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1. 1.1 Executive Summary

Neuroscience has expanded and diversified dramatically in recent decades. Yet the **integration of the structural and functional organization of the brain in physiology and disease continues to remain beyond our grasp**. In addition, thousands of Chilean patients suffer from neurological or psychiatric disorders with no satisfactory treatment. Moreover, the capacity to conduct clinical brain research sustained by cutting-edge basic Neuroscience is missing in the country. Tackling this complex issue requires an integrated transdisciplinary strategy. The Biomedical Neuroscience Institute (BNI) brings together a critical mass of leading basic and clinical neuroscientists along with mathematicians to accomplish world-class scientific research and training. For the past five years BNI has provided a unified vision to explore the structural and functional organization of the brain under normal physiology from whole organisms to cells, and the mechanisms underlying disease. BNI has led Neuroscience in Chile and the region through: (i) intense collaborative research initiatives, (ii) the association to major basic-clinical centers, (iii) a vast training potential, (iv) a young team coexisting in a single campus capable of developing the long term goals of the initiative, and (v) a growing interaction with the private sector and society in general. BNI operates under three guiding principles: (i) transdisciplinary research, (ii) a bottom-up multi-scale approach, and (iii) an integrated biomedical strategy.

Research at BNI is organized around interconnected thematic platforms. During 2015 approximately 200 people including 12 undergraduate students, 24 master's students, 56 PhD students and 29 postdoctoral fellows constituted the core of the institute. This period, 31 students completed their dissertation work in a vibrant and unique transdisciplinary environment. A number of these trainees have left BNI, continuing their career paths in other national institutions or abroad, while others have stay to pursue a higher degree or a postdoctoral position. Associated Investigators published 36 scientific articles with an average ISI impact factor of 6.74, which compares favorably to similar centers in the developed world. The majority of BNI papers were published with students as first authors (22/35 ISI). 113 presentations at scientific meetings, two patents, one spin-off and multiple protected brands position BNI as an international reference center for the exploration of the structure and function of the brain under physiological and pathological conditions. During 2015 an increasing number of national and international scientific events have contributed to create an exciting multidisciplinary atmosphere at BNI. A significant proportion of Millenium funds continue to be allocated to common strategic aims such as animal facilities, a BioMat team, infrastructure, equipment, outreach and administration. Two formal networks (*Optics & Microscopy* and *NeuroSur*) continue to improve research and technological capabilities through international collaborations with emphasis in South America. Testing of new ideas and attraction of young investigators have continued through dedicated *Seed Grants* and *Bridge Fellowships*. Organization of multiple basic and clinical meetings and a strong outreach program based on the online platform *loligo*, together with active media and press appearances have positioned BNI as a resource center for specialized neuroscientists, clinical practitioners, high-school students and the general public. A thorough and voluntary *on site* evaluation by an *International Advisory Board* and a solid organizational structure have prepared BNI for the growth required to consolidate an ambitious long-term plan. Multiple awards, including the prestigious Khwarismi International Award to C. Hetz and the invitation to A. Couve and C. Hidalgo to participate in the Presidential Commission "Science for Dvelopment" highlight the impact of BNI investigators. Outstanding Executive and Grant Management Offices have consolidated with dedicated professionals and highly motivated staff. Press coverage of the institute's activities has been valued in approximately USD \$700,000

with 30 interviews in magazines and newspapers, 150 minutes of appearance on TV, 155 minutes in 7 radio stations and 24 articles online. A new building, the *Connector Cube*, currently under construction, will constitute a centralized hub for all activities and an ideal setting to engage with the community.

1.2 Resumen Ejecutivo

La disciplina de la Neurociencia se ha ampliado y diversificado de manera espectacular en las últimas décadas. Sin embargo, la integración de la organización estructural y funcional del cerebro en condiciones fisiológicas y patológicas sigue estando fuera de nuestro alcance. Además, miles de pacientes chilenos sufren de trastornos neurológicos o psiquiátricos sin tratamiento satisfactorio. Por otra parte, la capacidad de llevar a cabo investigación clínica del cerebro apoyada por Neurociencia básica de vanguardia se encuentra poco desarrollada en el país. Abordar esta compleja temática requiere de una estrategia integrada transdisciplinaria. El Instituto de Neurociencia Biomédica (BNI) reúne a una masa crítica de neurocientíficos básicos y clínicos, junto a matemáticos para llevar a cabo investigación de clase mundial y contribuir a la formación de jóvenes científicos. Durante los últimos cinco años BNI ha proporcionado una visión unificada para explorar la organización estructural y funcional del cerebro en fisiología desde organismos completos a células, y los mecanismos que subyacen a enfermedades. BNI ha liderado la Neurociencia en Chile y la región a través de: (i) intensas iniciativas de investigación colaborativa, (ii) asociación con los principales centros básico-clínicos del país, (iii) un vasto potencial en la formación de capital humano avanzado, (iv) un equipo joven que coexiste en un mismo campus capaz de desarrollar los objetivos a largo plazo de la iniciativa, y (v) una creciente interacción con el sector privado y la sociedad en general. BNI opera bajo tres principios fundamentales: (i) la investigación transdisciplinaria, (ii) un enfoque multi-escala y (iii) una estrategia biomédica integrada.

La investigación en BNI se organiza alrededor de plataformas temáticas interconectadas. Durante 2015 aproximadamente 200 personas, incluyendo 12 estudiantes de pregrado, 24 estudiantes de magíster, 56 estudiantes de doctorado y 29 jóvenes postdoctorales constituyeron el núcleo del instituto. Durante este periodo, 31 estudiantes completaron su trabajo de tesis en un entorno transdisciplinario vibrante y único. Un número importante de estos alumnos continuaron sus carreras profesionales en otras instituciones nacionales o en el extranjero, mientras que otros han permanecido en el BNI para obtener un título superior o una posición postdoctoral. Los investigadores asociados publicaron 36 artículos científicos con un factor de impacto ISI promedio de 6,74, lo que se compara favorablemente con centros similares en el mundo desarrollado. La mayoría de los trabajos de BNI se publicaron con estudiantes como primeros autores (22/35 ISI). 113 presentaciones en reuniones científicas, dos patentes, una *spin-off* y múltiples marcas protegidas posicionan al BNI como un centro de referencia internacional para la exploración de la estructura y función del cerebro en condiciones fisiológicas y patológicas. Durante 2015, un número creciente de eventos científicos nacionales e internacionales han contribuido a crear una atmósfera multidisciplinaria estimulante en BNI. Una proporción significativa de los fondos Milenio sigue asignándose a objetivos estratégicos comunes, tales como instalaciones para animales, un equipo BioMat, infraestructura, equipamiento, difusión y administración. Dos redes formales (Óptica y Microscopía, y NeuroSur) siguen mejorando la investigación y las capacidades tecnológicas a través de colaboraciones internacionales con énfasis en América del Sur. La exploración de nuevas ideas y la atracción de jóvenes investigadores han continuado a través de *Fondos Semilla* y *Becas Puente*. Organización de múltiples reuniones básico-clínicas y un fuerte programa de difusión basado en la plataforma en línea *loligo*, junto con numerosas apariciones en los medios de prensa han posicionado al BNI como un centro de referencia para neurólogos, otros profesionales clínicos, estudiantes de enseñanza básica y media y público en general. Una evaluación voluntaria en terreno de un Consejo Asesor Internacional y una sólida estructura organizacional han preparado al BNI para el crecimiento requerido para consolidar un ambicioso plan a largo plazo. Múltiples reconocimientos, incluyendo el prestigioso premio internacional Khwarismi a C. Hetz y la

invitación a A. Couve y C. Hidalgo para participar en la Comisión Presidencial "Ciencia para el Desarrollo" subrayan el impacto de los investigadores BNI. Un sobresaliente equipo ejecutivo y oficinas de gestión se han consolidado con profesionales dedicados y altamente motivados. La cobertura de prensa de las actividades del instituto ha sido valorada en aproximadamente USD \$ 700.000 con 30 entrevistas en revistas y periódicos, 150 minutos de aparición en televisión, 155 minutos en 7 estaciones de radio y 24 artículos en medios digitales. Un nuevo edificio, el "*Cubo Conector*", actualmente en construcción, constituirá un espacio centralizado para todas las actividades en un entorno ideal para comprometerse con la comunidad.

2. Introduction

a) **Description of the Institute**

The Biomedical Neuroscience Institute (BNI) constitutes a broad umbrella that brings together a critical mass of leading basic neuroscientists, clinicians and mathematicians to explore the dynamic structural and functional organization of the brain under normal physiology and the mechanisms underlying disease from whole organisms to cells. BNI aims to: (i) accomplish world-class scientific research, (ii) train and host a new generation of leading researchers and clinicians in a vibrant, solid and unique transdisciplinary environment, (iii) produce high-standard clinical research and transfer the impact of its research to society, and (iv) become a resource center for specialized clinical practitioners and the general public. Research at BNI is built upon 8 interconnected thematic platforms. 5 platforms conduct research on the relationship between structure and function of the brain, following a bottom up, multi-scale approach in complementing model organisms (flies, zebrafish, mice, rats, and humans). Two transversal platforms foster the collaborative strategy conducting research and development in applied mathematics and biomedical informatics, and diseases affecting the nervous system and pharmacological target validation. A clinical research platform strengthens the bridge between basic and medical research, and promotes the translation of knowledge to and from the clinic. BNI's research is supported by students, postdocs, young investigators and young clinicians. An Executive Office contributes to connect with other sectors, a Grant Management Office is responsible for the financial administration, and a Board of Directors steers the Institute's strategy.

b) **Research Lines:**

Research lines embody the strategic aims and the core of the collaborative effort at BNI. They are envisioned as long-term research programs and therefore have remained unchanged.

RL1. Sub-cellular functional dynamics: Neuronal differentiation requires the secretory pathway and the cytoskeleton within neurons and glia. In this context, it is fundamental to understand how the dynamic structures of the secretory pathway and the cytoskeleton are organized in different cell types of the nervous system, and how this organization determines neuronal function or dysfunction.

RL2. Cellular identity and morphology: Morpho-functional features of differentiated neurons define a structural backbone upon which connectivity is established. These features determine how electrical signals are shaped to render simple elements of cell-to-cell communication and integrate them into sophisticated computational-like devices. A central question is how gene expression determines morpho-functional features throughout the development and the lifespan of neurons.

RL3. Supra-cellular development and circuits: The transformation of brain morphogenesis involves the re-organization of multi-cellular aggregates into nuclei and layers, and the migration of axonal growth cones to establish neuronal connectivity. Thus, it is fundamental to understand how gene activity is translated into brain morphogenesis, and how the acquisition of novel states of supra-cellular and connectional organization influences patterning and brain function.

RL4. Plasticity and behavior: Hippocampal synaptic plasticity is an activity-dependent neuronal response associated with learning and memory that entails significant modifications in the efficacy of synaptic transmission. Cytoplasmic and nuclear Ca^{2+} -dependent signaling cascades are required for sustained long-term potentiation (LTP) and alteration of neural assemblies. Thus, an essential question is how genetic interactions and signaling pathways control long-lasting memories.

RL5. Systems Neuroscience: While most paradigms used to examine the neuronal mechanisms of cognitive functions and to predict neuronal activity have employed simple and controlled stimuli, the responses of neurons to complex and more ecological situations differ substantially. Thus, it is

fundamental to examine, compare and model the neuronal activity when animals and humans engage in ecological behavioral paradigms and classical psychiatric conditions.

RL6. Neural dysfunction and pharmacological targets: This transversal platform fosters an *in vivo* approach centered on understanding the mechanisms by which disease-related genes affect common molecular/cellular/physiological processes leading to neuronal connectivity and synaptic function in neuropathological conditions, and developing technological approaches.

