 cm) was sent by post at room temperature to Grenoble, France, where the crystals were diffracted. The protein was solved at 3.1 Å, obtaining now the 90% of the Octarellin V.1 structure. This result demonstrates how a new crystallization technique may be useful to optimize the quality of a protein crystal. This technique is simple, low cost, able to be used for most of our laboratories and facilitate the process of manipulation and transport of the crystals from Chile to a synchrotron facility.

Proyecto VRID de Inicio Universidad de Concepción N° 217.037.023-1.0IN

4) TLR2 modulating peptides from the human microbiota as new drugs for metabolic diseases.

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Toll-like receptors (TLRs) are proteins that recognize structural patterns from microbe-derived molecules, as well as endogenous signals. To date, many studies have related TLR2 to several metabolic diseases. Peptide motifs from proteins from the human microbiota have been associated with the modulation of TLR2 under different conditions or diseases. Thus, TLR2 plays a role in the connection between immunity and gut microbiota. For example, obesity, type-2 diabetes (TD2) and metabolic syndrome are characterized by a low chronic inflammation and insulin resistance triggered by an increase in the expression of TLR2 and TLR4.

Additionally, several studies have associated the bacteria *Akkermansia muciniphila* (present in the intestinal microbiota) to weight loss and alleviating TD2, suggesting that this bacteria is beneficial for combating these diseases in humans. An outer thermostable membrane protein, Amuc_1100, has been shown to trigger the same effects as the complete bacteria. This protein is directly involved in the modulation of the TLR2 receptor and it exerted pronounced effects on obesity induced by high-fat diet, glucose tolerance and insulin resistance.

In the present study, we have characterized the key residues participating in the interaction between TLR2 and different modulators ligands, by using molecular dynamics simulation and binding free energy calculation. Additionally, by analyzing these systems, we here propose a possible molecular model of the interaction between TLR2 and Amuc_1100. Finally, we identified conserved motifs from natural modulators of TLR2 from the gut microbiota to generate new potential peptide drugs for metabolic diseases.

Acknowledgements :CONICYT Doctorado Nacional 2015-2018 fellowship and Ubiome Inc.

6) **Estimating Residence Time in Tripsin-Benzamide Complex through Enhanced Molecular Dynamics Approaches.**

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The residence time (τ) is defined as the inverse of dissociation rate constant ($\tau = 1/k_{off}$) or, in more simple terms, as the lifetime of a protein-drug complex (given in second, minutes or hours). The relevance of this parameter in drug design and discovery of new drugs has been recently recognized, and it is suggested that *"the key determinant of in vivo pharmacological activity and duration is not the binding affinity of a drug for its intended target but the lifetime, or residence time, of the binary drug– target complex"*. The first research work attempting to estimate τ was based in "brute force" MD simulations performed on the trypsin-benzamidine complex. The authors performed ~500 independent MD simulations (100 ns long each) that allowed the free diffusion of benzamidine from bulk solvent into the protein's binding site. They estimated the standard free energy of binding, $\Delta G° = -5.2 \pm 0.4$ kcal⁄mol (compared with the experimental value −6.2 kcal⁄mol), and a two-states kinetic model with $k_{on} = (1.5 \pm 0.2) \times 10^8$ M^{-1} s^{-1} and $k_{off} = (9.5 \pm 3.3) \times 10^4$ s^{-1} for unbound to bound transitions. In this work, some enhanced molecular dynamics methods like Adaptive Biased Force (ABF) and Steered Molecular Dynamics (SMD) will be used as more efficient methods to estimate τ with a lower computational demand, a better and efficient sampling of the potential energy surface (PES). The resulting and developed protocols will be used for the estimation and validation of τ in some protein kinase-drug complexes where this kinetic parameter has been already experimentally determined and become relevant in drug design.

FONDECYT No. 1181253

8) High glucose induces FoxO1-dependent oxidative stress by reducing FoxO3/SOD2 expression in Cardiac Fibroblasts.

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(Sponsored by Proyecto Fondecyt Iniciación 11160531 / Proyecto U-Inicia 2016-2018)

Diabetic cardiomyopathy is associated with oxidative stress which are regarded as main incentive to initiate ventricular remodeling, characterized by cardiac-hypertrophy, fibrosis and heart-dysfunction. In many cell types, ROS lead to the activation of the forkhead box O (FoxO) transcription factors which can mediate the effects of ROS through regulation of gene transcription. FoxOs have been implicated in diverse cellular processes including glucose metabolism and fibrosis. In addition to being activated by ROS, FoxOs plays a critical role in oxidative stress by upregulating expression of antioxidant genes.It is well established that FoxO3 activation induces expression of antioxidant enzymes such as SOD2 and catalase.Due to this our research team works to understand the cross-talk relationship between FoxO1 and FoxO3 and ROS levels under a high-glucose condition (HGC) in cardiac fibroblasts (CF). In this study we demonstrate that a HGC induces production of free radicals and FoxO1 is essential for this process. Our data showed an activation of FoxO1; a decrease in FoxO3, SOD2 expression and the subsequent rise in ROS production. Interestingly, depletion of *FOXO1* by siRNA attenuated high glucose-induced oxidative stress by decreasing protein level of FoxO3, SOD2 and ROS production. These results suggest that activation of FoxO1 through high-glucose-induced oxidative stress may be modulating FoxO3 effect which leads to a deregulation of antioxidative machinery resulting in a chronic oxidative loop. Therefore,attenuation of high-glucose-induced oxidative damage and the subsequent cardiac fibrosis through CFs activation are expected to exert beneficial effects and may be a potential novel therapeutic strategy for diabetic cardiomyopathy-

Proyecto Fondecyt Iniciación 11160531 and Proyecto U-Inicia 2016-2018

10) Effect of drug-drug interaction on transcriptional expression of metabolizying enzymes and a drug resistance protein in kidney and intestine tissues of rainbow trout (Oncorhynchus mykiss).

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Introduction:
Chilean salmonid farming has been exposed for decades to different kinds of diseases, causing high mortality and considerable economic loss to the industry. In order to control different pathogens many drugs are consecutively used, such as Emamectin Benzoate (EMB), Oxytetracycline (OXY), Florfenicol (FF) and Erythromycin (ERY). The aim of this study was to evaluate the effect of these treatments on transcriptional expression of the metabolizing enzymes CYP2K1, CYP2M1, CYP3A27, FMO, GST and the drug resistance protein, Pgp, after single treatments with EMB, antibiotics and EMB/antibiotic consecutive treatments.

Material and Methods:
Two independent experiments were carried out. In the first one, rainbow trout were independently administered with EMB, OXY, FF and ERYthrough feed. In the second experiment, rainbow trout were administered with EMB and then separately coadministered OXY, FF and ERY through feed. The transcriptional expression was determined by RT-qPCR.

Results:
EMB increased the transcriptional expression of metabolizing enzymes, mainly in kidney. Although EMB had no effect on the Pgp in any tissue. Intestine samples, EMB over-expressed CYP3A27 at the beginning of the experiment, however, the consecutive EMB/OTC increased the transcriptional expression of the metabolizing enzymes and Pgp.

Discussion:
The transcriptional effect of single treatments with EMB and antibiotics was very different to EMB/antibiotic consecutive treatments, evenon the same tissue, suggesting the existence of a mechanism of pharmacological interaction between EMB and the antibiotics tested. Thus, treatment schedules between antibiotics and antiparasitic drugs, as well as, the possible pharmacological interactions should be more deeply reviewed.

FONDECYT 1150934 and FONDAP 15110027. Dirección de Investigación y Desarrollo, Universidad Austral de Chile.

12) First approach to the identification of new antimicrobial peptides (AMPs) in the microalga Isochrysis galbana.

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Antimicrobial peptides (AMPs) are a promising alternative for the search of new antibiotics, due to their affinity to bacterial membranes as well as for their ability to modulate the immune response. Although thousands of AMPs have been described in several organisms, there are no studies about their presence in microalgae. Previous studies with extracts of *Isochrysis galbana* have shown antimicrobial activity against bacteria and other microorganisms. Nevertheless, this activity has never been attributed to peptides. The purposes of this study were to: 1) Assess the bactericidal activity of peptide enriched fractions of *I. galbana.* 2) Demonstrate the presence of peptides in these fractions. The enriched fractions were obtained by acid extraction followed by Sep-pack C18 chromatography, where the fraction 40% acetonitrile (ACN) was collected. The antibacterial activity was evaluated in microplate assay by minimal bactericide concentration (MBC) against different pathogenic bacteria. The presence of small peptides was determined by tris-tricine SDS-PAGE electrophoresis and the cationic molecules by acid urea page (AU-PAGE). In addition, the effect of trypsin on the enriched fractions was evaluated. Fractions shown bactericidal effect against all the tested bacteria, reaching MBC values under 0.2 µg * µL-1 for *P. aeruginosa* and *B. cereus*. Also, the tris-tricine SDS-PAGE confirm the presence of small peptides, with molecular weights between 5 to 10 kDa. In addition, cationic molecules are visible in AU-PAGE. HPLC profiles show 14 absorbance peaks, which have been purified for mass analysis. These results open the possibility to find, for the first time, AMPs in microalgae.

FONDECYT 1170379

14) A synchronized mechanism for extracellular pH-sensing in TASK-2 K2P channel.

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Two-pore domain potassium (K_2P) channels maintain the background conductance, stabilizing the resting membrane potential. Dimeric K_2P-channels possess intramembrane fenestrations that can be open or closed depending on the position of helix TM4. TASK-2 K_2P-channel is gated open by extracellular alkalinization with a $pK_{1/2}$ ~8.0. Neutralisation of residue R224 near the selectivity filter (SF) leads to extracellular pH (pH_o) sensitivity loss. The pH_o-dependence was hypothesized to be due to protonation/deprotonation of the R224 blocking/activating the channel through an electrostatic effect on the SF. Here, experimental mutagenesis was combined with pK_a calculations of titratable residues in TASK-2 channel to better understand the pH_o-gating mechanism. 1,200 homology models of TASK-2 channel were built for different open/closed fenestration states. Our pK_a calculations suggest a stably positively charged guanidine of R224. Concerning residue E228, the calculations yield mean pK_a value of 7.64 ± 0.71 for conformation with open fenestrations, therefore departing from free solution value of 4.25. Electrophysiological examination of mutant TASK-2-E228Q revealed a shift pH_o-dependence displacing the activation curve by >1 pH unit in the alkaline direction. The results are consistent with R224 and E228 exerting a combined electrostatic effect on the SF. In this hypothesis, an ion occupancy-favouring effect of charged E228 would be lost at acid pH_o as its side-chain becomes neutral. Under these conditions the electropositive effect R224 would predominate leading to channel closure. Therefore, the combined effects of R224 and E228 would control pH_o-gating with the latter acting in a switching role to tune pH_o-dependent electrostatic potential along the SF.