RL7. Applied mathematics and biomedical informatics: A deeper understanding of architectonic and functional principles of neuronal processes requires a transdisciplinary approach. Biophysics and applied mathematics combined with advanced imaging and computing clusters foster an integrative view to study the design of biological structures and their functional patterns. The central aim is to uncover novel neural processes based on mathematical models that reveal morpho-functional principles of organization at multiple scales.

RL8. Clinical research and capacity building: BNI provides a rich array of clinical research opportunities in Neuroscience, based on the access to patients and samples, reliable records, and motivated clinicians. Previously these opportunities have failed to produce the expected development in Chile due to dispersion of resources, lack of efficient channels of interaction of clinicians with scientific management structures and scarce access to state-of-the art technology. A central goal at BNI is the development and consolidation of clinical research and capacity building in the study of neurological and psychiatric pathologies.

c) Organization of researcher's team:

BNI consists of one Principal and ten Associate Investigators, all professors at the F Med, U Chile, with complementing backgrounds and expertise. Additionally, BNI is constituted by 6 Adjunct Investigators (**José Luis Valdés, Pablo Gaspar, Soledad Matus, René Vidal, Patricio Olguín and Andrea Paula-Lima**), 29 postdocs, 56 PhD, 24 Master, 12 undergraduate students, technicians and 10 central managing and administrative staff. The institute continues to attract a great number of young students, who have developed strong internal, national and international collaborations.

Specific strategies to foster interactions include: (i) definition of leaders that coordinate efforts and funds within and between thematic platforms, (ii) co-mentorship of students/postdocs/young investigators/clinicians in a cross-disciplinary, open-lab atmosphere to generate effective exchanges, (iii) shared facilities for microscopy, data analysis, genetic manipulation, and animal behavior, (iv) organization of internal seminars, and theoretical/practical courses to enhance a cross-disciplinary atmosphere, (v) weekly meetings to evaluate the progress of collaborative research, adjust strategies and maintain a strong sense of thematic direction and philosophy, and (vi) an outstanding Scientific Advisory Board. The majority of Millenium funds are allocated to common strategic aims such as animal facilities, a BioMat team, postdoctoral fellowships, pilot projects, infrastructure, equipment, outreach and administration. Approximately 30% of Millenium funds are allocated to operational expenses freely executed by each Associate Investigator within BNI's guiding principles. Millenium funding constitutes approximately 1/3 of the total operating costs for scientific activities. Other national and international sources fund individual and collaborative projects and contribute to the overall impact of the institute. Each BNI investigator is responsible for specific tasks such as reviewing postdoctoral Bridge Fellowship applications or Seed Projects, coordinating collaborative networks, organizing databases, editing the scientific content of outreach activities, connecting with clinicians, and organizing scientific events. The research team is supported by an Executive Office, which contributes to the organization of scientific activities, outreach, press and connection with other sectors, and by a Grant Management Office, which provides accounting and legal support.

3. Scientific and technological research:

a) **Current status of research lines:**

Each line involves the interaction of multiple laboratories. To facilitate the revision process in this and other sections we have used initials to refer to each BNI scientist involved in a particular project, publication or other activity: A. Couve (**AC**), C. Hetz (**CHz**), M. Concha (**MC**), S. Härtel (**SH**), M. Herrera-Marschitz (**MH**), C. Hidalgo (**CH**), M. Kukuljan (**MK**), L. Leyton (**LL**), P. Maldonado (**PM**), J. Sierralta (**JS**), H. Silva (**HS**). We've discussed publications and presentations within this section to enrich the discussion.

RL1. Sub-cellular functional dynamics: Key findings from these studies have been published in leading journals, they include: the regulation of Golgi outpost formation (*Quassollo et al., 2015 Curr Biol*) (**AC**); the role of the foldase ERp72 in the accumulation of misfolded prion proteins (*Torres et al., 2015 J Biol Chem*) (**CHz**). PERK endoplasmic reticulum stress (ER) sensor regulates the miR-424 cluster and this downregulation is necessary for the fine tuning of IRE1 α and ATF6 activation (*Gupta et al., 2015 Sci Rep*) (**CHz**); Caveolin-1-increased expression enhances cell migration (*Díaz-Valdivia et al., 2015 BMC Cancer*) and its phosphorylation in tyrosine enhances the palmitate induced cell death (*Wehinger et al., 2015 BBA*) (**LL**); Ryanodine inhibits Ryanodine receptor activation in hippocampal neurons without decreasing ER calcium (*Adasme et al., 2015 Biochem Biophys Res Commun*) (**CH**). Calcium release via ROS activated Ryanodine receptor dependent is needed for insulin release (*Llanos et al., 2015 PLoS ONE*) (**CH**). Finally cholesterol removal from adult skeletal muscle alters the location of the voltage activated calcium channel of the T tubule and reduced the electrically evoked calcium transients and promotes glucose uptake via GLUT4 (*Barrientos et al., 2015 Front Physiol; Llanos et al., 2015 Am J Physiol Endocrin Metab*). International recognition of the expertise of BNI investigators has been demonstrated once again by invitations to write reviews in leading journals (*Nature Cell Biol; Expert Opin Ther Targets; Semin Cancer Biol; Front Aging Neurosci; Virus Res; Cancer Discov*); editorial comments (*Cell; Cell Death Dis; EMBO Rep*). Filamin A was found to physically associate with IRE1- α using a yeast two-hybrid screening, uncovering a novel role of the unfolded protein response in cell migration that will be published soon (**CHz/AC/MK**). Other interactions including PDIA6 were discovered using an RNAi screen (**CHz**). This project was complemented with the identification of IRE1 interactions using mass spectrometry to identify novel modulators of stress responses in neurons. The study was centered in Hsp47 and was validated in cell culture and also in fly models (**CHz/JS**) the paper will be soon published.

RL2. Cellular identity and morphology: The role of CTIP1 in neuronal morphogenesis has been studied by *in utero* electroporation in mice. Our results are compatible with a role of CTIP1 in the specification of subclasses of projection neurons in layer V of the cerebral cortex have been published (*Cánovas et al., 2015 J Neurosci*) (**JS/MK**). Using the same technique we have studied the role of partners of the chromatin-remodeling protein CoREST identified by proteomics (*Saud et al., in preparation*) (**MK**). We have followed the study of the transcription network regulated by the transcription factor Hindsight. We have also determined that one of the direct targets of HNT is Jitterburg, a *Drosophila* homolog of Filamin. These have been published (*Oliva et al. 2015 Dev Neurobiol*) (**JS/P Olgún**). We have used electrophysiology and microscopy to study the MAGUK regulation of synapse function and morphology. We demonstrated that DLG proteins are essential for efficient presynaptic neurotransmitter release and localization of voltage activated Ca²⁺ channels (*Astorga et al., under review in Scientific Reports*) (**JS**). We continue the study of lactate metabolism and glia-neuron relationship with the study a lactate transporter that is essential for

viability expressed in *Drosophila* glial cells (*Barros et al., 2015, TINS; Delgado et al, under preparation*) (**JS**). We have expanded the study to other genes of the same family. This project won support from CONICYT Associative Research Program (PIA, Programa de Investigación Asociativa) through an Anillo Grant awarded to **JS** and **P Olgún**. We have also continued the study of atlastin and the search for modifiers of the motor phenotype associated to the decreased expression of atlastin, a gene directly associated to Hereditary Spastic Paraplegias (HSP) in humans. This project is a collaboration between three BNI labs (**AC/JS/P Olgún**) and has obtained support from an International Collaboration CONICYT-USA Grant associated to UMASS (**AC/JS/P Olgún**) (*De Gregorio et al., submitted*).

RL3. Supra-cellular development and circuits: We continued the study of mechanisms that direct supra-cellular organization and circuit formation using live imaging and genetic manipulation in model organisms. We also implemented new technologies for *in vivo* imaging of nervous system development (light sheet fluorescent microscopy) and improved image tools (optical flow) in collaboration with the BNI-BioMat platform (see RL7). Some results obtained include:

(i) Left-right asymmetry in the brain: We continued our approach to understand the origin of asymmetries in the zebrafish epithalamus focusing on the role of Nodal signaling in the process. This work led to a research proposal that was recently awarded with a Fondecyt Regular Grant. We also performed comparative neuroanatomical studies to reveal a novel teleost fish model, which in contrast to the widely used zebrafish, does not develop asymmetries in the epithalamus. This model will serve to address developmental and evolutionary questions on the origin of laterotopic circuit designs. We are currently performing characterization of the model (**MC/SH**).

(ii) Role of tensile forces in directing cell migration and fate: we finished our embryological and genetic approaches and developed a mathematical model to demonstrate that collective cell movement can be directed *in vivo* by mechanical signals through coupling the motile and adhesive properties of collective cell groups to morphogenesis of neighboring tissues. We also demonstrated that such coupling serves to protect cell fate. A manuscript with these results is in preparation (**MC/SH**).

(iii) Directed cell migration driving tissue spreading *in vivo*: we continued our approach that combines embryological and genetic experiments with mathematical modeling to demonstrate that mesenchymal-like tissues can use mechanical input from cellular substrates to direct their motility *in vivo*. We also show that mesenchymal cells migrate as individuals on the basal surface of epithelia. These represent novel mechanisms of cell migration that have been only shown *in vitro*. A manuscript with these results is in preparation (**MC/SH**).

(iv) Habenular asymmetry in humans: We finished our post-mortem neuroanatomical studies to demonstrate for the first time that the lateral habenula in humans shows structural asymmetries. The manuscript is currently under revision in *Brain Structure & Function* (**MC/SH**).

(v) Chemokine and Robo-Slit signaling and habenular-IPN connectivity: We finished our experiments that linked Cxcr4b activity and internalization with the silencing of Robo3-mediated repulsion of connectivity *in vivo*. We found evidence for a role of Robo3b in mediating repulsion through the ligand Slit2, however, we still do not have a ligand for Cxcr4a. We are currently investigating if Nell2 could be that possible ligand in the process (**MC/CH**).

(vi) New zebrafish model of LRRK2: We continued the development and characterization of new transgenic zebrafish developed in our lab that express constitutively the human wild type and G2019S mutant forms of LRRK2, as possible models of Parkinson's disease. We observed that dopaminergic neurons are impaired at larval stages, which suggests developmental problems that we are currently investigating (**MC/SH**).

Based on our contributions, results were published (*Image Processing On Line*) and/or presented in international and national meetings. International: *74th Annual Meeting of the Society for Developmental Biology (USA)*, *VII International Meeting of the Latin American Society for Developmental Biology (Brazil)* and *the International Course/Meeting From Molecules to Systems: Modern Neurobiology at a Glance (Mendoza, Argentina)*. National: *XXIX Annual Meeting of the Chilean Society for Cell Biology*, *XI Annual Meeting of the Chilean Society for Neuroscience*, and *the Annual Meeting of the National Association of Biochemical Students*.

RL4. Plasticity and behavior: Studies are in progress on the role of calcium release from the endoplasmic reticulum (ER) on hippocampal long-term potentiation (LTP) and structural plasticity, and hippocampal-dependent behaviour. In particular, emphasis is placed on calcium release mediated by ryanodine-receptor (RyR)/calcium release channels, which are highly sensitive to changes in neuronal redox state. In the reported period **CH** generated the following results, in collaboration with the Adjunct Investigators **JL Valdés**, **A Paula-Lima**, young researcher T. Adasme and postdoc A. Arias:

(i) In primary hippocampal neurons, the Alzheimer's disease associated soluble amyloid beta oligomers (A β O) induced mitochondrial calcium uptake and promoted reactive oxygen species (ROS) generation (*Lobos et al., submitted 2015*). Suppressing RyR activity with inhibitory ryanodine concentrations - which by effectively abolishing RyR-mediated calcium release while preserving ER calcium levels constitutes a sound strategy to suppress neuronal RyR function (*Adasme et al., 2015*) - prevented the enhanced mitochondrial calcium-uptake induced by A β O. In addition, the general antioxidant N-acetyl-cysteine (NAC) and the mitochondrial antioxidant EUK134 inhibited the mitochondrial calcium-uptake and fragmentation and prevented the RyR2 decrease induced by A β O. We propose that the stimulation of RyR activity by A β O requires ROS and that both antioxidants agents, NAC and EUK-134, prevent the noxious effects of A β O by decreasing RyR activity and the ensuing abnormal calcium signals.

(ii) Primary hippocampal neurons transfected with RyR2 shRNA displayed significant reduction of agonist-triggered RyR-mediated calcium release and lacked BDNF-induced spine remodeling.

(iii) Studies in progress, using RyR2 shRNA, showed that RyR2 channels play a significant role in the propagation to the nucleus of intracellular calcium waves in dendrites of primary hippocampal neurons (**AC/SH/CH**). A manuscript with these results has been submitted.

(iv) In hippocampal slices, LTP induction for 1 h by theta burst stimulation (TBS) increased significantly RyR1/RyR2 mRNA levels and RyR2 protein content, but did not affect RyR3 levels. RyR inhibition, which prevented LTP induction by TBS but did not affect paired-pulse responses suggesting post-synaptic effects, prevented the associated increase in RyR1/RyR2 mRNA and RyR2 protein levels.

(v) Training rats in various hippocampal-dependent memory tasks (spatial recognition, oasismaze and contextual fear memory) increased hippocampal RyR2 protein content, as did fear memory extinction, which entails new learning. Rats injected intra-hippocampus with RyR2 antisense oligonucleotides or with A β O exhibited decreased RyR2 hippocampal protein contents and displayed impaired performance in learning and memory tasks. Based on these combined results, we suggest that calcium signals generated via RyR2-mediated calcium release are essential for synaptic plasticity and hippocampal-dependent spatial memory processes, and that deficient RyR2-mediated calcium signaling contributes to A β O-induced memory deficits.

(vi) Young, but not aged rats, performed well in a hippocampus-dependent spatial recognition task (SRT) at long-term (24-h). After performing this task, the CA1 region from young rats displayed increased RyR2/RyR3 mRNA and increased RyR2/RyR3/IP3R1 protein levels, raising the possibility that spatial recognition requires this up-regulation. These changes did not occur in aged

rats, which displayed increased basal RyR2/RyR3 protein contents compared to young control rats, and more oxidized RyR2 channels. Additionally, young rats displayed increased synaptic efficacy after the SRT whereas aged rats showed significantly impaired LTP induction before and after the SRT. We suggest that the increased basal expression of calcium release channels, plus the increased RyR2 oxidation levels, contribute to the abnormal Ca^{2+} signaling and behavioral impairments exhibited by aged rodents. During the reported period, we presented our work in several national and international meetings.

RL5. Systems Neuroscience: During 2015, we have continued a series of studies to determine the neuronal correlates of cognition. We have explored mechanisms related to visual perception and active sensing. In addition, we studied neuronal activity associated to interoception and the activity in the hippocampus during learning and memory. We have also continued the search to translate this new knowledge into clinical research by looking for biomarkers in schizophrenia (**PM/HS**). This line of research included the work of many young scientists including 2 postdocs, 6 PhD students, 10 Master's students, and 2 engineers. We presented 4 national and 7 international meeting abstracts and have 3 manuscripts in revision. An important event has been the incorporation of Adjunct Investigator P. Gaspar MD-PhD.

Three masters students completed their degree working on visual perception (R. Loyola, A. Campos and C. San Martín). They found that object segmentation relates to microsaccades, an eye movement that reflects local visual processing. These eye movements are also dependent on the nature of the cognitive task, as their properties differ during memory of search task. We are finishing work in two manuscripts on these studies. On a related topic, we are still working on event related potentials (ERP) to that occur after each eye movements. Because reviewers demanded additional experiments we acquired more data and are working in a revised manuscript. Finally, we have completed the analysis of several studies performing pupillary responses to visual images. G. Varas submitted a paper (in revision) showing that patients with radimedullar lesions have different pupillary responses during an emotional recognition task, suggesting relevant changes in autonomic function. S. Bruges is completing a manuscript aimed at examining the consequences of pharmacological inhibition of the sympathetic and parasympathetic components of the pupillary response to emotional stimuli. Her results show differences in pupillary responses to negative versus positive and neutral emotional stimuli early on the pupillary contraction phase of the response. With E. Brunetti MD-PhD, we are also completing a manuscript showing the dependence of the pupillary response to emotional stimulus on valence and arousal. These results have been included in a bio-engineering project to develop new tools to analyze and improve the design of web pages (**PM/AC**). Indeed, working in collaboration with researcher J. Velásquez (Instituto Milenio Sistemas Complejos de Ingeniería, ISCI), we have used eye movements and pupillary responses together with *Web Intelligence*. We have been granted CORFO and FONDEF grants to explore the commercial applications of these studies. We published a first paper on this topic (*Loyola et al., 2015*) and the dissertations of two electrical engineers were based on the project (K. Muñoz and S. Madariaga).

We have completed studies on the neuronal mechanisms involved in interoception (**PM**). Recording the activity of the insular cortex in a model of alcohol-addicted rats we have tested whether alteration of the vagus nerve modulates craving behavior. This study was the basis of a Ph.D thesis (C. Ibañez). We found that alteration of the vagus nerve by sectioning, not microstimulation, significantly altered the first consumption of alcohol after re-installation. This result is important because it confirms that vagal information, putatively to insular cortex, is essential in addictive behavior. In the same topic S. Vicencio completed his recordings from the insular cortex of rats while they were expose to alcohol consumption and received his PhD. The results showed that 25% of the insular cortex neurons increased their firing rate leading up to the

moment in which the animals pressed a lever to obtain an ethanol solution, demonstrating that neural activity modulation of the insular cortex participates in drug craving. We are currently working on two manuscripts to report these studies.

During this period, we have continued to combine basic and clinical efforts to study psychiatric patients. A central study involves two BNI Associated Investigators (**HS/PM**) and aims at establishing biometrics for schizophrenic patients. We continue to study a group of diagnosed patients in order to obtain behavioral, genetic, and electroencephalographic (EEG) markers for this pathological condition. The study involves Adjunct Investigator **P Gaspar** and Clínica Psiquiátrica. This work is also the basis of R. Mayol's PhD thesis. We have recorded EEG signals from more than 30 patients and 10 control subjects. Along with EEG recordings, we have recorded eye movements and pupil dynamics. We are currently exploring the impact of visual saliency in the behavioral lack of exploration seen in these patients.

RL6. Neural dysfunction and pharmacological targets: We have developed projects to address novel disease mechanisms using genetic manipulation in complementary animal models to uncover pathogenicity in neurological conditions and also test new therapeutic strategies. We have continued studying the role of protein homeostasis alterations in neurodegenerative diseases, including ALS, Parkinson's, Alzheimer's and Huntington's. We have established a strong collaboration with R. Brown at UMASS to identify novel factors contributing to ALS pathogenesis. Using genomic sequencing of nearly 100 patients we have identified novel mutations in endoplasmic reticulum (ER) chaperones (known as PDI and ERp57) that may drive ALS that were not present in more than 1000 healthy subjects (*Woebhler et al., 2015 Gene*). In collaboration with BNI Associate and Adjunct Investigators we are currently using mouse and zebrafish models (**CHz/MC/S Matus/R Vidal**). This project received one of the two international awards from the Frick Foundation in Switzerland. We have also explored the role of ER chaperones in neuronal loss in Parkinson. We made a neuronal specific model for ERp57 and analyzed the susceptibility to undergo dopaminergic neuron degeneration. Despite a strong correlative literature in the area we did not observe any neuroprotection in this model (*Castillo et al., 2015 PLoS One*). However, when we studied peripheral nerve degeneration in the transgenic model we detected significant enhancement in axonal regeneration, suggesting that the ER proteostasis network underlies differential neuronal vulnerability. ERp57 is part of the calnexin and calreticulin cycle, mediating the formation of disulfide bonds found in glycoproteins. We demonstrated that ERp57 controls the expression of the prion protein, expanding the therapeutic potential of this ER component (*Torres et al., 2015 J Biol Chem*).

We are also currently studying other targets from the ER stress response in ALS in collaboration with S. Oakes and F. Papa at UCSF to test novel drugs to decrease chronic damage. This project was awarded one of 5 grants funded by the CDMRP ALS Research Program (ALSRP) Therapeutic Idea program from the US (**CHz**). In addition, complementary support was received by the Muscular Dystrophy Association. We have also tested novel therapeutic approaches in models of peripheral nerve degeneration and Parkinson's disease (**CHz/R Vidal**). These studies included collaboration with Genzyme (US) to generate gene therapy tools to treat diseases. Although growing evidence indicates that ER stress is a hallmark of the disease, its exact contribution to the pathogenic process is not well understood. Last year we found that developmental ablation of XBP1, a key regulator of the unfolded protein response (UPR) in the nervous system, protects dopaminergic neurons against a PD-inducing neurotoxin. We are currently investigating the impact of this concept to other diseases such as Alzheimer's disease and peripheral nerve damage. In agreement with this, gene therapy to deliver an active form of XBP1 provided neuroprotection in ALS (**CHz/S Matus**). We have developed a novel strategy to improve learning and memory by delivering active XBP1 into the

hippocampus using AAVs and submitted a publication on the subject (**CHz/R. Vidal/JL Valdés**). A patent has been filed (**CHz**). Finally, together with **S Matus** we are studying new factors that drive ALS using genetic manipulation in mouse models. A new platform for gene therapy in ALS was established through funding from the ALS Therapy Alliance in the US.

We are currently developing projects to generate a novel gene therapy strategy for PD in collaboration with Genzyme Corporation in the US. We are also developing projects to study cell repair after mechanical injury to the CNS (**CHz/LL**). A novel platform was developed for drug discovery in Chile. Through FONDEQUIP support we have acquired a high-throughput microscope (Cellomic, Thermofisher). Through support from the COPEC UC Foundation we are now consolidating a library of natural compounds from Chilean plants to screen for neuroprotective factors (**CHz/R Vidal**).

Based on our contributions several reviews and editorial comments were published in leading journals (*Nat Cell Biology*, *Trends Cell Biol*; *EMBO J*, *Frontiers Aging Neurosci* among others). This platform is developing and establishing new models of neurodegeneration, including transgenic mice of Alzheimer's disease, new models of ALS, and modified animals for stress genes. These studies will be strengthened by a current International CONICYT-US Grant secured for international collaborations (**CHz**).

Additionally, we have addressed the hypothesis that perinatal asphyxia primes CNS development, increasing the vulnerability to a subsequent metabolic insult, identifying markers and targets for therapeutic interventions (**MH**). We have accumulated evidence demonstrating that PARP-1 overexpression is an early endpoint of perinatal asphyxia, triggering a metabolic cascade involving inflammatory signalling and cell death (*Neira-Peña et al 2015*, *Neurotox Res*). The idea of inhibiting PARP-1 expression with interference RNA (siRNA) is explored, studying gold nanoparticles (AuNP) as vectors for siRNA administration. The issue is evaluated in a collaboration with the McGill Department of Pharmacology, Montreal, Canada.