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González W. thanks Fondecyt 1140624 & a Millennium Nucleus of Ion Channels-Associated Diseases (MiNICAD).

16) **Towards the identification of proteins involved in the binding of infectious pancreatic necrosis virus to fish cells.**

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Introduction:
Infectious pancreatic necrosis virus (IPNV) is the viral pathogen with the highest dissemination in salmonids. The syndrome caused by this virus is the cause of millions of losses in the salmon industry, mainly due to the high mortality generated in salmonids in the freshwater stage, reaching up to 90% when the infection is due to high virulence strains. Viruses are restricted to the use of specific interaction / penetration mechanisms to the target cell to initiate its replication and propagation. In this study, we show preliminary advances towards the identification of cell membrane proteins involved in the binding mechanism of IPNV to fish cells.

Material and Methods:
VOPBA assays were performed using different protein fractions obtained from cell cultures infected with high and low virulence IPNV isolates.

Results:
Several protein bands of different molecular sizes were individualized, which were subsequently separated and enriched, as preparatory experiments for the performance of proteomic analysis by LC-MS / MS.

Discussion:
These preliminary experiments allow us to advance towards the identification of plasma membrane proteins that participate in the initial interaction between the cell and the infectious pancreatic necrosis virus, IPNV. The knowledge generated will allow to identify therapeutic targets for the development of biotechnological solutions against this pathogenic complex that strongly affects Chilean and global salmon farming.

FONDECYT 1150934 and FONDAP 15110027, CONICYT-CHILE. Vicerrectoría de Investigación, Desarrollo y Creación Artística (VIDCA), Universidad Austral de Chile.

18) Biochemical Characterization of the ATPase-like Activity of a Catalytically Active Self-Assembled Peptide Amyloid.

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Amyloids are highly ordered protein aggregates, characterized by their elongated fibrillar architecture that is stabilized by a β-sheet structural core. The amyloid conformation has been classically associated to protein misfolding disorders such as Alzheimer's and Parkinson's diseases among others but in the past two decades reports on novel functional roles for these aggregates have increasingly emerged. Their unique mechanical properties have also positioned amyloids as promising novel bionanomaterials. The recent discover that rational design of amyloidogenic peptide sequences can yield catalytically active amyloids have opened up new venues for biotechnological and biological research. The observed activities typically emerges by alternating polar and apolar residues that enable the coordination of divalent metals on the polar side, giving rise to a metal-peptide amyloid arrangement that structurally mimic the active site of certain enzymes. Previous work from our group showed that the assembly into amyloids of a peptide containing the catalytic sequence from a nucleotydiltransferase (SDIDVFI) is dependent on coordination of divalent metals magnesium (Mg+2) or manganese (Mn+2) ions. In this work, we showed that this peptide exhibits an ATPase-like activity that is observed only for the amyloid-Mn+2 complex. We performed a kinetic characterization of the activity using different nucleotides in order to gain details about substrate specificity. The results from our work will provide novel insights on amyloid reactivity and its potential impact on diverse aspects such as amyloid toxicity and molecular evolution.

20)**Role of Endothelin Converting Enzyme-1c in malignant progression of lung adenocarcinoma cells.**

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Several deregulated signaling pathways have been described in non-small cell lung cancer (NSCLC), including the endothelin-1 (ET-1) axis, which has been related to proliferation, cell invasion and poor prognosis. ET-1 peptide activation depends of Endothelin Converting Enzyme-1c (ECE1c), a key enzyme into the ET-1 axis. We have recently shown in colon cancer cells that a super-stable ECE1c mutant promotes cancer stem cells formation, as well as drug resistance and tumor growth, however, its role in malignant progression of NSCLCcells remains to be determined. Here we studied the role of ECE1c in A549 lung adenocarcinoma cells. Lentiviral bicistronic expression of mCherry and FLAG-tagged super-stable (ECE1c-SS) and wild-type (ECE1c-WT) forms were used to get A549 cell clones, which were sorted by flow cytometry. Protein stability was analyzed in presence of CHX with an anti-FLAG antibody. Cancer stem cells features were evaluated by detecting surface markers CD133 and CD44 by RT-qPCR, as well as sphere formation assay. Cell migration was evaluated by a wound healing assay, and viability and death by MTS and trypan blue assays.ECE1c-SS displayed more protein stability in relation to ECE1c-WT in A549 cells. CD133 and CD44 mRNA levels and sphere formation correlated with cancer stem cell formation in A549 expressing the ECE1c forms, as well as viability and migration capabilities.Super-stable ECE1c overexpression promotes malignant characteristics in A549 lung adenocarcinoma cells presumably by activating the ET-1 axis.

FONDECYT grants 1161219 (FA), 11150624 (MVG), and 1160889 (JT).

22) High-fat diet-induced obesity disrupts glucocorticoid response in the liver.

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Introduction:
The overweight and obesity have a significant world rising in the last decades. It has been postulated that obesity could produce an inadequate response to stress, originating higher levels of plasmatic cortisol by an augmented activation of hypothalamic-pituitary-adrenal (HPA) axis. However, if this increase is associated an augmented glucocorticoid response in the liver is not known.

Objectives:
The aim of this work is to study if the high fat diet (HFD)-induced obesity disturbs liver response to glucocorticoids.

Materials & Methods:
Mice C57BL/ wild type was separate in two groups, feed by 3 months with a Low-Fat Diet (10% fat) or High Fat Diet (60% fat), after were injected with a single dose of dexamethasone (2 g/kg) for 8 h and then were sacrificed. Fasted glycaemia and glucose tolerance test were performed. The mRNA expression of GR, 11b-HSD1, FKBP5, KLF15, PDK4 were assessed in liver by real-time qPCR. The protein levels of FKBP5, p-GR211 and GR were assessed by western blot.

Results:
The mRNA expression of FKBP5 and PDK4 were increased in comparison to control diet in response to dexamethasone. By contrast, the increase in protein levels induced by glucocorticoid of FKBP5 and the phosphorylated form of GR were less in obese mice in comparison to control diet mice.

Conclusion:
HFD induces an increase in gene response to glucocorticoids, but at protein level has a reduced response, which suggest a deregulation between the receptor activation, gene expression and protein synthesis regulated by glucocorticoids.

This work was supported by Enlace FONDECYT-Universidad de Chile (RT), FONDECYT 1180157 (MCh) and FONDAP 15130011 (RT & MCh).

24) Adenosine promotes invasiveness in Glioblastoma stem-like cells under hypoxia through A2B receptor and MEK/ERK signalling pathway.

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Introduction:
Glioblastoma (GBM) is the brain tumour with worst prognosis anddespite the advances in current therapies, the survival rate does not exceed 15 months. This is mainly due to the high migratory/invasive capacity of a cell subpopulation called Glioblastomas Stem-like Cells (GSCs) that persists in hypoxic niches and are capable to infiltrate healthy brain tissue. The hypoxic microenvironment, increases adenosine levels activating its low affinity receptor A2B (A2BAR) that in several cellular models promotes the activation of MEK/ERK pathway. Adenosine increase the migratory/invasive capacity of GSCs, however it is unknown if it is through the activation of A2BAR and the subsequent activation of the MEK/ERK pathway. The aim of this study was to understand the role of A2BAR-MEK/ERK in modulating the migratory/invasive capacity of GSCs under hypoxia.

Methodoly:
GSCs derived from U87MG were cultured under normoxia and hypoxia (0.5% O2). Expression and activity of MMP-9 were evaluated by western blot and zymography assay, respectively. Migratory and invasive capacity of GSCs, we analyzed by transwell and matrigel assay, respectively. To evaluate the role A2BAR and MEK/ER, we used MRS1754 (A2BAR antagonist) and PD98059 (MEK inhibitor) respectively.

Results:
Migratory and invasive capacity of GSCs increased under hypoxia. A2BAR blockage and MEK inhibition decreased the migratory and invasive capacity of GSCs, downregulating MMP-9 expression and activity.

Conclusion:
Extracellular adenosine, under hypoxia conditions, is capable of regulating the migratory/invasive capacity and MMP-9 expression and activity in GSCs through the activation A2BAR-MEK/ERK signalling.

Fondecyt Regular 1160777Fondecyt postdoctorado 3180621

26) Long-term intermittent and chronic hypobaric hypoxia and AMPK activation in pulmonary artery in rats.

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Introduction:
Pulmonary arterial hypertension (PAH) leads to right ventricular failure and premature death. The exposure to Chronic Intermittent Hypobaric Hypoxia (CIH) and Chronic Hypobaric Hypoxia (CH) leads to PAH. Hypoxic pulmonary vasoconstriction (HPV) and pulmonary vascular remodeling play key roles in PAH. In pulmonary artery, AMPK suppress the proliferation cellular and triggers vasodilatation, where both endothelial NO production and NO-mediated signaling in VSMC are targets and effectors of the AMPK signaling pathway. The role of AMPK-dependent signaling cascades in hypoxic pulmonary artery hypertension is currently unknown.The aim was to determine level activated AMPK in endothelium of pulmonary arteries in rats exposed to CIH and CH.

Method:
Wistar rats randomly assigned in 3 groups: CIH (n= 10), CH (n=10), and normoxia (NX) (n=10). Hypoxia was simulated in a hypobaric chamber at 428 Torr (4.600 m) for 30 days. Were measured; Body weight, hematocrit, right ventricular hypertrophy (RVH), and level phosphorylated AMPK in endothelium of pulmonary arteries. Here, 3 mm length pulmonary artery segments were cut and analyzed in confocal microscopy.