RL7. Applied mathematics and biomedical informatics: During 2015, the mathematics and biomedical informatics group (BNI-BioMat) and associated members of SCIAN-Lab (SH) advanced in the following: BNI-BioMat member J. Jara published *An Implementation of Combined Local-Global Optical Flow* (*J. Jara et al 2015*, *Image Processing On Line*, www.ipol.im) together with young investigator M. Cerda. Publication in IPol is embedded within a new 2-year international research project financed by *STIC AMSUD* Reproducible Research in Image and Signal Processing (ReRISiP). ReRISiP gathers participants from France and four Latin American countries (Uy, Arg, Br, Ch), a kick-off meeting was organized in Marceiò (Brazil) in March 2015. Young investigator M. Cerda, academic at the F-Med (U Chile) and former BNI-BioMat member, was involved in *Translational cancer research comes of age in Latin America*, published by investigators of the US–Latin America Cancer Research Network in *Science Translational Medicine*. J. Mansilla and Former BNI-BioMat members L. Briones have started Master theses in data center management (FONDEQUIP project: *Sistema de Almacenamiento y Servicios Informáticos Biomédicos Avanzados* (SASIBA) **SH**) and digital pathology (FONDEF project *Microscopía Virtual - Centro de Patología Digital Asistida* (CPD) (**SH**)) within the first International Program for Medical Informatics in Latin America at U Chile (Academic Director **SH**, www.magisterinformaticamedica.cl). BNI-BioMat and associative members continued to foster:

(i) New imaging techniques: Super-resolution Optical Fluctuation Imaging, SOFI (**SH**), the *Unidad de Microscopía de Dinámica Celular*, a laser ablation system coupled to live cell imaging (with BNI-BioMat member O. Ramírez), together with the new PALM (**AC**) have been installed at a new imaging facility within REDECA (*Red de Equipamientos Científicos Avanzados*, at the F Med, director **SH**). Within a FONDEQUIP project (**MC/SH**) we finished the installation of a 4 lens-light

sheet microscope in collaboration with U. Kubischek (U Bonn, Ger). Former BioMat member J. Rodriguez now performs his PhD thesis (DAAD scholar) at U Bonn to foster collaboration on LSM with Chile. **SH** and young investigator M. Cerda advanced with the setup of a new Data Center (FONDEQUIP, **SH/ M. Cerda**) at the F Med and the installation of a 10GBps connectivity to REUNA (*Red Universitaria Nacional*) and FCFM (*Facultad de Ciencias Físicas y Matemáticas, U Chile*) via the project BioMed-HPC (director **SH**).

(ii) High-, mid-, and low-level mathematical-computational methods for microscopic image analysis in combination with high performance computing (HPC): Beyond the mentioned projects (BioMed-HPC) and besides the publications mentioned above we contributed to publications fostering digital pathology *Higher blood vessel density in comparison to the lymphatic vessels in oral squamous cell carcinoma (J Clin Exp Pathol)*. Applied image processing routines in *Transactivation activity and nucleocytoplasmic transport of β -catenin are independently regulated by its C-terminal end (Gene)*, *Trypanosoma cruzi Infectivity Assessment in 'in vitro' Culture Systems by Automated Cell Counting (Acta Tropica)*, and *Trypanosoma cruzi Calreticulin Topographical Variations in Parasites Infecting Murine Macrophages (Am J Trop Med Hyg)*. Acceleration of existing and novel image processing algorithms was tackled in the new regular FONDECYT project 2015-2017 *Image Processing and Physical Models for the Interpretation of Cell Migration with 4-Lens Light Sheet Fluorescence Microscopy (SH)*.

(iii) R&D of internet assisted services for diagnosis and clinical research: The *spin-off* for Internet Assisted Medical Services CEDAI SpA (**SH**) has finished the first phase for clinical validation with *Clínica las Condes (Subsidio Semilla de Asignacion Flexible Fase 1: CORFO Innova, 2015)*, and digital pathology is further integrated into remote services for image-based analytics for clinical practices and education of remote histopathology courses in collaboration with postgraduate students of the Master Program for Medical Informatics mentioned above.

Selected publications include: *Investigators of the U.S.–Latin America Cancer Research Network (2015) Translational cancer research comes of age in Latin America Science. Science Translational Medicine, Vol. 7(319), pp. 319fs50*; Maturana-Ramírez A, Espinoza I, Reyes M, Aitken JP, Aguayo F, Hartel S, & G Rojas-Alcayaga (2015) *Higher blood vessel density in comparison to the lymphatic vessels in oral squamous cell carcinoma. Journal of Clinical and Experimental Pathology, 8(10), pp:13677-86*; Jara J, Cerda M, Delpiano J, and S Härtel (2015) *An Implementation of Combined Local-Global Optical Flow. Image Processing On Line, 5, pp. 139–158*; Maturana J, Niechi I, Silva-Pavez E, Huerta-Castro H, Cataldo R, Härtel S, Barros F, Galindo M & J Tapia (2015) *Transactivation activity and nucleocytoplasmic transport of beta-catenin are independently regulated by its C-terminal end. Gene 573(1), 115–122*; Limpi A, Castillo C, Cerda M, Droguett D, Duaso J, Barahona K, Hernandez A, Luján C, Fretes R, Härtel S, Kemmerling U *Trypanosoma cruzi Infectivity Assessment in 'in vitro' Culture Systems by Automated Cell Counting. Acta Tropica, 143:47-50*; González A, Valck C, Sanchez G, Härtel S, Mansilla J, Ramirez G, Fernandez S, Arias JL, Galanti N and Ferreira A (2015) *Trypanosoma cruzi Calreticulin Topographical Variations in Parasites Infecting Murine Macrophages. The American Journal of Tropical Medicine and Hygiene, 9, May;92(5):887-97*

RL8. Clinical research and capacity building: We have made progress in the following projects:

(i) Translational psychiatry in High Risk Psychosis syndromes: We are studying a group of first episodes SZ patients (FEP) and high-risk psychosis disorders (HRP) in order to find behavioral, neuroimaging, electroencephalographic (EEG) and genetic potential biomarkers for this disease. During 2015, we have performed time-frequency analyses to investigate the role of impaired alpha ERD in visual processing deficits in schizophrenia patients (Sz). Sz were significantly impaired in the attention-related modulation of ongoing alpha activity for both HSF and LSF stimuli. These

deficits correlated with patients' behavioral deficits in visual information processing as well as with visually based neurocognitive deficits (*Martínez A, et al., Front Hum Neurosci, 2015*). We have presented four abstracts of these studies at the 2015 annual meeting of the Society for Neuroscience in Chicago, USA and a manuscript is under preparation.

On other hand, we have critically discussed the clinical and molecular evidence on metabolic alterations induced by SGAs, the evidence on the efficacy of classical antidiabetic drugs and the emerging concept of antidiabetic polyphenols as potential coadjutants in SGA-induced metabolic disorders (*Rojo LE, Pharm Res 2015*). These 2 papers represent a starting point of collaboration between our laboratory and A. Martínez from the department of Psychiatry of the Columbia University and L.E. Rojo from the University of Santiago.

(ii) Pharmacogenomics of antipsychotic responses in Schizophrenia: We have analyzed clinical information as well as biomarkers (blood BDNF) and genetic information (BDNF Val66Met polymorphism). Future directions include carrying out a more extensive genomic analysis. A recent development originating from our preliminary study is the collaboration between two BNI labs as a result of the approval of a Pilot Project 2014 (**HS/CHz**). To employ a multi-scale approach, from genes to behavior, we have measured and correlated clinical parameters with BDNF protein and RNA levels in blood, and studied their modulation by a transcription factor currently under investigation at BNI and a likely candidate in the BDNF functional pathway (**CHz**).

(iii) The biobank initiative: We are functioning with a formal relationship with the Department of Psychiatry, North Division of the F Med, who provided additional funding for the acquisition of minor lab equipment and reagents for the advancement of the project. Some items necessary for the functioning of the biobank were acquired through funding from BNI and support from the Department of Psychiatry. The software purchased by the Department of Psychiatry is being used for samples that enter the biobank.

(iv) During 2015 we have continued with the incorporation of new patients in the studies of first episode of schizophrenia, BDNF as biomarker of cognitive function in schizophrenia and bipolar and borderline personality disordered patients.

b) Publications:

During this funding period BNI published 36 articles, 35 of them ISI and 22 coauthored by students. Their relevance and impact for each research line have been described in section 3a. *See Summary Table below.*

Summary table

Category of Publication	MSI Center Members	Number of Publications coauthored by students	Total Number of Publications
ISI Publications or Similar to ISI Standard	Associate Researchers	21	35
	Other Researchers	0	0
SCIELO Publications or Similar to SCIELO Standard	Associate Researchers	0	0
	Other Researchers	0	0
Scientific Books and chapters	Associate Researchers	0	0
	Other Researchers	0	0
Other Scientific Publications	Associate Researchers	1	1
	Other Researchers	0	0
Total of Publications		22	36

Other achievements:

During 2015 BNI hired a full time tech-transfer specialist, S. Reyes, to promote intellectual property protection, technology transfer, applied research and collaborate with the central R&D office at U Chile.

Patents:

As a direct result the work of S. Reyes' work two additional patents were filed during 2015:

1. Gene therapy treatment using AAV-XBP1s / GFP virus, and its use in the prevention and treatment of Amyotrophic Lateral Sclerosis.
2. AAV/UPR-plus virus, UPR-plus fusion protein, genetic treatment method and its use in treating neurodegenerative diseases such as Parkinson's disease, among others.

Intellectual property:

During 2015 we continued to protect the corporate image of BNI and a number of brands associated to the Institute. Our legal advisor J. Díaz has efficiently led this process. New brands that were filed for protection during 2015 included:

1. BNI: our institute corporate name and logo.
2. UPRplus: trademark name for the new patented treatment and logo.

Congress Presentations:

During this funding period BNI Associate Investigators and their teams attended, presented their work and organized 113 national and international presentations. To evaluate them in the context of the corresponding research line they have been described in section 3a when appropriate. *See Summary Table below.*

Summary Table

Type of presentation	National Events [Number]	International Events [Number]
A. Associate Researchers		
Conferences, oral communications, poster communications, others (specify)	29	25
Invited presentations (not included in above row)	28	31
B. Other researchers (Adjunct Researchers, Senior Researchers, Young Researchers, Postdoctoral Researchers and Students)		
Conferences, oral communications, poster communications, others (specify)	0	0
Invited presentations (not included in above row)	0	0

Organization of Scientific Events:

During 2015 we continued our weekly Investigator meetings. Starting this year they have included not only Associate Investigators but also Adjunct Investigators in order to put into practice our new structure for the next 5 years and have continuity with our meeting aims: to exchange information of research lines and drive BNI's cross-disciplinary atmosphere into concrete collaborative projects. At the same time the scientific discussions have been improved with new perspectives from special guests (e.g. Alejandro Jofré, Director of Centro de Modelamiento

Matemático) and they have fostered an appropriate environment to sustain rich research related conversations while allowing time to organize and steer the institute.

As in the previous years we have organized regular seminars in topics that connect Neuroscience and medicine, and which include local and international speakers. The list of 2015 topics and speakers included: *Regulación de cascadas transduccionales que promueven remielinización en el sistema nervioso central* (G. González, University of Cambridge, UK); *De la biología del desarrollo al desarrollo tumoral: interacciones entre células y su ambiente* (C. Carmona, Memorial Sloan Kettering Cancer Center, New York, USA); *Spatio temporal dynamics of sensory processing dysfunction in schizophrenia* (A. Martínez, Columbia University, USA); *Breaking symmetry in the brain: from genes to circuits and behaviour* (S. Wilson, University College London, UK); *Esquizofrenia: de lo cognitivo a lo social* (F. Aboitiz, PUC); *A glia to neuron transdifferentiation is required for sex specific learning in c. Elegans* (R. Poole, University College London, UK); *c-abl signaling in Alzheimer disease and other neurodegenerative diseases: projections for drug searching* (A. Álvarez, PUC); *Plasticidad filogenética en los sistemas sensoriales. Algunos ejemplos* (J. Mpodozis, U Chile); *Relaciones íntimas entre la glia y su axón en programas degenerativos y regenerativos* (F. Court, PUC); *Neuromodulación de la médula espinal para el mal de Parkinson* (R. Fuentes, U Chile); *Increased neuronal noise is related to the psychosis like effects of 9 – Tetrahydrocannabinol* (J. Cortez-Briones, Yale University); *The functional organization of axon in health and disease* (M. Rasband, Baylor College of Medicine, USA); *Regulation of proliferation and differentiation in an adult stem cell lineage* (M. Fuller, Stanford University, USA); *Enfermedad de Parkinson: prolegómenos, debut y progreso. Roles de señales inflamatorias y fagocitos y células gliales* (M. Herrero, University of Murcia, Spain); *Exploring neurogenic niches in the adult brain* (K. Whitlock, U Valparaíso); *Vías de señalización intracelular implicadas en la disquinesias inducidas por L DOPA en la enfermedad de Parkinson y mecanismos de neurotoxicidad por drogas de diseño* (R. Moratalla, Instituto Cajal, Madrid, Spain); *Interacción entre estrés y adicción* (K. Gysling, PUC); *Necessity and feasibility of brain - scale simulations: steps in the European Human Brain Project* (M. Diesmann, Jülich Research Center, Germany); *Relating large scale neuronal activity to behaviour: aspects of statistics, analysis and reproducibility* (S. Grün, Jülich Research Center, Germany); *Functional organization of synaptic circuits in the thalamo - hippocampal axis* (P. Fuentealba, PUC); *The SUR1 regulated channel and novel treatment for traumatic CNS injury and stroke* (H. Eisenberg, University of Maryland, USA); *La importancia de los embriones de aves para entender la transición dinosaurio – ave* (A. Vargas, U Chile); *Interacciones nervio glia celular sensorial regulan la capacidad regenerativa en la línea lateral de pez cebra* (M. Allende, U Chile); *Sinucleína: buscando una función fisiológica* (K. Vargas, Yale University); *Bioquímica a nivel de moléculas individuales: cinética enzimática y motores moleculares* (C. Wilson, U Chile).

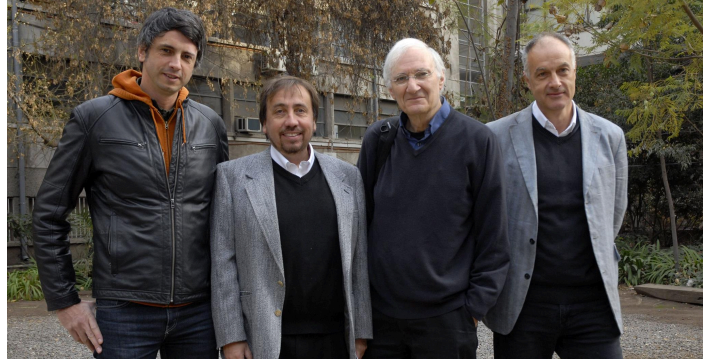
In addition to our regular seminars, we co-organized the workshop *Herramientas de Análisis Espectral en EEG (March 13th)* funded by the Massachusetts Institute of Technology (MIT). Concepts and applications of EEG analysis were discussed with the participation of E. Brown and F. Flores from MGH Harvard and MIT, J. Díaz (U Chile), J.C. Letelier (U Chile), T. Ossandón and E. Rodríguez from PUC.

Besides, we organized the International Workshop *Recent advances in ALS from discovery to therapies* (March 17th), which gathered speakers from Chile and the University of Massachusetts. International speakers included R. Brown, D. Bosco and F. Gao from the U Massachusetts. Local speakers included C. Hetz (BNI), B. Van Zundert (UNAB), P. Lillo (Hospital Barros Luco), J. Henríquez (U Concepción), S. Matus (NeuroUnion Foundation) and M. Campero (Clínica Alemana). In addition, we organized the 5th Basic-Clinic Encounter (October 30th 2015) on the subject of *New Therapeutic Frontiers in Neurology*, in which took part as speakers F. Pitossi (Leloir

Institute, Argentina), P. Manque (Universidad Mayor), B. Schneider (EPFL, Switzerland), F. Court (PUC), C. Hetz (BNI), C. Luhr (Hospital Militar) y R. Vidal (BNI).

Finally, to foster cooperation between BNI's laboratories, an internal seminar series was held every month. Each seminar included presentations of three students or postdocs from three different laboratories that explained their main discoveries. They received enthusiastic feedback from Investigators and students from other labs of the institute.

During 2015 we received the visit of three members of our Scientific Advisory Board, M. Raff, C. Soto and J. Henley. They produced a written evaluation report that was instrumental to prepare the renewal strategy of BNI, which was submitted in October 2015. (Photograph, A. Couve, left, with members of the Scientific Advisory Board at BNI, from left C. Soto, M. Raff, and J. Henley).



Scientific Editorial Boards: BNI investigators continue to participate in editorial boards of general and specialized international journals covering Neuroscience and biomedical research. Currently BNI researchers are editors of *Frontiers in Synaptic Neuroscience* (AC, Review Editor), *Current Molecular Medicine* (CHz, Associate Editor), *Mechanisms of Development* (MC, Editor), *Open Behavioral Sciences Journal* (MC, Editor), *Neurotoxicity Research* (MH, Associated Editor), *Amino Acids* (MH, Editor in Chief), *Journal of Amino Acids* (MH, Associated Editor), *Journal of Pediatric and Neonatal Individualized Medicine* (MH, Editor), *Frontiers in Skeletal Muscle Physiology* (CH, Editor), *Biochemical and Biophysical Research Communications* (CH, Editor), *Developmental Neurobiology* (MK, Editor), *Frontiers in Integrative Neuroscience* (PM, Editor), *The World Journal of Biological Psychiatry* (HS, Editor), *Asia-Pacific Psychiatry* (HS, Editor), *Revista Chilena de Neuro-Psiquiatría* (HS, Editor), *Gaceta de Psiquiatría Universitaria* (HS, Editor?), *Trastornos del ánimo* (HS, Editor), *Revista de Psiquiatría Clínica* (HS, Editor), *Acta Psiquiátrica y Psicológica de América Latina* (Argentina). BNI Adjunct Investigator **P Gaspar** is currently associated Editor in *Frontiers in Psychiatry*. Additionally BNI members are committed to raising the impact of *Biological Research*, an ISI indexed national journal (CH and LL, Editors).

Awards: During 2015 BNI investigators received exciting individual awards and recognitions. CHz received the prestigious Khwarismi International Award (KIA), first place, for invaluable achievements and contributions to the development of science and technology, in particular for his research in neurodegenerative diseases. In addition, this prize was accompanied by a UNESCO special award. He received these recognitions in an international ceremony celebrated in Iran.

2015 was of particular importance for scientific policies in Chile. AC and CH were part of Presidential Commission "Science for Development", that set the bases for the creation of the science and technology ministry in 2017. CH was elected Vice-President of the Chilean Academy of Sciences, being the first woman to hold that position, together with the new President, Astronomer M. Teresa Ruiz, constituting an important step for gender equality in Chilean sciences. The MIM museum set CH's name in the "science walk of fame", where they distinguished national prizes for science.



(Photographs, left, the Chilean President Michelle Bachelet receiving the document "Science for Development", C. Hidalgo and A. Couve were active members of the comision; right, C. Hetz receiving the KIA prize in Iran).

D. Rojas, a former student with **CHz** received the award for best doctoral thesis by the Chilean Academy of Sciences. The Latin American Society for Developmental Biology recognized G. Reig, a postdoctoral fellow with **MC** with a young investigator award 2015. J. Toledo, D. Salas, J. Fresco, C. Gonzalez, S. Hartel, A. Couve won best image Macro at the 7th meeting of young researchers in neurosciences, Córdoba Argentina. Likewise J. Toledo, F. Valdés, C. Reyes, D. Flores, C. Allende-Castro, M. Díaz, E. Díaz, A. García, S. Hartel won the second image prize in the Chilean Society for Cell Biology. We also highlight young investigators who obtained Fondecyt Postdoctoral grants: P. Ahumada, V. Chang, M. Brenet, K. Palma, C. González, V.H. Cornejo, H. Urra, E. Pulgar. Additionally, C. Oliva y D. Medinas, were granted FONDECYT Iniciación sponsored by BNI for the first time. Finally, we emphasize the active media appearances of BNI investigators. The opinion column written by **CHz** was the most read article at Qué Pasa Magazine, while the interviews to **AC** in Tendencias/La Tercera newspaper and **CHz** in Qué Pasa Magazine reached the top ten most read articles in 2015.

4. Education and Capacity Building

a) **Education and capacity building:**

BNI operates in the context of U Chile, the main public educational institution in Chile, providing the largest and most diverse network of undergraduate and graduate programs in biomedical sciences, including Neuroscience. Currently the F Med hosts 6 PhD and 16 Master programs. Thus, BNI provides advanced training, supporting institutional efforts, in close interaction with central administration and F Med authorities. BNI Investigators play a leading role at doctoral and master programs, chairing a number of academic committees at the Medical, Chemical & Pharmaceutical Sciences, and Science Faculties, U Chile. BNI Investigators also organize Advanced Graduate Courses in Neuroscience and related disciplines, including Cell Physiology, Molecular Mechanisms of Neurodegenerative Disease, Molecular & Clinical Pharmacology, Topics in Biomedicine and Neuropsychopharmacology. Importantly, 5 BNI investigators are members of the executive committee for the PhD Program in Biomedical Sciences, the largest in the country (**PM** Director of the program, **LL**, **AC**, **MC**, **CHz**) and the Masters in Neuroscience (**JS** Director) and Medical Informatics (**SH** Director). BNI scientists also participate in graduate programs in other Faculties at U Chile (Engineering & Mathematics, Chemistry & Pharmaceutical Sciences, Sciences, Dentistry, Veterinary) and programs in other universities in the metropolitan and regional areas. BNI provides a framework for a number of undergraduate and graduate students, carrying out their investigation units and thesis in one or several BNI labs. Furthermore, BNI facilities and equipment are available for faculty members and students of the Institute of Biomedical Sciences (ICBM) at large and associated clinical campuses. The focus is on education and capacity building, and in training neuroscientists involved in basic and clinical research. One main contribution is on medical specialties, contributing to the education of psychiatrists, neurologists, neuro-pediatricians, pharmacologists and other clinical specialities. Initiatives involve American Universities, such as Columbia, Harvard (USA) and McGill (Canada), as well leading Universities and Institutes in the European Union (Göttingen, Heidelberg, Magdeburg, Mannheim Institute of Mental Health J5, Germany; Jülich Forschungszentrum, Germany; Karolinska Institutet, Sweden; Cagliari University, Italy; Jaume I University, Castellon, Spain). International collaborations have provided a framework for research stays of graduate and associated scientists. A number of graduate students (>50 students) are receiving full or partial stipends, easing their progress and completion of their doctoral programs. Furthermore, associated BNI scientists participate in multiple evaluation committees, warranting the excellence required by the graduate programs. Young scientists holding a PhD degree are invited to apply to BNI *Bridge Fellowships* twice a year (fall and spring). Eligibility includes commitment to apply for a Fondecyt postdoctoral fellowship during the corresponding academic period. Applications are managed and reviewed by BNI scientists according to a protocol that emphasizes competitiveness and minimizes conflicts of interest. BNI provides both full postdoctoral fellowships through Bridge Fellowships and contributes indirectly to support other postdoctoral initiatives. The results of this program are summarized in the attached tables. We have funded 36 bridge-fellowships with 27 investigators securing a subsequent Fondecyt Postdoctoral Fellowship, constituting an impressive ~75% success rate.

BNI encourages the interaction of students with more than one laboratory and mentor, as a manner to enrich the opportunities and cross-fertilizing fields. Thus, several PhD theses are currently co-directed by BNI members, the students sharing the facilities and educational opportunities, including BNI daily activities. These interactions are stimulating publications and thesis co-authored and co-directed by more than one BNI investigator, as well as initiatives for 21 granting opportunities. Postdocs, graduate and undergraduate students take the initiative and are the

organizers of regular seminars (G. Delgado and D. Rojas) and symposia in the framework of the BNI, inviting scientists visiting the country, or national postdocs carrying out research periods abroad, coming to Chile for short-term visits. Particularly notable is the initiative involving the University Clinical Psychiatry, where periodical seminars are carried out involving scientists from American and European Universities, with an active participation of BNI students. Similar initiatives are planned to be carried out with other clinical campuses of the F Med.

b) Achievements and results:

128 students (undergraduate through postdoctoral) are presently associated to BNI. We are training 12 undergraduate students, 24 master's students, 56 PhD students and 29 postdoctoral fellows. This period, 31 students completed their dissertation work. A number of these trainees have left BNI, continuing their careers paths in other national institutions or abroad, while others have stayed to pursue a higher degree or a postdoctoral position. The majority of BNI papers are published with students as first authors (22/35 ISI). BNI students participate regularly in national and international meetings, in poster and oral sessions (see Congress Presentations summary table). Several BNI students are carrying out research and trainee periods abroad. BNI's support of students has allowed the completion of projects, smoothing transitions, supporting further students without additional fellowship support. BNI was instrumental in creating and running the first International Master in Medical Informatics at the F Med U Chile (**SH**). The Master is implemented within collaboration with Heidelberg University (Germany), and includes the support of four visiting professors per semester, student exchange, and the installation of a double degree in 2015/2016.