Results:
Weight loss and increases in hematocrit and RVH were found in **CIH and CH** groups ($p<0.05$). Interestingly, **Immunostaining showed** reduced endothelial expression of phosphorylated AMPK in pulmonary arteries in CIH and CH groups, compared with control NX ($p<0.05$).

Conclusion:
In rats exposed to CIH and CH, itwas observed a reduced endothelial expression of phosphorylated AMPK in pulmonary arteries, which could be one molecular pathways involved in the development of hypoxic pulmonary hypertension in this condition.

Keywords: Hypoxia hypobaric, pulmonary arterial hypertension, AMPK.

FIC GORE TARAPACÁ BIP30477541-0 and Arturo Prat University

28) Weak Optical Tweezers Technique for Measure Antioxidant Effect of Resveratrol in Single Red Blood Cells Membranes.

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Introduction:
The human red blood cells (RBCs) membrane has elastic capabilities which can be described measuring membrane edge fluctuations and mechanical properties by multiples optical techniques. The RBC elastic properties can be affected by changes in the surrounding media. In the attempt to elucidate the molecular mechanisms of the interaction of resveratrol with cell membranes and the effect as a protective agent against oxidation, we studied the mechanical properties of RBC membranes.

Methodology:
In our work, we study the protective antioxidant effects of the resveratrol on RBCs membranes in presence of the oxidant agent hypochlorous acid (HClO). To prove it, we measure the RBC fluctuations to obtain mechanical parameters of RBCs membranes using a weak optical tweezers. This technique uses a laser with low power (<1mW) to measure membrane edge fluctuation amplitudes by deflection of light with nanometric resolution. From thepower spectrum density (PSD) of the signal we obtain mechanical parametersby fitting the data to a mathematical model. The fit allows obtaining the *bending modulus* (κ), *membrane tension* (σ) and effective viscosity (η_{eff}).

Results and Conclusions:
Our results suggest that the elastic capabilities on RBC change with low concentration of HClO, a concentration at which there are no morphological changes. However, if there is resveratrol in presence of HClO, the deformation and decrease of elastic capabilities on RBC are slower. This indicate that the resveratrol produce a protective effect in RBC in presence of HClO.

Fondecyt 1171013 and CONICYT-PCHA/2016-21160093

30) Structural characterization and molecular docking simulation of CBM-FaEXPA2 and CBM-FaARA1 from strawberry.

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Several cell wall enzymes are carbohydrate active enzymes that contain a putative Carbohydrate Binding Module (CBM) in their structures. The main function of these non-catalitic modules is to facilitate the interaction between the enzyme and its substrate. Expansins and Arabinofuranosidases are proteins present in the cell wall, and their structure includes a CBM in the C-terminal that bind to cell wall polymers such as cellulose, hemicelluloses and or pectins. We studied the structural properties of the Expansin2 CBM (CBM-FaEXP2) and arabinofuranosidase1 CBM (CBM-FaARA1) from strawberry (*Fragaria x ananassa*). The models obtained display similar structures comprising 8 β-sheets helix in CBM-FaEXP2 and 15 β-sheets and one 310 helix in CBM-FaARA1. Additionally, the interaction of a set of putative xyloglucan substrates (XG), cellulose and one homogalacturonan octamer with the CBMs was explored using molecular docking simulation. Both CBMs showed favorable affinity energies for binding XG, homogalacturonan and cellulose substrates, however to CBM-FaARA1 the better stability complex was with the homogalacturonan substrate, while CBM-FaEXP2 the better stability complex was with the cellulose substrate. These findings might offer a tool to controlling physiological processes where cell wall disassembly is relevant, such as fruit softening.

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32) Effect of atorvastatin on the Rho-kinase (ROCK) pathway and the polarization of human macrophages infected with *T. cruzi*.

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Chronic Chagas Cardiomyopathy (CCC) is the most serious form of Chagas Disease (CD), which is caused by the protozoan *Trypanosoma cruzi* (*T. cruzi*). The current treatment of CD is benznidazole, a trypanocidal drug that is not effective against CCC, so it is necessary to develop new pharmacological strategies. When *T. cruzi* enters the organism, it is recognized by macrophages, which obtain a proinflammatory M1 phenotype to try to eliminate the parasite. The persistence of the parasite produces a chronic miocarditis, which is the main cause of death. Therefore, changing the phenotype of macrophages from proinflammatory (M1) to immunoregulatory (M2) could be a new pharmacological target for CCC. Rho Kinasa (ROCK) is a serine/threonine kinase activated by small GTPase RhoA that is involved in the polarization of macrophages towards M1, however, the effect of *T. cruzi* on this pathway is still unknown. Atorvastatin inhibits the enzyme HMG-CoA reductase and the synthesis of geranyl pyrophosphate, necessary for the activation of RhoA. Therefore, we evaluated the effect of *T. cruzi* and atorvastatin on the activation of ROCK and the polarization of macrophages. To verify this, human macrophages were infected with *T. cruzi* and treated with atorvastatin. ROCK pathway and macrophages phenotypes was evaluated by Western Blot and RT-qPCR respectively. *T. cruzi* activated ROCK inducing M1 phenotype and atorvastatin inhibited ROCK activation, changing the polarization towards M2 phenotype. In conclusion, atorvastatin, by changing polarization of macrophages through inhibition of RhoA/ROCK pathway could constitute a new therapy to prevent the chronic inflammation produced in CCC.

FONDECYT Regular N° 1170126-FONDECYT Iniciación N° 11160531

34) DNA modifications in the immune system and their contribution to gene expression.

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During the past decade, we have learnt that the most common DNA modification, 5-methylcytosine (5mC), which plays crucial roles in development and disease, can be actively modified to 5-hydroxymethylcytosine (5hmC) and reversed to its unmodified form by a cyclic enzymatic cascade mediated by DNA methyltransferases (DNMTs), ten-eleven translocation (TET) family enzymes and thymine DNA glycosylase (TDG). Previous work of the laboratory and other groups have shown that a set of specific genes in CD4+ T cells are found unmethylated and hydroxymethylated at intragenic regions of the gene body. It has been reported that patterns of unmethylated cytosines, 5mC and 5hmC are cell type-specific and that these marks can be recognized by several types of methyl-binding proteins. These proteins can in turn affect alternative splicing or recruit nucleosome remodelling complex members to modify the transcriptional status of a gene. In order to examine if unmethylated cytosine and 5hmC modulate the expression of CD4+ T cells genes by recruiting specific readers, we used splenic CD4+ T lymphocytes isolated from 7-week old C57BL/6 male mice. By performing chromatin immunoprecipitation (ChIP) and a RT-qPCR we are defining the involvement of these readers in the regulation of the expression of the studied genes. Identifying the readers of specific DNA modifications in the immune system as well as their target genes, is the first step to predict the impact of mutations in epigenetic regulators and their contribution to autoimmune disease and cancer development.

This work is supported by CONICYT - FONDECYT 1171004

36) Isolation and Biochemical Characterization of acp-tx-ii a new phospholipase a2 from Agkistrodon contortrix pictigaster snake venom.

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Introduction:
PLA2 are among the most abundant components of snake venoms. Understanding the biochemical basis for their diverse toxic activities is still a challenging task. We describe the purification and biochemical characterization of ACP-TX-II, a new phospholipase A2 from *A. contortrix pictigaster*.

Methodology and Results:
ACP-TX-II was purified from *A. contortrix pictigaster* venom through by one step analytical chromatography reverse phase HPLC. The homogeneity of the ACP-TX-II fraction and its molecular mass was evaluated by SDS-PAGE, indicating molecular mass of ~14.KDa, constituted of a single polipeptidic chain.The enzymatic activity of ACP-TX-IIwas measured using the chromogenic substrate 4-nitro-3-(octanoyloxy) benzoic acid and expressed as the initial velocity of the reaction.The kinetic assay demonstrated a catalytically active ACP-TX-II, which would indicate an aspartic acid residue at position 49. The PLA2 activity of ACP-TX-II (29.31 ± 1,62nmoles/min/mg) was higher than whole venom (8.9 ± 0.53nmoles/min/mg). Under the conditions used, ACP-TX-II showed a discrete sigmoidal behavior, mainly at low concentrations. V*max* and K*m* were calculated to be 31.76 ± 2.58nmoles/min/mg and 6.26 ± 0.98mM, respectively. Maximum enzyme activity occurred at 40°C and the pH optimum was 8.0. The ACP-TX-II PLA2 showed a strict dependence on calcium ions (10mM) for full activity. The addition of Mg2+, Mn2+, Cd2+ and Zn2+ (10mM) in the absence or presence of low Ca2+ concentration (1mM) decreases significantly (89 ± 3.8%) the enzyme activity.

Conclusion:
ACP-TX-II is a catalytically active PLA2 from *A. contortrix pictigaster* snake venom, this novel enzyme is Ca2+-dependent and exhibits enzymatics characteristics that show structural similarities with other PLA2.

38) Effect of demethylating agent on response of RTS-11 cells to IPNV challenges: Approach to epigenetic modulation in aquaculture.

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Introduction:
The massive salmon farming associated to aquaculture industry has brought a significant increase in infectious diseases, thereby generating economic losses. The constant interaction of cultured fish with pathogens makes it necessary to search for new alternatives to reduce the mortalities generated by infectious diseases in the aquaculture industry. This study explore the effect of 5-azacytidine and 5-Aza-2'-deoxycytidine on response of RTS-11 to necrosis pancreatic infectious virus (IPNV).

Methodology:
Treatments with DNA methyltransferase (DNMT) inhibitor 5-azacytidine and 5-Aza-2'-deoxycytidine were performed on RTS-11 cells before infection with IPNV. We measure the capacity of these drugs of enhancer the expression cytokines trough qPCR and the effect on the viral clearance.

Results:
We observed that DNA methyltransferase inhibitors treatments were able to modulate the mRNA expression of interferon system genes. Additionally, the use of these drugs on RTS-11 shows a drop in viral titers respect to infection control.

Conclusions:
These results show that cytokines expression is benefit by the use of demethylating agent, which could be correlate with a global demethylation of DNA. Our work suggested that epigenetic mechanisms could participate in the regulation of host genes expression in IPNV infection, and provide a new insight into understanding the mechanisms of viral infection.

Funding Fondecyt 3170881, Fondap 15110027 and Fondef VIU16E0165.

40) Kinetic and thermodynamic consequences of the protonation of an evolutionary-conserved histidine in the stability and dimerization properties of human FoxP1.

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Forkhead box P (FoxP) proteins are versatile transcription factors that control the spatiotemporality of expression of multiple genes during cell development, immunity and tissue homeostasis. Different to other Fox proteins, FoxP members possess the ability to form domain-swapped dimers through their DNA-binding domains, allowing the spatial organization of distant chromosome elements by bridging two DNA molecules. Furthermore, FoxP proteins contain a specific histidine residue located in helix H3, only conserved in FoxO and FoxM, possibly responsible for tertiary structural changes modulated by pH, as previously observed in FoxP2. Here we explore the consequences on folding and dimerization of the forkhead domain of human FoxP1 due to changes in the protonation state of this residue. Using dissociation kinetics and equilibrium unfolding experiments, we demonstrated that protonation of this residue leads to destabilization of the domain-swapped dimer, causing an increase in the free energy difference between the monomeric and the transition state of the dimerization process. Alanine substitution of this residue generates a mutant protein whose dimerization propensity is pH–independent. Finally, anisotropy changes using single–cysteine mutants in helix H3 and in the proximal helix H5, showed that pH impacts only the stability of helix H3. This shows the relevance of histidine 59 in the dynamics of this secondary element and in the domain swapping properties of FoxP1. Our findings are relevant to the understanding of this evolutionary–conserved side chain in the modulation of the domain swapping dimerization in FoxP proteins

FONDECYT 1170701

42) β-Hydroxybutyrate supplementation increases endurance capacity by controlling mice skeletal muscle mitochondrial morphology.

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Introduction:
β-Hydroxybutyrate (βHB) is the main ketone body generated by the liver under starvation or ketogenic diets. βHB maintains ATP levels by its oxidation in mitochondria. This organelle can modify its shape and function depending on nutritional status. However, it remains unknown whether βHB supplementation regulates mitochondrial morphology and function as well as exercise capacity. Our aim was to investigate if βHB supplementation modifies endurance capacity by controlling mitochondrial morphology and function.

Methods:
Eighteen C57BL/6 mice fed with normal diet supplemented with βHB (n=9) (3g/kg βHB) or control (n=9) (CT) for 2 weeks. At baseline and every 6 days, mice were submitted to an acute endurance test where distance, time to exhaustion and total work were recorded. At the end of the 2 weeks, tibialis anterior, gastrocnemius and soleus muscles where obtained to determine mitochondrial proteins (MFN2, OPA1, Fis1, DRP1), enzyme activity (succinate dehydrogenase and cytochrome-c oxidase) and mitochondrial morphology by electron microscopy (TEM).

Results:
βHB supplementation increases blood βHB levels, distance, time to exhaustion and total work when compared to CT. βHB group increased mitochondrial fission proteins DRP1 and Fis1 while decreased mitochondrial fusion protein MFN2 and OPA1 on tibialis and gastrocnemius. Succinate dehydrogenase activity increase only in tibialis anterior of βHB while cytochrome-c oxidase activity was unchanged on both groups. TEM revealed a decrease on mitochondrial number, density and sarcoplasmic reticulum to mitochondria distance while increase of abnormal cristae and mitochondrial volume.

Conclusion:
βHB supplementations increase endurance capacity by modifying skeletal muscle mitochondrial morphology.

This work was supported by Dr. Abraham Stekel scholarship (MM), FONDAP 15130011 (RT & SL) and FONDECYT 1161156 (SL) and 1180157 (MC).

44) Thermal decomposition of the cell wall constituents isolated from different stages of ripening of strawberry fruit.

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Fruit softening during ripening is mainly a consequence of solubilization and depolymerization of cell wall components mediated by the action of a complex set of enzymes and proteins. In the present work, we performed a comparative study of the changes in physiological properties, cell wall-associated polysaccharide contents and thermogravimetry and derivative thermogravimetry study during different fruit developmental stages of strawberry (*Fragaria x ananassa* Duch. cultivar Camarosa). The Camarosa cultivar showed a decline in the fruit firmness values. In other hand, the thermogravimetric (TG) curves showed the cell wall polymer stability at temperatures around 200 °C and exothermic peaks characteristic of mass loss close to 250 °C which was higher as the fruit matured, showing a loss in the polymer fraction. Additionally, the TG analysis showed that the sample dry of large green (LG) stage have a mayor thermal stability probably by the higher inter-chain hydrogen bonding of the cell wall, in contrast, the ripe stage showed a lowest thermal stability. Finally, the results showed that exist a correlation between cell wall-modifying enzymes, physiological properties and firmness, which would explain the fruit softening process that reduces post-harvest life.

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46) Plasmatic Concentrations of ADMA and Homocystein in Llama (Lama glama) and Regulation of Arginase Type II: An Animal Resistent to the Development of Pulmonary Hypertension Induced by Hypoxia.

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There are animal species that have adapted to life at high altitude in the Andean highlands. One such species is the llama, which seem to have developed efficient protective mechanisms to avoid maladaptation, such as a resistance to the development of hypoxia -induced pulmonary hypertension. On the other hand, it is widely known that different models of hypertension can arise as a result of changes in endothelial function. The respect, one of the common causes of deregulation in endothelial vasodilator function have been associated with down-regulation of the NO synthesis and an increase in levels of asymmetric dimethylarginine (ADMA) and homocysteine. The objective of this study, was to determine the baseline concentrations of ADMA and homocysteine in llama, and to evaluate their effect on the arginase. METHOD: Lowland and highland sheep and llama were investigated. RESULTS: The basal concentrations of ADMA and homocysteine were determined in llama, and they were found to be significantly lower than those found in other species and in addition, the exposure to hypoxia is unable to increase its concentration. On the other hand, it was observed that the llama exhibited 10 times less arginase II activity as compared to sheep, and the expression was not induced by hypoxia.Finally, ADMA y Hcy, has no effect on the type II arginase pathway. CONCLUSION: Based on our results, we propose that low concentrations of ADMA and homocysteine found in llamas, the low expression of arginase type II, could constitute an adaptation mechanism of these animals to the hypoxia.

Plasmatic Concentrations of ADMA and Homocystein in Llama (Lama glama) and Regulation of Arginase Type II: An Animal Resistent to the Development of Pulmonary Hypertension Induced by Hypoxia
The research leading to these results has been supported by FONDECYT 11075096 and 1140647.

48) Disruption of FAM162A, a novel mitophagy-related mitochondrial protein, deteriorates mitochondria and cell viability.

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FAM162A is a mitochondrial protein described to be involved in hypoxia-induced apoptosis. Interestingly, it shows up in terminal erythropoiesis when all mitochondria are cleared out by mitophagy, having a similar transcript expression pattern than LC3 and NIX, two very well-known mitophagic proteins. In addition, FAM162A has a LC3 interacting region (LIR) domain which is conserved among autophagic proteins. Disruption of mitophagy has been associated with mitochondrial dysfunction and cell death. Thus, we have hypothesized that FAM162A is a novel autophagic protein and its disruption alters mitochondrial function. COS-7 cells were transfected with siFAM162A and mitochondrial function was assessed through the measurements of mitochondrial membrane potential and oxygen consumption rate by means of TMRE staining – microscopy and Seahorse technology respectively. Cell viability was determined by Trypan blue staining. Furthermore, COS-7 cells were co-transfected with GFP-mCherry-LC3 and siFAM162A constructs to assess the autophagic flux. FAM162A knock-down COS-7 cells displayed depolarized mitochondria and reduced oxygen consumption rate which are associated with mitochondrial disfunction. As expected, cell viability dropped by 50% at 36 hrs. post-transfection. Furthermore, a significant accumulation of autophagosomes was observed as compared with control cells. Our results suggest that FAM162A is essential for mitochondrial function, having a potential role in selective autophagy of mitochondria.

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50) Atomic force microscopy reveals structural insights into heteromeric connexin hemichannels.

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Connexin (Cx) hemichannels are hexameric membrane proteins ubiquitously distributed through the organism, responsible for cell communication and associated to a variety of diseases. Although homomeric forms have been described from the crystallized Cx26, the heteromic hemichannel structures exhibiting different selectivity and transport properties are still unresolved. To address this, we used heteromeric connexin hemichannels formed by two isoforms expressed in HeLa cells that contain a haemagglutinin tag in one isoform. The presence of the heteromers was confirmed by mass spectrometry and western blot analysis. To assess heteromeric hemichannels, purified samples were imaged using air tapping mode atomic force microscopy (AFM). Molecular volumes obtained for the hemichannels were correlated well with the expected volume predicted from their molecular weights. To determine the number of each subunit and its subunit arrangement in the complex, the hemichannels were incubated with anti-tag antibody and imaged by AFM. Single protein bound to one or more antibodies were found, showing a variety of isoform conformations.

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52) Changes in plasma and liver lipid profiles and metabolic pathways in rats under chronic intermittent hypobaric hypoxia.

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Introduction:
It has been demonstrated that chronic hypoxia leads to an increase of triglycerides by *de novo* biosynthesis in liver. Humans exposed to chronic intermittent hypobaric hypoxia (CIHH) also show hypertriglyceridemia.The aim was to assess, in a rat model, the effects of exposure to CIHH on plasma, liver lipid profile and the role of proteins involved in *de novo* biosynthesis pathways.

Method:
CIHH was simulated in a hypobaric chamber (4600m). Wistar rats (n=20) were randomly allocated into 2 types of exposure, during 30 days: CIHH (2 days hypoxia/2 days normoxia) and control (normobaric hypoxia; Nx). The following variables were measured: Body weight, hematocrit, plasma and liver lipid profile. SCD-1, HMG-CoA reductase and HIF1-α protein levels in liver (Western Blot).