As part of our aim to internationalize BNI, we also promoted international experience for our students. During this period 13 students visited foreign laboratories to carry out research. Students visited laboratories in Europe (Germany, England, France and Italy) and in the USA. Additionally we received 5 international students from Japan, Spain, France, and Germany who performed research at BNI labs.

To promote interactions and incorporate young investigators to the central activities of the institute we have conducted a yearly internal competition of *Seed Grants* (approximately US\$ 7,000). Adjunct Investigators have had access to these grants, in collaboration with Associated Investigators, to develop new and high-risk ideas. 13 grants have been funded between 2011-2015: 4 secured additional funding from Conicyt International Proposals, FONIS, Chilean and US foundations.

c) Destination of Students:

BNI undergraduate and master students normally follow advanced studies (PhD, MD-PhD) or are directly involved in clinical research. Most BNI graduate students are recruited for scientific and academic careers, conducting research as postdoctoral fellows or faculty members in Chile or abroad. 11 students graduated during 2015 and 3 postdocs continued their scientific careers elsewhere. 7 graduates have remained in science and academia. Some national institutions that have incorporated former BNI young investigators include U Chile, Pontificia U Católica de Chile, U Valparaíso, U A. Hurtado, and U D. Portales.

5. Networking and other collaborative work

a) Networking: During 2015, BNI continued to enhance national and international associations with leading experts in Neuroscience, developmental biology, microscopic imaging, and biomedical informatics. To increase the impact of our 2015 network budget, we decided to merge the events of our two formal networks *Network 1 (Advanced Optics)* and *Network 2 (NeuroSur)* into one single event that will take place in March 2016. Two main advantages of this strategy were envisioned: (i) students from international courses, speakers from the symposia, and members of the NeuroSur community will have the chance meet for the first time (within our new BNI building) providing additional interaction opportunities for Latin American established and young scientists, (ii) the international course *Optics, Forces & Development II* (www.cellmorphodynamics.cl/ofd2016), organized by **MC/SH**, with 12 students from different Latin American countries and international lectures could be organized in synchrony with a new training course on *Processing and Analysis of Fluorescence Microscopy Images* (<http://pasteur.uy/en/courses/pafmi#prettyphoto/0>), held at the Pasteur Institute in Montevideo (Uruguay) just before the summer school, symposia, and NeuroSur IV meeting in Santiago. (Figure: the evocative logo of our regional network initiative).



The coordination of both international courses was performed during 2015 with the director of the Signal Processing Laboratory at the Pasteur Institute (F. Lecumberry) in close association with **SH**. The installation of the Signal Processing Laboratory at the Pasteur Institute in Montevideo was catalyzed during the first NeuroSur I meeting 2012 in Montevideo (Pasteur Institute in Montevideo, www.bni.cl/nv_detailed.php?did=358), and coordination continued during NeuroSur II meeting 2013 in Buenos Aires (www.bni.cl/nv_detailed.php?did=372). The coordinated courses at Pasteur (Montevideo) and BNI (Santiago) opened the possibility that students from the institutes could participate in both courses and gain closer insight in the host institutions. Several lecturers (**SH**, M Cerda, F. Lecumberry, and U. Kubischek) will participate in both courses. The first course in Montevideo will focus on hands on image processing, while the second course will focus on hands on microscopy and *in vivo* biology.

In addition to the planning of courses and events in 2015, BNI investigators from **SH's** lab, Institute Pasteur and Clemente Estable (Uruguay) performed mutual visits. They initiated the STIC AMSUD project *Reproducible Research in Image and Signal Processing* (ReRISiP) in collaboration with researchers from Argentina, Brazil, and France. ReRISiP performed a kick-off meeting in Maceio (Brazil) where all members initiated strategies to foster reproducible research, ethics, and standards for publication of scientific code within the IPOL and the new IPOL-LA strategy (www.ipol.im). In this context, BioMat member J. Jara published a first article in *Image Processing On Line*, www.ipol.im together with M. Cerda/**SH**. ReRISiP organized the first THOR Workshop "Training and Hands-On Workshop for Reproducible Research" on November 13-14th 2015, providing tools for reproducible research and training on the IPOL Journal publication process within the 20th Iberoamerican Congress on Pattern Recognition (CIARP 2015, www.ciarp.org/xx/) in Montevideo.

b) Other collaborative activities: Strong collaborative initiatives not included as formal BNI networks have continued to be promoted by BNI scientists. BNI has provided additional support for exchange of students, postdocs and expertise with laboratories in Chile, Latin America, US and Europe. During 2015 the German Academic Exchange Service (DAAD) granted further five years for the development the Centre of Excellence (Medical Informatics) Santiago de Chile – Heidelberg, a Center of Excellence for Innovative Research and Training (academic director **SH**). In addition, the DAAD also announced funding of CHIP: the Chilean Health Info and Process Challenge, a four year (2015-2019) partnerships for the Health Sector in Developing Country (PAGEL) between U-Heilbronn (C Fegeler, Ger), U-Chile (**SH**, BNI), and U de la República (F Simini, Uruguay).

On a national scale, the U-Redes Project BioMedHPC fostered the installation of a 10 Gbps network between the F-Med, and the National Laboratory for High Performance Computing (www.nlhpc.cl), allowing the implementation of BNI imaging and data analyses capacities towards new dimensions in size, speed, and connectivity. Network building within HPC strategies fostered new FONDEQUIP project for the installation of the first data center within SASIBA (*Sistema de Almacenamiento y Servicios Informáticos Biomédicos Avanzados*, FONDEQUIP **SH/M**. Cerda).

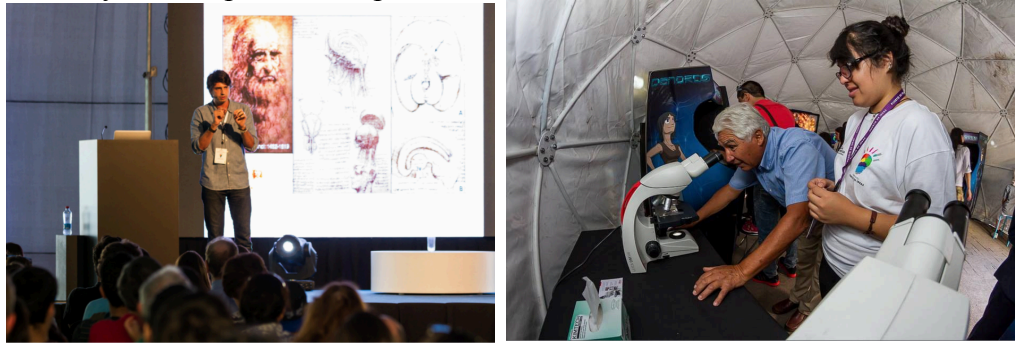
Other ongoing collaborations have been pursued: Millenium Centers (F. Aboitiz, JL. Valdés, E. Couve), FONDAP-CEMC (A. Quest, S. Lavandero), PBCT-Research-Rings (F. Court, A. Maas, C. Best, C.P. Heisenberg, G. Randall), U-Redes (E. Vera, N. Hitschfeld-Kahler), European Union (S. Wilson), the Harold Leila Mathers Foundation (L. Glimcher), FONDEF (J. Velásquez), FONDECYT (P. Morales, F. Bronfman, U. Kubicek, C. Linker, R. Kaufman, T. Blanpied, A. Cáceres, C.P. Heisenberg), CONICYT-USA (V. Budnik, R. Brown), and others (G. Kroemer, M. Castro, J. Torres, C. González). Network initiatives have been set between BNI associated centers and research Institutions in Latin America and Europe.

6. Outreach and connections with other sectors

a) Outreach: During 2015 our outreach program fine-tuned its vision and purpose: to contribute to create a strong scientific culture in Chile. Taking this into consideration, we decided to include formal education activities in order to have a greater impact in society and support science education. Since formal education is one of the greatest challenges both in Chile and globally, and it is not completely within our field of expertise, we sought to develop key alliances to help us implement this new dimension of our outreach program.

During April 2015, we were invited to exhibit our brain-dome (Neuroscience interactive gaming and education room) in the science and cultural festival *Puerto de Ideas* in Antofagasta. We installed the brain-dome in an open public square in downtown Antofagasta, where we received almost 1,000 visitors in 2 days. R. Tapia was responsible

for the project. During the same festival AC gave a general interest lecture, "*Biología, memoria y olvido*", to an audience of 300 in downtown Antofagasta.



(Photographs: left, A Couve lecturing at Puerto de Ideas; right, the brain-dome in Antofagasta).

We established our first collaboration in the area of education with the Center for Research and Interdisciplinarity (CRI) in Paris, France. This Center focuses in developing culture through interdisciplinary work. In order to learn from their experience, our outreach director R. Tapia participated in the program "*Teaching through research*" at the CRI in Paris.

Another key alliance was built with the outreach program Biointeractive from Howard Hughes Medical Institute (HHMI). This program is dedicated to support biology education at schools in the USA through the use of audiovisual material, movies, documentaries and animations. R. Tapia visited the Biointeractive headquarters in the USA during May 2015 to formally establish the collaboration and to participate in educational activities together with the Biointeractive staff. Our alliance with Biointeractive is based on translating their material to Spanish, hosting it in our newly developed website (www.loligo.cl) and using it in collaboration with Biointeractive to improve science education through hands-on workshops with Chilean school-teachers. During the second semester of 2015 we worked on the selection of the material and in the translation process. We will launch this program in 2016 in Chile.

Throughout the year our doors were opened to receive multiple school visits. We continued working in our Project "*Neuro-Bug*" in collaboration with one of our emblematic public schools for girls, Liceo 1. A new group of four students joined the program and will do research on consciousness during 2016. PhD student R. Loyola is leading the initiative.

New funding allowed us to improve our "*Dendros games*". We updated our 3 games with new features that were tested during September through collaborations with the SIP network of schools and the Faculty of Design U Chile. The new games will be released in 2016. We released the 8th chapter of our successful web interactive comic "*Dendros*". This chapter is mainly focus on Parkinson's Disease.

We participated in multiple cultural and educational events:



(Photographs, school visits to the institute's laboratories guided by BNI graduate students).

BNI investigators, young scientists and graduate

students participated regularly in open lectures to the public and school students. R. Tapia was invited to dictate a workshop on “*Scientific Culture*” to 50 people from different areas in the “Cultural Mediation Workshop” at the Cultural Center, Palacio de La Moneda. AC was invited to give a seminar at the “*International Conference of Scientific Culture*” organized by U Andrés Bello in Santiago with more than 200 assistants. R. Tapia was invited to give a seminar for teachers at the “*International Congress of Television and Education*” in Santiago. We also took our brain-dome gaming room to this two-day event with more than 300 assistants.