Results:
CIHH rats showed: a decrease in body weight; an increased hematocrit; an increase in plasma and liver triglycerides (TG) and VLDL-cholesterol; an up-regulation of SCD-1 and HIF-1α and no changes in HMG-CoA reductase. Changes in cholesterol and subsets, except VLDL, are not attributable to hypoxia nor to HMG-CoA reductase expression.

Conclusion:
These results suggest that under CIHH conditions a dyslipidemia might be prompted as a result of alterations in liver metabolism and a *de novo* TG synthesis. The alterations in TG and VDL-Chol, via SCD1 and HIF 1α activation, along with the increased hematocrit, might contribute as cardiovascular risk factors. If these results could be extrapolated to individuals, is a matter to be elucidated.

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54) Synthesis of triacylglycerol with EPA and DHA and acid caprylic catalyzed by the lipase of Thermomyces lanuginosus under supercritical CO2. Optimization through methodology surface response.

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The n-3 long chain polyunsaturated fatty acids (n-3LCPUFA), EPA and DHA, have obtained an increasing attention due to their beneficial roles in human health. Salmon, mackerel, tuna, anchovy and sardine are the main sources for human consumption. The main goal of this study was to synthesize structured triacylglycerides (sTG), with EPA or DHA from belly oil of rainbowtrout (*Oncorhynchus mykiss*) in the *sn*-2 position and caprylic acid 8:0 (CA) in the *sn*-1 and *sn*-3 positions of the TG, through enzymatic esterification with the lipase from *Thermomyces lanuginosus* (TLL) using supercritical CO_2 ($SCCO_2$) as a solvent of the reaction. The variables of the process included: LCPUFA:CA concentrate ratio, percentage of glycerol, time, temperature and pressure in $SCCO_2$, using the response surface methodology (RSM) through a central composite design of 2^{5-1}+star. The response variables studied were incorporation of EPA, DHA and CA in the sTG and multiple optimization of the incorporation of EPA with CA or DHA with CA in the sTG. The combined optimization of the variables, allowed to obtain an optimal sTG with 50% of CA and 16% of EPA and a sTG with 50% of CA and 12% of DHA in the structure.The mass spectrometry analysis resulted in the synthesis of acylglycerols with EPA or DHA at the position *sn*-2 of the structure. The results confirm the hypothesis that it is possible to synthesize TG that have in its structure high biological value molecules such as EPA and DHA.

FONDECYT 1120627

56) Relationship between color development, anthocyanin, flavonoid and phenols and pigment related gene expression in four different cultivars of Fragaria ananassa.

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Strawberry is one the most widely consumed fruits in the world, but under certain environmental conditions the fruit exhibits inadequate red color development, causing economic losses due to lower product quality. In the present work, a comparative study of antioxidant properties, anthocyanins acumulations, total phenols, total flavonoids and transcriptional analysis of pigment related genes were performed in four strawberry (*Fragaria x ananassa* Duch.) cultivars (Camarosa, Cristal, Monterey and Portola). The four cultivars showed an increasein their red color during fruits development. The anthocyanin accumulation in the four cultivars was concomitant with the particular progress of the transcriptional activity of genes involved in the biosynthesis of flavonoid pigments. The greatest increase was observed in Monterey and Camarosa cultivars, thus we have found a correlation between fruit color, anthocyanins and mRNA abundance levels for *FaPAL, FaANR, FaANS, FaFLS*.The results could usefully to take decisions in future breeding programs to improve the content of healthy compounds in strawberry fruits.

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58) Levels of hypoxia-inducible microRNAs miR-21 & miR-126 are associated with changes in the gene expression of NO-dependent vasodilation in FGR.

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Background:
Fetal growth restriction (FGR) is associated to intrauterine chronic hypoxia and, short and long term endothelial dysfunction that would results from an altered eNOS expression mediated by epigenetic mechanisms. Studies have demonstrated the contribution of DNA methylation and histone post-translational modifications in this FGR-induced eNOS programming; however no studies have determined the role of hypoxia inducible microRNAs (miR-21 and miR-126).

Methods & Results:
Levels of miR-21 and miR-126, as well as, eNOS, DDAH1, Nrf2 y ARG2 mRNA were determined by qPCR in primary cultures of umbilical artery (HUAEC) and vein (HUVEC) endothelial cells from FGR (n=7) and control (n=7) pregnancies. Additionally, HUAEC and HUVEC from control patients were exposed to hypoxia (1% O2, for 6 to 48 h) and the expression of the miRNA and mRNA quantified. FGR EC showed higher levels of miR-126 along with lower expression of the pro-NO genes. Levels of miR-21 were negatively associated to eNOS expression in FGR endothelial cells. Conversely, *in vitro* exposure of HUAEC to hypoxia led to a transient increase in pro-NO genes (eNOS, DDAH1) along with a decrease in miR-21. Conversely, Hypoxia decreased eNOS expression in HUVEC, paralleled by an increase in miR-21, DDAH1, Nrf2 and ARG2 at 48 h.

Conclusion:
Micro-RNA miR-21 and miR-126 are differentially expressed in HUAEC and HUVEC from FGR pregnancies and their expression is associated with heterogeneous levels of pro-NO genes. The differential regulation of these miRNAs by in vitro hypoxia and FGR suggest that miR-21 and miR-126 participate in the early and late responses to hypoxia.

Time-course modeling of the vascular epigenetic programming by fetal growth restriction: role of endothelialderived miRNAs on hypoxia- and oxidative stress-induced responses. FONDECYT 1182341

Modeling the epigenetic programming of vascular dysfunction by oxidative stress in the intrauterine growth restricted fetus: Role of prenatal antioxidants in preventing long-term vascular dysfunction. FONDECYT 1130801

60) Super-stable endothelin converting enzyme-1c promotes drug resistance and tumor growth in colorectal cancer cells.

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Introduction:
Cancer stem cells (CSCs) are suggested responsible of drug resistance and metastasis in CRC. Different proteins are linked to CSCs formation, as endothelin-1 (ET-1). Activation of ET-1 depends of endothelin converting enzyme-1c (ECE1c), a key enzyme into the ET-1 signaling pathway, which is aberrantly working in CRC by promoting malignancy. ECE1c has been shown to be phosphorylated by CK2, increasing its proteasome-dependent stability and, when over-expressed, promoting invasion of CRC cells. Thus, we studied whether a non-ubiquitinable super-stable mutant is involved in CSC formation, in vitro drug resistance and in vivo tumor growth of CRC cells.

Methodology:
Lentiviral bicistronic expression of mCherry and FLAG-tagged super-stable (ECE1c-SS) and wild-type (ECE1c-WT) forms were used to get DLD-1 cell clones, which were sorted by flow cytometry. CSC population was determined with CD133/CD44 antibodies by flow cytometry. Drug resistance was analyzed in presence of 5-FU by MTS and side population assay. Tumor growth was evaluated by injecting DLD-1 clones in NOD/SCID mice.

Results:
Cells expressing the ECE1c-SS mutant increased $CD133^+/CD44^+$ fraction of cells. When incubated in presence of 5-fluoro-uracil, cells showed a higher viability compared to control, as well as displayed a higher capacity to drive out the drug. Finally, cells expressing the ECE1c-SS had higher tumor growth in NOD/SCID mice.**Conclusions.** Blockage of ubiquitination in ECE1c promotes CSC traits in CRC cells, including $CD133^+/CD44^+$ expression, drug resistance and higher ability to growth in immunocompromised mice.

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62) Chronic exercise improves high fat diet-induced hepatic steatosis.

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The liver is a fat-storage organ, however the mechanisms by which the liver mobilizes stored lipid for energy production is unknow. Autophagy could contribute to the correct handling of lipids in hepatocytes, through a specific process called lipophagy. Several studies have described that autophagy is decreased in conditions of obesity and non-alcoholic fatty liver disease (NAFLD). On the other hand, endurance physical exercise increases autophagy levels. NAFLD is the most common liver pathology in the western society, being strongly associated to obesity, metabolic syndrome and type 2 diabetes.

Objective:
Our aim was to study if the chronic exercise improves the impairment of autophay process associated to hepatic steatosis.

Methods:
C57BL/6 mice were fed with control or HFD for 12 weeks, then were exposed to 8 weeks of aerobic exercise 5 times/ week.

Results:
We found that chronic aerobic physical exercise reduces liver weight, fasting glucose and insulin, and alanine aminotransferase plasma levels in mice fed with HFD. In addition, reduces the size of lipid droplets and hepatic triglycerides levels. HFD also increases the levels of the autophagy LC3II, an autophagy marker and AMPK phosphorylated. Exercise did not produce any changes in these markers.

Conclusions:
Chronic exercise decreases liver weight, liver damage, improves glucose metabolism and reduces the size of lipid droplets, however the role of autophagy in the beneficial effects of exercise in NAFLD need further research.

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64) Low temperature induces a change in the secondary structure of CCT chaperonin. At low temperatures hydrolysis of ATP is much higher.

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The type II chaperonin CCT is a barrel shaped protein complex of 1 MDa, formed by eight different subunits. Its cellular function is to assist the folding of other "client" proteins in a mechanism that involves the binding and hydrolysis of ATP. CCT purified from bovine testis was analyzed by circular dichroism at different temperatures (from 10 to 80 °C) in the absence and in the presence of saturating ATP (1 mM) revealing an important conformational change. The results showed that at 10 °C the content of secondary structure is higher than physiological temperatures (35-37 °C). This temperature induced secondary structure change is smaller in the presence of nucleotide. Titration with ATP showed that the secondary structure change is higher at 10°C suggesting an increment in the nucleotide binding. ATPase activity was also measured at 10 and 30 °C and it was found that the initial velocity of ATP hydrolysis was much higher at 10 °C. This result did not follow the typical Arrhenius behavior and we explain this as an activation of CCT induced at low temperatures.

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66) Study of the structural and phylogenetics relationship of the Ric-8 protein family.