BNI investigators appeared regularly in the press during 2015. There were 30 interviews in magazines and newspapers, 150 minutes of appearance on TV (news and talk shows), 155 minutes in 7 radio stations and 24 articles online (articles and interviews). In particular, BNI scientists were very active during the science awareness campaign that took place during 2015, which was triggered by the open letter “*Our governments have chosen ignorance*” which was published in *El Mercurio* and *La Tercera*, two influential national newspapers. AC is co-author of the letter. Numerous press articles, TV and radio appearances with opinions and interviews followed publication of the letter. Networks were established with politicians, industry representatives and the press to continue the awareness campaign during 2016. Press coverage of the institute's activities has been valued in approximately USD \$700,000.

b) Connections with other sectors: During 2015, we began to develop our area of applied research with Chilean companies, looking for touching points between science and business. We have signed our first technology contract with a Chilean company in the field of private security, where BNI performs applied research to solve a business problem using our scientific expertise in neuroscience.

A new area of donations and philanthropy is being developed, we have started a fundraising campaign to furnish and equip our new corporate building the *Connection Cube*. Our goal is to raise approximately USD \$97,000 USD through a Chilean incentive program of cultural donations. (Photograph: a visit of BNI Investigatorts and staff to the *Connection Cube* construction site during 2015).



7. Administration and Financial Status

Organization and administration: BNI operates as a non-profit organization (RUT 65.059.721-4) and has fulfilled all the legal requirements of the Ministry of Justice and the Municipalidad de Independencia. 2 meetings of the Directory Board were held during 2015. The Board is constituted by **AC** (Pres), **CHz** (Vicepres), **MC** (Sec), **MK** (Tres), **CH** (Dir), C. Sepúlveda, Ex-Dean of the FMed (Dir), L. Michea, Ex-Director of Research and Development FMed (Dir). The constitution of the Board will be revised during May 2016. Managing the institute, coordinating internal and external activities, leading the outreach program, linking the institute to the F Med, promoting innovation, communicating with the clinical community and, importantly, establishing numerous contacts with the private sector are now areas covered by several professional staff to allow specialization of responsibilities and long-term operations. The Executive Office is constituted by C. Cubillos, an economy and finance professional that focuses on BNI administration, production of scientific events and group managing. S. Reyes, originally trained in agricultural sciences focuses on applied projects, innovation, fundraising and translational efforts. A. Sanguinetti, a reporter focuses on web, social networks and press activities to connect with the public and high-school students. J. Díaz, an experienced lawyer provides legal assistance, and R. Tapia, BNI's artist in residence has acquired increasing responsibilities and established our successful outreach program *Loligo* as a national reference in scientific communication and impact. C. Pardo is the Director Assistant. A.



(Photograph: Executive and Grant Management Offices of BNI)

Timmermann, who has extensive expertise in Millenium funds, constitutes the Grant Management Office E. Colipe and K. Miranda assistant accountants, and J. Mansilla, informatics expert. Mrs. Timmerman monthly financial reports to the Ministerio de Economía continue to be of the highest quality. N. Vasquez, graphic designer, and I. Llambías, journalist, contribute to consolidate BNI's corporate image and promote its activities. BNI staff work closely with administrative and technical personnel distributed among the 11 groups.

See Summary Table below.

Category	Female	Male	TOTAL
Assistant & Technicians	28	22	50
Administrative Staff	13	6	19
TOTAL	41	28	69

b) Financial Status:

See annexes 9.2 Outcome structure

Annexes

Annex 1.- Institute Researchers

1.1 Associate Researchers

Full Name	Research Line	Nationality	Gender	Date of birth	Profession	Academic Degree	Affiliation	Current Position	Relation with Center
Andrés Oscar Couve Correa	RL1. Sub-cellular functional dynamics. RL2. Cellular identity and morphology. RL3. Supra-cellular development and circuits. RL4. Plasticity and behavior. RL7. Applied mathematics and biomedical informatics. RL8. Clinical research.	Chilean	M	23-10-68	Biologist	D	University of Chile	Associate Professor	1
Claudio Andrés Hetz Flores	RL1. Sub-cellular functional dynamics. RL4. Plasticity and behavior. RL6. Neural dysfunction and pharmacological targets. RL8. Clinical research .	Chilean	M	24-03-76	Biotechnology Engineering	D	University of Chile	Full Professor	2
Miguel Luis Concha Nordemann	RL1. Sub-cellular functional dynamics. RL2. Cellular identity and morphology. RL3. Supra-cellular development and circuits. RL7. Applied mathematics and biomedical informatics. RL8. Clinical research .	Chilean	M	06-03-66	Physician	D	University of Chile	Full Professor	2
Mario G.G. Herrera-Marschitz Muller	RL1. Sub-cellular functional dynamics. RL3. Supra-cellular development and circuits. RL6. Neural dysfunction and pharmacological targets. RL8. Clinical research .	Chilean	M	25-06-44	Pharmacologist	D	University of Chile	Full Professor	2
María Cecilia Hidalgo Tapia	RL4. Plasticity and behavior. RL6. Neural dysfunction and pharmacological targets.	Chilean	F	10-06-41	Biochemist	D	University of Chile	Full Professor	2
Lisette Leyton Campos	RL1. Sub-cellular functional dynamics. RL3. Supra-cellular development and circuits. RL6. Neural dysfunction and pharmacological targets.	Chilean	F	22-07-59	Biochemist	D	University of Chile	Associate Professor	2
Jimena Sierralta Jara	RL2. Cellular identity and morphology. RL3. Supra-cellular development and circuits. RL7. Applied mathematics and biomedical informatics.	Chilean	F	12-09-62	Biochemist	D	University of Chile	Associate Professor	2
Hernán Silva Ibarra	RL5. Systems Neuroscience. RL7. Applied mathematics and biomedical informatics. RL8. Clinical research.	Chilean	M	01-07-49	Physician	D	Psychiatry and Mental Health, Faculty of Medicine, Universidad de Chile	Full Professor	2

Full Name	Research Line	Nationality	Gender	Date of birth	Profession	Academic Degree	Affiliation	Current Position	Relation with Center
Steffen Härtel Gründer	RL1. Sub-cellular functional dynamics. RL3. Supra-cellular development and circuits. RL5. Systems Neuroscience. RL6. Neural dysfunction and pharmacological targets. RL7. Applied mathematics and biomedical informatics.	German	M	24-11-68	BioPhysics	D	University of Chile	Assistant Professor	2
Pedro Esteban Maldonado	RL5. Systems Neuroscience. RL7. Applied mathematics and biomedical informatics.	Chilean	M	30-04-60	Biologist	D	University of Chile	Associate Professor	2
Manuel Kukuljan Padilla	RL2. Cellular identity and morphology. RL3. Supra-cellular development and circuits. RL7. Applied mathematics and biomedical informatics. RL8. Clinical research.	Chilean	M	08-08-63	Physician	D	University of Chile	Full Professor	2

1.2 Young Researchers

Full Name	Research Line	Nacionality	Gender	Date of birth	Profession	Academic Degree	Affiliation	Current Position	Relation with Center
Tatiana Adasme Rocha	RL4. Plasticity and behavior.	Chilean	F	21-02-77	Biochemist	D	University of Chile	Researcher	2
Carlos Oliva	RL3. Supra-cellular development and circuits.	Chilean	M	17-01-82	Biochemist	D	Biomedical Neuroscience Institute	Young Researcher	2
Daniel Rojas	RL7. Applied mathematics and biomedical informatics.	Chilean	M	01-09-75	Biologist	D	University of Chile	Researcher	2
José Ignacio Egaña	RL5. Systems Neuroscience. RL7. Applied mathematics and biomedical informatics.	Chilean	M	09-10-73	Physician	D	University of Chile	Assistant Professor	2
Danilo Bilches	RL6. Neural dysfunction and pharmacological targets.	Brazilian	M	23-11-81	Chemist	D	Biomedical Neuroscience Institute	Young Researcher	2

1.3 Senior Researchers

There is no register in this section.

1.4 Others (Adjunct Investigators)

Full Name	Research Line	Nacionality	Gender	Date of birth	Profession	Academic Degree	Affiliation	Current Position	Relation with Center
José Luis Valdés	RL4. Plasticity and behavior.	Chileno	M	16-12-75	Biologist	D	University of Chile	Assistant Professor	2
Andrea Paula-Lima	RL4. Plasticity and behavior. RL6. Neural dysfunction and pharmacological targets.	Brasileño	F	20-11-77	Technician in Biotechnology	D	University of Chile	Assistant Professor	2
Patricio Olguin	RL3. Supra-cellular development and circuits. RL2. Cellular identity and morphology.	Chileno	M	23-10-75	Biochemist	D	University of Chile	Assistant Professor	2
Pablo Gaspar	RL5. Systems Neuroscience.	Chileno	M	20-08-75	Physician	D	Universidad de Chile	Assistant Professor	2
René Vidal	RL1. Sub-cellular functional dynamics. RL6. Neural dysfunction and pharmacological targets.	Chileno	M	03-05-79	Biochemist	D	Neurounion Biomedical Foundation	Researcher R&D area	2
Soledad Matus	RL1. Sub-cellular functional dynamics. RL6. Neural dysfunction and pharmacological targets.	Chileno	F	23-06-74	Biochemist	D	Neurounion Biomedical Foundation	Principal Investigator Neurounion Biomedical Foundation	2

NOMENCLATURE:**[Gender]**

[M] Male [F] Female

[Academic Degree][U] Undergraduate [M] Master
[D] Doctoral**[Relation with Center]**

[1] Full time [2] Part time

Annex 2.- Research Lines

N°	Research Line	Research Line Objectives	Description of Research Line	Researcher	Research Discipline	Starting Date	Ending Date
1	RL1. Sub-cellular functional dynamics	To understand how the dynamics structures of the secretory pathway and the cytoskeleton are organized in different cell types of the nervous system, and how this organization determines neuronal function or dysfunction.	We have developed methodologies to analyze subcellular components in cultured neurons and astrocytes at high spatio-temporal resolution using fluorescent microscopy and investigated neuropathological conditions where organelle and cytoskeletal functions are dramatically affected. Here we combine manipulation of gene expression in cultured brain cells with the use of genetically modified organisms to study: (i) the morpho-functional organization of the endoplasmic reticulum and the consequences of altered organelle structure in protein trafficking and in human disease (XBP-1/ATF4 deficiency); (ii) the role of recently identified proteins (Marlin 1) in the functional and structural organization of the cytoskeleton; (iii) the spatio-temporal activation of signaling molecules downstream of cell adhesion receptors governing changes in astrocyte and neuron morphology during neurodegeneration and injury. This strategy provides a quantitative view of the dynamics of sub-cellular structures and their implications in normal and disease conditions.	Steffen Härtel Gründler. Andrés Oscar Couve Correa. Miguel Luis Concha Nordemann. Lisette Leyton Campos. Claudio Andrés Hetz Flores. Mario Herrera- Marschitz René Vidal Soledad Matus	Métodos numéricos y computación. Otras especialidades de la física. Biofísica. Biología celular. Biología del desarrollo. Biología molecular. Ingeniería en computación.	28-06-11	
2	RL2. Cellular identity and morphology	To understand how gene expression determines morpho-functional features throughout the development and lifespan of neurons.	We have combined fluorescent microscopy and expression in <i>Drosophila</i> , mice and zebrafish to address the genetic mechanisms involved in the control of neuronal morphology. Here we combined these experimental models with electrophysiology and tools to quantify morpho-topological features of cells and neuronal networks to study the role of: (i) transcriptional control by chromatin remodeling complexes in the acquisition and maintenance of neuronal morphology (REST/NRSF and CoREST) and (ii) novel genes identified by ongoing genetic screens in <i>Drosophila</i> and zebrafish and candidate molecules involved in cytoskeleton dynamics in neuronal morpho-functionality (Marlin 1).	Andrés Oscar Couve Correa. Miguel Luis Concha Nordemann. Jimena Sierralta Jara. Manuel Kukuljan Padilla. Patricio Olguin	Biología celular. Biología del desarrollo. Biología molecular.	28-06-11	