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The Ric-8 protein is one of the non-canonical GEF (Guanine Exchange Factor) involved in the heterotrimeric G protein-signaling pathway. The function of this protein is keeping the G protein signal active by promoting the exchange of GDP to GTP in the recently deactivated Gα subunit. This allows to several processes, which depends on continuous activation without external signaling of the pathway, to be accomplished. These processes include meiotic arrest, embryonic development, neuronal migration, and synapsis. The Ric-8 protein is present from yeast to higher order animals, with 2 paralogous in the vertebrates with different specificities over the several types of Gα proteins. As result of the lack of structural information about the Ric-8, there are only predictions about the mechanism of how it interacts with Gα triggering the GDP/GTP exchange. Our work is aimed to study a possible structural conservation along all the Ric-8 family from yeast to mammals. This conservation would suggest a conserved mechanism of recognition over Ga proteins. To accomplish this, we used Ric-8 structural prediction, using bioinformatics tools and theoretical approaches, combined with Bayesian phylogenetic analysis. Our results suggested that every protein in the Ric-8 family is an “armadillo” protein and exist a strong conservation of the protein sequence on their respective paralogous clade in the phylogenetic tree. This supports the incredible importance of this protein on the organism, with a high evolution pressure that keeps structure and function within species. Nevertheless, the experimental determination of the structure is required to fully validate the model.

Proyecto VRID de Inicio Universidad de Concepción N° 217.037.023-1.0IN

68) Delimitation of the catalytic region in agmatinase like protein (ALP).

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Agmatine is a neurotransmitter with hypoglycemic actions and anticonvulsant, anti-neurotoxic and antidepressant-like effects. It is converted to putrescine and urea by agmatinase and also by an agmatinase-like protein (ALP), a new type of enzyme which is present in human and rodent brain tissues. Recombinant rat brain ALP is the only mammalian protein that exhibits significant agmatinase activity *in vitro* and generate putrescine under *in vivo*conditions. ALP, in spite of differing in amino acid sequence, like all members of the ureahydrolase family, it is strictly dependent on Mn^{2+} for catalytic activity. However, the Mn^{2+} ligand are yet undefined and any approximation to the enzyme active site is impeded by the lack of structural information, and the low sequence identity of ALP with all known ureohydrolases. ALP contain 523 amino acids, and in this work we have cloned and expressed a sequence of 210 amino acids, here designed as ALP-central, that include the putative metal ligands. A comparative model was also generated considering the very low sequence similarity between ALP and the template of crystals structures of prokaryotic agmatinases. The results indicated that ALP-central is catalytically active as agmatinase, with a 5-fold increased K_m for agmatine and a decreased k_{cat} value. Like the wild-type ALP species, ALP-central resulted to be activated by Mn^{2+} and maintained the typical thermostability of the urea hydrolases. Results obtained indicate that ALP-central contain the active site for agmatine hydrolysis and support our proposal for a Mn^{2+} binding site in ALP.

VRID-Enlace 217.037.022-1.

70) Role of cytoplasmic N6-methyladenosine (m6A) readers on HIV-2 protein synthesis.

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N6-methyladenosine (m6A) is the most abundant internal modification in eukaryotic mRNA and has been involved in the post-transcriptional regulation of gene expression. The effects of this modification are mainly exerted by the recruitment of any of the m6A reader proteins YTHDF1, 2 and 3 or YTHDC1 and YTHDC2 to the methylated mRNA. m6A has also been reported in several viral RNA including that of HIV-1, HCV, ZIKV, amongst others. In the case of HIV-1, it was reported that DF proteins binds the unspliced mRNA to promote Gag synthesis. In this work, we have investigated the role of m6A readers in HIV-2 protein synthesis and the subcellular localization of the unspliced mRNA. Our results indicate that, in contrast to what was reported for HIV-1, overexpression of DF proteins exerts different effects on HIV-2 protein synthesis. As such, while overexpression of YTHDF1 and 2 promotes Gag and Vpx synthesis, overexpression of YTHDF3 negatively regulates this process. Interestingly, we observed that DF proteins relocalize together with the HIV-2 gRNA to stress granules, sites where the viral genome is stored in the absence of active translation. Together, these data show that HIV-2 protein synthesis is differentially regulated by DF proteins and that these m6A readers associates with the HIV-2 unspliced mRNA and are relocalized to stress granules during viral replication. HIV-2 is less pathogenic and replicates at very low rates when compared to HIV-1. We are currently investigating whether these features of HIV-2 are regulated at the epitranscriptomic level.

Fondecyt grant N° 1160176 to RSR—Conicyt fellowship folio N° 221160818 to SR

72) The role of Zinc, inflammation and duodenal mucosal integrity in cholesterol gallstone diseases.

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Cholesterol Gallstone (GSD) is a common multifactorial disease characterized by an aggregation and growth of cholesterol crystals in the gallbladder. The global prevalence of GSD is ~10-20% in adult population, but in Chile is 28%, 17% men and 30% women, respectively. The small intestine has been identified contribute of developing gallstone, however, the molecular mechanism of the small intestine in the GSD pathogenesis have been poorly studied. Therefore, our aim was to identify the molecular mechanism of the small intestine in GSD subject. Duodenal biopsy samples were obtained from patients with GSD and healthy volunteers. Presence or absence GSD was defined by abdominal ultrasonography. We performed transcriptome studies using the Illumina HiSeq 2500. We used real-time PCR and immunofluorescence to validate the differentially expressed genes identified in GSD subjects. The number of intraepithelial lymphocytes and lysozymes expression were assessed by immunohistochemistry and immunofluorescence, respectively. We identified 548 differentially expressed genes in GSD compared with control subjects. We observed enriched biological process related to cellular response to zinc, immune and antimicrobial responses, epithelial tube morphogenesis, apoptosis, DNA replication, and phospholipid metabolic process. Patients with GSD showed lower metallothionein and NPC1L1 expression, zinc level, and tight junction gene expression, in change, an increased in immune and antimicrobial genes. We identify for the first time that upper small intestine of GSD subject has altered the zinc level, immune and antimicrobial responses and duodenal barrier function. This evidence allows us to hypothesize that the small intestine may have a key impact on GSD pathogenesis.
Acknowledgment: Funded by FONDECYT 3160400. FONDAP Center for Genome Regulation 15090007.

74) Lignans from Piper cubeba: action in head and neck cells comparing with normal cells

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Introduction:
Head and neck cancer causes many deaths in developing countries and the treatment includes surgery, radiation therapy and chemotherapy. However, these methods are highly invasive and can cause irrecoverable aesthetic lesions. Because of this, *Piper cubeba* have being studied in the alternative medicine. The present project evaluated the potential cytotoxic and genotoxic of lignans on cell morphology, proliferation and migration in the tumorigenic cells.

Materials and Methods:
Two tumorigenic (Hep-2 and SCC-25) and one normal fibroblast cell lines (F5) was used, treated with five lignans (cubebin, hinokinin, dihydrocubebin, ethylcubebin and methylcubebin), all extracted from *Piper cubeba* seeds, in three different concentrations (10, 50 and 100µg/mL) for 4, 24, 40 and 72 hours. Results: The morphology of the cells did not change after the treatment with the lignans, but the proliferation and migration cell decreased. In the cytotoxicity experiment, by MTS assay, it was possible to observe that these lignans were not so toxic to the three cells studied, but by comet assay, we concluded that the lignanas were genotoxic to the cells.

Conclusions:
It seems that, the lignans work on the tumorigenic cells, causing cell death and achieving a decrease of the cell growth and migration. These data are the starting point for genetic studies, such as modulation of gene expression or functional assays. The results increase our understanding of how lignans of the *Piper cubeba* participate in the tumorigenic processes and open new possibilities for the therapy of head and neck cancer.

CAPES, CNPq, FAPESP (2017/02100-3 to FCR-L)

76) Transcriptomic analysis reveals lncRNAs variation after ADAR upregulation on breast cancer cell line MDA-MB-231.

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The Adenine-to-Inosine (A-to-I) edition, a co/post-transcriptional modification performed by Adenosine deaminase acting on RNAs (ADAR) enzymes, has been largely described as a regulatory event in both coding and non-coding RNAs. Among the latter, long non-coding RNAs (lncRNAs) (>200 bp in length) have emerged as modulating actors in cellular processes both in physiological and pathological conditions. In cancer, lncRNAs have been described as key regulators of cell proliferation, migration and invasion, suggesting possible roles in oncogenic transformation and tumor-suppressors pathways. There are a few reports in the literature that examine and study the A-to-I edition of specific lncRNAs. Nevertheless, there is still much to understand on a genome wide scale. By using RNA-seq, we detected that ADAR upregulation in the breast cancer cell line MDA-MB-231 induces the differential expression of 1184 lncRNAs transcripts (FDR < 0.001). 131 of them corresponded to novel lncRNAs whereas 1053 to known lncRNAs. We kept a subgroup of 71 upregulated and 61 downregulated lncRNAs for further characterization; the fact that most of them play a role in cell viability, proliferation, apoptosis, invasion and migration, makes them promising candidates for further experimental analysis. We postulate that the altered edition of lncRNAs by ADAR overexpression modifies their proper function and is a key mechanism in breast cancer progression.

This work is supported by: CONICYT PhD Fellowship 21161206 (to PRdS), CONICYT-FONDECYT 1171004 (to MS), CONICYT-FONDECYT 1151446 (to RA), Center of Excellence in Precision Medicine, Pfizer Chile, CORFO funded project.

78) Neuronal control of astrocyte energy metabolism revealed by genetically encoded FRET nanosensors in brain tissue.

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The potassium ion, K^+, a neuronal signal that is released during excitatory synaptic activity, produces acute activation of glucose consumption together an inhibition of oxygen consumption in cultured astrocytes, phenomena mediated by the sodium bicarbonate cotransporter NBCe1 (SLC4A4). We have explored here the relevance of this mechanisms in brain tissue by imaging the effect of neuronal activity on astrocytic pH, glucose, ATP, pyruvate, lactate and brain oxygen dynamics by using fluorescent dyes, genetically encoded FRET nanosensors and oxygen-sensitive microlectrodes. Electrical stimulation of Schaffer collaterals produced fast activation of glucose consumption with a parallel increase in intracellular ATP and pyruvate in astrocytes. These responses were blocked by TTX and were absent in tissue slices prepared from NBCe1-KO mice. Extracellular K^+ induced decrease in oxygen level, but stimulation of the same slice in the presence of TTX, resulted in increased local oxygen level. We conclude that glycolytic pathway in astrocytes *in situ* is acutely sensitive to neuronal activity, and that extracellular K^+ and NBCe1 cotransporter are involved in metabolic crosstalk between neurons and astrocytes to provide an adequate supply of lactate, a metabolite which acts as neuronal fuel and an intercellular signal. Inhibition of astrocytic oxygen consumption via stimulation of aerobic glycolysis by extracellular K^+ may be seen as a novel strategy whereby extra oxygen is made available to neurons "on demand" without jeopardizing the energetic status of astrocytes. References

Ruminot et al (2017) JCBFM Jan 1:271678X17737012 Fernández-Moncada et al (2018) PNAS 115(7), 1623–1628

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80) iNKT cell stimulation by glycolipid ligands modified from α-galactosylceramide results in differential cytokine secretion profiles.

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Invariant natural killer T (iNKT) cells are a specialized group of unconventional T cells that recognize glycolipids presented by the surface protein CD1d, expressed by most antigen-presenting cells. This results in the rapid secretion of a wide array of cytokines and without the need for prior antigen immunization, thus making iNKT cells an attractive target for immunotherapy. Marine sponge sphingolipid α-galactosylceramide is a potent agonist for iNKT cell activation, characterized for inducing both Th1 and Th2-like cytokine secretion profiles. There is an increasing interest for the development of Th1- and Th2-polarizing ligands for more focused immunotherapeutic applications. In the present work, we generated and isolated clones from iNKT cell hybridomas derived from a partially humanized mouse, consisting of a knock-in of the human CD1d gene. This allowed us to select, by flow cytometry, iNKT cell populations reactive to α-galactosylceramide presented in the context of the human CD1d molecule. Additionally, we evaluated activation of iNKT cells by C6" modified α-galactosylceramide derivatives and obtained a diverse cytokine response depending on the structural modifications of ligands and on the individuality of the iNKT cell clones. In several cases, this response was observed to be more potent than that induced by stimulation with α-galactosylceramide. Our results highlight differences between mouse and human lipid antigen presentation, as well as differences in the magnitude of the cytokine response amongst clonal populations. Our ongoing work aims to elucidate the mechanism for this observation by performing Next Generation Sequencing of the TCR chains of the responding clones.

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82) The circadian regulation on the Z-ring formation during cell division of multicellular cyanobacteria. Are there differences with unicellular cyanobacteria?

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Cyanobacteria are the oldest known organisms with a functional circadian mechanism. Many studies about this have been performed on unicellular cyanobacteria, but the knowledge on multicellular such as *Anabaena sp.* PCC7120 (hereafter *Anabaena*) is very limited. Nowadays, it is well known that in *S. elongatus* PCC 7942 (unicellular model), KaiABC clock temporarily blocks cell division through a specific inhibition of Z-ring formation, an essential component of the process, and allows the division's synchronization in a cell culture by exposing it to certain light-dark cycles. However, circadian clock absence doesn't affect the cytokinesis, but it influences the temporality in which the event occurs (without this, it is impossible synchronize a cell culture). On the other hand, in *Anabaena* this regulation is not yet known, although some recent studies show that throughout its filament the cells divide differentially over time. Therefore, this suggests differences in circadian regulation between both organisms (multicellular and unicellular). In this study, we generated KaiABC clock mutants (individual components and full cluster) in a strain with the fluorescent construction *ftsZ-sfgfp* in order to evaluate a circadian regulation on the Z-ring formation in the *Anabaena´*s cell division process. Then, these were analyzed by optical and epifluorescence microscopy to determine the effects of these deletions on the FtsZ location. Our results showed that the absence of KaiABC clock affects the Z-ring formation dynamics in *Anabaena* which suggests that the circadian regulation in multicellular and unicellular organisms have differences. In addition, implications on cell cycle synchronization will be discussed.

Fondecyt Grant 1161232 and CONICYT-PCHA/Doctorado Nacional/2016-21160240

84) Role of Phytochrome-Rapidly Regulated 1 (PAR1) in the synthesis of carotenoids in the dark-grown carrot storage root.

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Carotenoids are isoprenoid pigments that contribute to light-harvesting and photoprotection during photosynthesis and serve as scavengers for oxidative damage. Carotenoids also play important roles in human health acting as vitamin A precursors and antioxidants. Carotenoid synthesis is upregulated by light through the signal transduction mechanism induced by photoreceptors such as phytochromes (PHYs) and negatively regulated by phytochrome interacting factors (PIFs). *Arabidospsis* Phytochrome-rapidly regulated1 (AtPAR1) is a co-factor that binds and inhibits AtPIFs, inducing expression of the carotenogenic *PSY* gene, promoting carotenoid synthesis *Daucus carota* (carrot) synthesizes and accumulates high levels of carotenoids in the storage root that grows in darkness. Contrary to other plants, light impairs carotenoid accumulation, root thickening and the expression of carotenogenic genes such as *PSY*. To find genes controlling carotenoid synthesis we performed a RNA-Seq of roots grown in dark and light conditions. We found that genes involved in light signaling, like *DcPAR1*, *DcPIF3* and *DcPHYs*, were unexpectedly upregulated in dark-grown roots.In this work we present evidences on the role of *PAR1* in carotenoid synthesis in carrot.Our results indicate that *35S:AtPAR1* transgenic carrot lines show higher carotenoid levels in storage roots and greater expression of *DcPSY1* demonstrating that *AtPAR1* participates in this process. Regard *DcPAR1*, we determined that DcPAR1 binds to AtPIF7, as was shown for its homologue AtPAR1. Moreover, RNAi transgenic carrot lines with lower *DcPAR1* expression level present a thin and white mature root with lower carotenoid content, which confirmed that *DcPAR1* is essential for carotenoid synthesis and carrot storage root development.

Fondecyt Grant 1180747

86) TGF-β signaling targets CD73.

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Introduction:
The progression of Diabetic Nephropathy (DN) is driven by an extensive fibrosis that correlates with declined renal function. TGF-β is the master regulator of renal fibrosis in DN. During the progression of DN the level of extracellular adenosine (ADO) increases, depending partly on the enhanced activity of the 5'-ectonucleotidase (CD73). The aim of this work was to evaluate the role of TGF-β signaling on CD73 induction at the promoter level.

Methods:
HK-2 cells were treated during 48 h with TGF-β 10 ng/ml and histone code changes were evaluated by ChIP-qPCR.

Results:
The results indicate that TGF-β treatment modifies chromatin associated histones at the CD73 promoter. We observed that the repressive mark H3K9me3 diminished after TGF-β treatment and moreover, both activation associated marks H3K9/14ac and H3K4me3 were upregulated after treatment.

Conclusion:
TGF-β signaling induces changes in the H3 histone at the CD73 gene promoter favoring its transcriptional activation.

Fondecyt regular 1171340. Fondecyt Postdoc 3170812

88) Role of nucleoside transporters in glioblastoma stem like cells (gscs).

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Introduction:
Glioblastoma (GBM) is the cerebral tumor with worst prognosis, high recurrence and low survival rates. It has been described that within the tumor there is a subpopulation called Glioblastoma Stem-like cells (GSCs), which would be responsible for the chemoresistance and recurrence of GBM. It is described that the GSCs present high levels of extracellular adenosine (ADO), which has been associated with the great quimoresistance that these cells present. Adenosine is captured from the extracellular space by nucleoside transporters could be concentrative (CNTs) and/or equilibrative (ENTs). The aim of this study is to determine the differences in expression or activity of CNTs and ENTs between GSCs and non-GSCs.

Methods:
Adherent cells and neurospheres (GSCs) of the U87 cell line were used. Adenosine content was evaluated by HPLC. mRNA and protein levels were measured by western blot and RT-qPCR, respectively. Adenosine transport assays were developed to evaluate the activity of CNTs and ENTs in GSC and non-GSC U87 cells.

Results:
The GSCs presented higher level of extracellular adenosine with respect to the non-GSCs cells. qPCR assays showed that GSCs exhibit high levels of both CNTs and ENTs with respect to non-GSCs cells. In western blot assays, we observed that GSCs have a higher level of ENT1 and ENT2 than non-GSC cells. In adenosine transport assays, transport mediated by ENTs modulates mainly the level of extracellular protein in GSCs.

Conclusion:
The extracellular level of adenosine is regulated differentially by both CNT and ENT in GSC and non-GSC.

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90) Differential expression of key proteins for vitamin D uptake and metabolism in breast cancer tumors.

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Diverse studies show that vitamin D regulates proliferation, survival and differentiation, playing an important role in cancer including breast carcinoma. Vitamin D metabolism is regulated through a complex process, involving vitamin D receptor (VDR) and the enzymes CYP27B1 and CYP24A1. The first crucial step for all this process is vitamin D internalization. In the kidney, internalization of vitamin D is accomplished by Megalin, a membrane protein with multiple ligands. Until today reports published in relation to the mechanism of vitamin D uptake and its metabolism in breast cancer are scarce. In addition, it has been shown a relationship between serum levels of vitamin D and breast tumor subtypes, being decreased in patients with triple negative tumors (TNBC). We aimed to study the expression of Megalin, CYP24A1 and CYP27B1 in breast cancer tumors and normal breast tissue through immunohistochemistry. Further, we evaluated the expression of these proteins in T47D (luminal), HCC1937 (TNBC) breast cancer cell lines by immunocytochemistry. Our study shows that Megalin is localized apically in epithelial cells of normal breast tissue. In tumors, Megalin was localized mainly in the cellular membrane of luminal tumor cells, however, showed a very scarce membrane localization in TNBC tumors. CYP24A1 expression was higher in luminal tumors compared to TNBC tumors. Interestingly, we found similar levels of CYP27B1 in both tumor subtypes. We obtained comparable results in breast cancer cell lines. In conclusion, we observed an alteration in vitamin D internalization and metabolism in both analyzed breast cancer subtypes, being pronounced in TNBC tumors.

Supported by CONICYT: 21161571

92) Evaluation of phosphorylated Tau, nitric oxide metabolites and Cu2+ and Fe2+ in cerebrospinal fluid samples of clinically suspected patients with Creutzfeld-Jakob disease for improving the diagnosis.

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Creutzfeld-Jakob (CJD) has difficult diagnosis at initial states and no clear biomarkers account for this state. In cerebrospinal fluid from patients—12 with clinically suspected sporadic CJD (sCJD), 14 with familial CJD (fCJD)—and 16 controls with no neurological disease we studied the possible significant differences between the three groups respect to a) prion protein followed by immunodot blot, b) Tau and Tau phosphorylated threonine 181 (pT181) quantifed by ELISA; c) Cu^{2+} and Fe^{2+} quantified by atomic absorption spectrometer with graphite furnace and d) nitrite and nitrate followed by capillary electrophoresis. Our results showed significant higher contents of nitrite + nitrate in samples from both patient groups compared with controls, additionally, the values from patients with fCJD were significantly higher than the other samples. The amount of total Tau was greater in samples from both sCJD and fCJD patients respect to controls. Although, there was no significant difference in the proportion of pT181/Tau between the two CJD groups, the ratio of pT181/total Tau was significantly lower in CJDs than in control samples. The Cu^{2+} content was higher in samples from both groups of patients, while, the content of Fe^{2+} was significantly larger only in samples from sCJD patient group. The amount of 14-3-3 protein, used as positive control reported control, was significantly increased in samples from sCJD group. We conclude that both forms of CJD can be distinguished from controls by the biomarkers panel: nitrite, nitrate, Cu^{2+} and Fe^{2+} together with the ratio of the specifically reduced proportion of Tau-pT181/Tau.

94) Activation by AMP in bifunctional ADP-dependent sugar kinases from archaea: evolutionary history and kinetic characterization.

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In several archaea the Embden–Meyerhof pathway presents unique modifications, such as the ADP-dependence of glucokinase (GK) and phosphofructokinase (PFK) activities. Moreover, in organisms from the order *Methanococcales* only one bifunctional enzyme performs both activities. These enzymes are evolutionarily related and have been reported as non-regulated. Surprisingly, we found that the bifunctional enzyme from *Methanococcus maripaludis* (MmPFK/GK) is activated by its reaction product AMP. To address the kinetic mechanism of the AMP-mediated activation of MmPFK/GK and the evolutionary history of this trait, we perform a comparative kinetic study that includes enzymes from other branches of this family, such as *Thermococcales,* along with three resurrected ancestors from the *Methanococcales* and *Thermococcales* branches. Through steady-state kinetics, we determine that AMP activates both enzymatic activities of MmPFK/GK and that the reaction takes place through an ordered sequential mechanism, where MgADP is the first substrate to bind to the enzyme. Binding of AMP increase significantly the affinity for the sugar substrate and also leads to substrate-inhibition through the binding of the sugar to the free enzyme, generating a non-productive complex. Evolutionarily, AMP activation was determined to be ancestral, and it goes along with bifunctionality. It was observed in the ancestor of *Methanococcales* and also in the last common ancestor of *Methanococcales* and *Thermococcales* enzymes. However, it is absent in the ancestor as well as in current specific enzymes (GKs and PFKs) from *Thermococcales*, which allow us to conclude that AMP activation was lost during the evolutionary trajectory towards GK and PFK specificity.

Fondecyt 1150460

96) Molecular insights into the dopamine transporter inhibition mediated by G proteins.

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Dopamine transporter (DAT) is a plasma membrane protein that regulates dopamine homeostasis within the brain by driving the energetically “uphill” movement of extracellular dopamine into presynaptic neurons, which is coupled to pre-existing sodium and chloride transmembrane gradients. DAT function can be regulated by multiple intracellular and extracellular mechanisms including protein–protein interactions. Recently, it has been reported a novel mechanism describing the regulation of DAT by heterotrimeric G-proteins. Motivated by these findings, we used computational approaches to reveal the structural basis of protein–protein interactions between DAT and Gβγ subunits. Using *ab initio* modeling, the x-ray structure of the *Drosophila melanogaster* dopamine transporter (dDAT) was refined by adding the missing residues of the N- and C-terminal domains. The full-length dDAT model was then used to generate a molecular assembly of dDAT and Gβγ subunits through protein–protein docking and molecular dynamics simulations. In agreement with previous experimental data, residues situated in the carboxy-terminal region of dDAT showed to play the most important role in the interaction with Gβγ subunits. Interestingly, those residues make direct contact with a group of polar residues previously identified to lie in the binding interface between Gβγ subunits and other proteins. Dysfunction of DAT has been associated with multiple neurological and psychiatric disorders. Therefore, DAT regulation by protein–protein interactions is a promising pharmacological target, which may be crucial for structure-based drug design as well as identifying key residues modulating the function of DAT and other neurotransmitter transporters.

FONDECYT #11170223 and Millennium Nucleus of Ion Channels-Associated Diseases (MiNICAD).

98)FoxO1 is crucial to cardiac fibroblasts differentiation triggered by high glucose.

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Diabetes and concomitant hyperglycemia promote diabetic cardiomyopathy (DMC), characterized by cardiac dysfunction and tissue fibrosis. Cardiac fibroblasts (CF) are responsible for the extracellular matrix (ECM) homeostasis, under normal conditions CF maintain the balance between the synthesis and degradation of ECM, whereas in pathological conditions such as hyperglycemia, CF are activated (differentiation) generating an imbalance towards the synthesis of ECM, which results in tissue fibrosis. FoxO1 is imporatant in the physiopathology of diabetes, participant in hepatic gluconeogenesis and failure kidney. In our work we wanted to determine if FoxO1 is important for the differentiation of CF induced by hyperglycemia.

To simulate hyperglycemia, CF obtained from adult Sprague-Dawley rats were incubated in high glucose 30 mM (HG). CF activation was evaluated by determining the expression of α-SMA and Collagen I; the secretion of TGF-β1; and cell proliferation. The activation of FoxO1 was evaluated analyzing the phosphorylation and nuclear localization of FoxO1. AS1842856 was used to inhibit the activity of FoxO1. Metformin was used as a positive control.

HG induced the differentiation of CF (increase of α-SMA and Collagen I expression, increase of TGF-β1 secretion; decrease of CF proliferation), and increased the activity of FoxO1. AS1842856 blocked the activation of CF induced by HG, whereas metformin inhibited the effects of HG on FoxO1 and CF activation.

HG induced the differentiation of CF and FoxO1 activation, whereas the inhibition of FoxO1 blocked the effects of HG on CF. Thus FoxO1 could be a novel antifibrotic target in the context of the CMD.
Proyecto Fondecyt Iniciación 11160531 and Proyecto U-Inicia 2016-2018.

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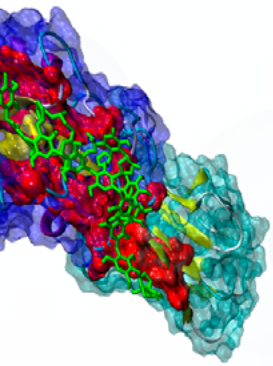

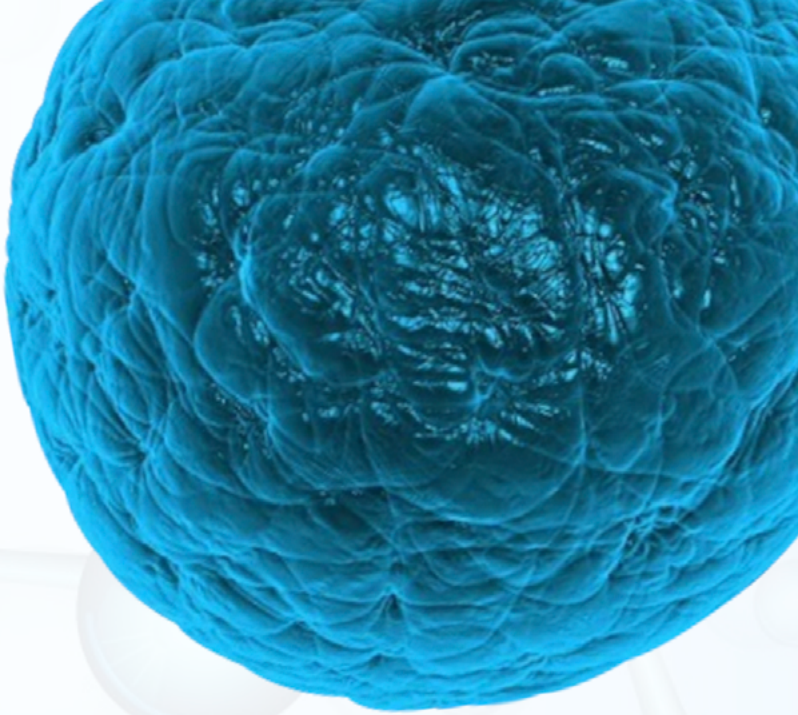

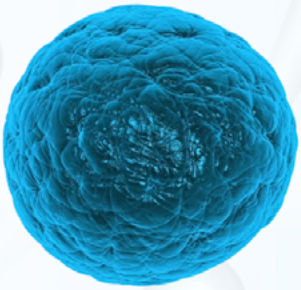

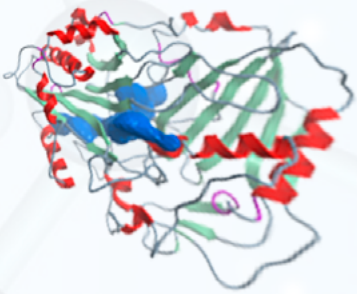

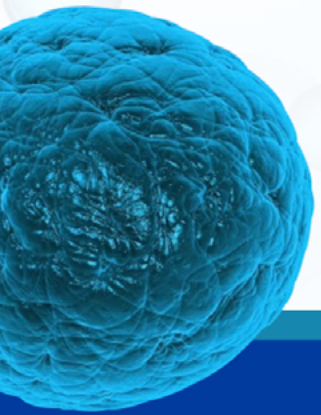

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