N°	Research Line	Research Line Objectives	Description of Research Line	Researcher	Research Discipline	Starting Date	Ending Date
3	RL3. Supra-cellular development and circuits	To understand how gene activity is translated into brain morphogenesis, and how the acquisition of novel states of supra-cellular and connectional organization in turn influences patterning and functions.	Here we combine the use of genetic approaches in GFP-transgenic zebrafish and in hippocampal organotypic cultures with in vivo 3D confocal visualization and analysis of neuronal structure and function to study: (i) the cellular mechanisms that control adhesive, tensile and polarity changes leading to cell migration, formation of cell sheets and brain nuclei, and wound healing, (ii) the genetic and morphogenetic mechanisms that guide axonal growth cones and establish neuronal connectivity in vivo, focused on Wnt/PCP, FGF, Chemokines and Robo/Slit, and neurogenesis in hippocampal circuits, and (iii) the dynamic configuration and functional correlate of neuronal circuits using optogenetic probes and in vivo electrophysiology. This strategy provides a contextual view of the mechanisms that drive form, supra-cellular structure and neuronal circuit development, revealing general principles of brain organogenesis and function.	Steffen Härtel Gründler. Andrés Oscar Couve Correa. Miguel Luis Concha Nordemann. Lisette Leyton Campos. Jimena Sierralta Jara.. Manuel Kukuljan Padilla. Mario Herrera- Marschitz . Jose Luis Valdes Guerrero. Patricio Olguin	Métodos numéricos y computación. Otras especialidades de la física. Biofísica. Biología celular. Biología del desarrollo. Biología molecular. Bioquímica farmacología. Farmacología. Farmacia, farmacología clínica, laboratorio. Ingeniería en computación.	28-06-11	
4	RL4. Plasticity and behavior	To understand how genetic interaction and signaling pathways control long-lasting memories.	We have established methodologies to study the role of ryanodine-receptor (RyR) dependent Ca ²⁺ signals on hippocampal long-term potentiation (LTP) and behavior (mazes, object recognition and contextual fear conditioning). By combining these approaches with cell and molecular biology, live-cell imaging and electrophysiology (single channel studies in bilayers, high density electrophysiology in freely moving animals) here we investigate: (i) the effect of RyR activity on the expression of plasticity related mRNA/proteins and the role of RyR-generated Ca ²⁺ signals on LTP (via pharmacology, intra-hippocampal delivery of antisense nucleotides or shRNAs), (ii) the effect of experience, neuromodulators, and modulators of RyRs on the dynamics of hippocampal neural assemblies, and (iii) their behavioral correlates.	Andrés Oscar Couve Correa. Claudio Andrés Hetz Flores. María Cecilia Hidalgo Tapia. Jose Luis Valdes Guerrero. Andrea Paula-Lima	Biología celular. Biología molecular. Fisiología biofísica.	28-06-11	

N°	Research Line	Research Line Objectives	Description of Research Line	Researcher	Research Discipline	Starting Date	Ending Date
5	RL5. Systems Neuroscience	To examine, compare and model the neuronal activity when animals and humans engage in more ecological behavioral experimental paradigms and classical psychiatric conditions.	While most paradigms to examine the neuronal mechanisms of cognitive functions have used simple and controlled stimuli, the responses of neurons to complex and more ecological situations differ substantially. Because current models of functional organization fail significantly to predict neuronal activity during more realistic experimental conditions here we implement methodologies to study neuronal activity using single and multiple unit recording, local field potentials, and electroencephalographic recording under: (i) goal directed or (ii) naturalistic behaviors. We develop new analytical/statistical tools in signal processing and propose new models to account for the inclusion of top-down mechanisms in cognitive function.	Steffen Härtel Gründler. Pedro Esteban Maldonado Abogast. Hernán Silva Ibarra. Jose Luis Valdes Guerrero. Pablo Gaspar	Métodos numéricos y computación. Otras especialidades de la física. Biofísica. Fisiología biofísica. Medicina psicosomática (incluyendo psiquiatría). Ingeniería en computación.	28-06-11	
6	RL6. Neural dysfunction and pharmacological targets	To develop knowledge, expertise and technological approaches to gain a better understanding of the mechanisms by which disease-related genes affect common molecular, cellular and physiological processes involved in neuropathological conditions.	We implement disease models to mimic conditions associated with human pathologies, including transgenic mice, gene therapy, and cell biology approaches, in addition to human studies, to uncover pathological aspects underlying (i) Parkinson's disease, (ii) Alzheimer's disease, (iii) nerve injury/regeneration and Amyotrophic lateral sclerosis (ALS), (iv) Creutzfeldt-Jacob Disease (CJD), and (v) epigenetics by characterizing the short and long-term effects of metabolic insults occurring at birth. We define the consequences of genetic manipulation of the disease model and identify novel targets for pharmacological interventions. Scientific aims benefit from new analytical mathematical approaches to model complex features related to neural dysfunction	Steffen Härtel Gründler. Lisette Leyton Campos. Claudio Andrés Hetz Flores. María Cecilia Hidalgo Tapia. Jose Luis Valdes Guerrero. Andrea Paula-Lima René Vidal Soledad Matus	Biología molecular. Métodos numéricos y computación. Otras especialidades de la física. Biofísica. Ingeniería en computación. Bioquímica farmacología. Farmacología. Farmacia, farmacología clínica, laboratorio. Biología celular. Fisiología biofísica	28-06-11	

N°	Research Line	Research Line Objectives	Description of Research Line	Researcher	Research Discipline	Starting Date	Ending Date
7	RL7. Applied mathematics and biomedical informatics	To uncover novel neural processes based on mathematical models that reveal morphofunctional principles of organization at multiple scales.	Biophysics and applied mathematics combined with advanced imaging and computing clusters foster an integrative view to study the dynamic design of biological structures and their functional patterns, which emerge from the building process per se and/or as a requirement of functions at higher levels. This transdisciplinary approach allows the study of pattern organization in neurons in 2/3D and colocalization in confined subcellular compartments and fosters new approaches to: (i) localize/track proteins within sub-cellular organelles, (ii) study dendrite branching and axonal wiring, (iii) model cellular and supra-cellular descriptors for multi-cellular rosette formation based on partial differential equations, (iv) develop statistics to study spike trains in multiunit recordings, (v) model neuronal assembles to account for activity during natural behavior, and (vi) implement mathematical tools for image based tele-analysis within clinical research and diagnostic medicine.	Steffen Härtel Gründler. Pedro Esteban Maldonado Abogast. Hernán Silva Ibarra. Andrés Oscar Couve Correa. Miguel Luis Concha Nordemann. Jimena Sierralta Jara. Manuel Kukuljan Padilla..	Métodos numéricos y computación. Otras especialidades de la física. Biofísica. Biología celular. Propagación de plantas. Bioquímica farmacología. Fisiología biofísica. Ingeniería en computación. Matemáticas del uso de los recursos.	28-06-11	
8	RL8. Clinical research	To build the capacity and consolidate clinical research in the fields of neurological and psychiatric pathologies.	Here we provide the means to solve the lack of efficient channels of interaction between clinicians and the scientific management structures and the scarce access to state-of-the-art technologies by establishing a program focused on the training of clinical scientists and specialists with international standards of competence, and by defining specific projects that include: (i) development of diagnostics tools such as chaperones for molecular markers in Creutzfeldt-Jacob Disease (CJD) and genetic/molecular markers for early prediction of anti-depressive treatments, (ii) therapeutic approaches such as gene therapy and small molecule testing in Amyotrophic lateral sclerosis (ALS) and Parkinson's, (iii) genetic comparison of patients with bipolar disorders, and (iv) autism spectrum disorders and alterations of neural development.	Hernán Silva Ibarra. Andrés Oscar Couve Correa. Miguel Luis Concha Nordemann. Claudio Andrés Hetz Flores. Manuel Kukuljan Padilla. Mario G.G. Herrera-Marschitz Muller. Jose Luis Valdes Guerrero.	Biología celular. Biología del desarrollo. Biología molecular. Bioquímica farmacología. Farmacología. Farmacia, farmacología clínica, laboratorio. Medicina psicosomática (incluyendo psiquiatría).	28-06-11	

Annex 3.- Publications (Total or partially financed by MSI)

Category of Publication	MSI Center Members	Reference
ISI Publications or Similar to ISI Standard	Associate Researchers	Mardones P, Martínez G, Hetz C. , (2015),Control of systemic proteostasis by the nervous system. , Trends in cell biology
		Mercado G, Castillo V, Vidal R, Hetz C , (2015),ER proteostasis disturbances in Parkinson's disease: novel insights, Frontiers in aging neuroscience
		Dufey E, Urrea H, Hetz C , (2015),ER proteostasis addiction in cancer biology: Novel concepts, Seminars in cancer biology
		Hetz C , Chevet E, (2015),Theme Series - UPR in cancer, Seminars in cancer biology
		Chevet E, Hetz C , Samali A, (2015),Endoplasmic reticulum stress-activated cell reprogramming in oncogenesis, Cancer Discovery
		García-Huerta P, Rivas A, Hetz C , (2015),Stressing out the ER in aminoglycoside-induced hearing loss, Cell death & Disease
		Carreras-Sureda A, Hetz C , (2015),RNA metabolism: putting the brake on the UPR, EMBO Reports
		Hetz C , Chevet E, Oakes SA, (2015),Proteostasis control by the unfolded protein response, Nature Cell Biology
		Rivas A, Vidal RL, Hetz C , (2015),Targeting the unfolded protein response for disease intervention, Expert Opinion on therapeutic targets
		Mardones P, Hetz C , (2015),Peroxisomes Get Loud: A Redox Antidote to Hearing Loss, Cell
		Gonzalez-Perez P, Woehlbier U, Chian RJ, Sapp P, Rouleau GA, Leblond CS, Daoud H, Dion PA, Landers JE, Hetz C , Brown RH, (2015),Identification of rare protein disulfide isomerase gene variants in amyotrophic lateral sclerosis patients, Gene
		Gupta A, Hossain MM, Read DE, Hetz C , Samali A, Gupta S, (2015),PERK regulated miR-424(322)-503 cluster fine-tunes activation of IRE1 and ATF6 during Unfolded Protein Response, Scientific Reports
		Llanos P, Contreras-Ferrat A, Barrientos G, Valencia M, Mears D, Hidalgo C , (2015),Glucose-Dependent Insulin Secretion in Pancreatic β -Cell Islets from Male Rats Requires Ca^{2+} Release via ROS-Stimulated Ryanodine Receptors, Plos one
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		Llanos P, Contreras-Ferrat A, Georgiev T, Osorio-Fuentealba C, Espinosa A, Hidalgo J, Hidalgo C , Jaimovich E, (2015),The cholesterol lowering agent methyl- β -cyclodextrin promotes glucose uptake via GLUT4 in adult muscle fibers and reduces insulin-resistance in obese mice, American journal of physiology. Endocrinology and metabolism
		Adasme T, Paula-Lima A, Hidalgo C , (2015),Inhibitory ryanodine prevents ryanodine receptor-mediated Ca^{2+} release without affecting endoplasmic reticulum Ca^{2+} content in primary hippocampal neurons, Biochemical and Biophysical research communications
		Maturana-Ramírez A, Espinoza I, Reyes M, Aitken JP, Aguayo F, Härtel S , Rojas-Alcayaga G, (2015),Higher blood vessel density in comparison to the lymphatic vessels in oral squamous cell carcinoma, International Journal of Clinical and Experimental Pathology
		Maturana JL, Nische I, Silva E, Huerta H, Cataldo R, Härtel S , Barros LF, Galindo M, Tapia JC, (2015),Transactivation activity and nucleocytoplasmic transport of β -catenin are independently regulated by its C-terminal end, Gene
		Liempi A, Castillo C, Cerda M , Droguett D, Duaso J, Barahona K, Hernández A, Díaz-Luján C, Fretes R, Härtel S , Kemmerling U, (2015),Trypanosoma cruzi infectivity assessment in "in vitro" culture systems by automated cell counting, Acta Tropica
		González A, Valck C, Sánchez G, Härtel S, Mansilla J , Ramírez G, Fernández MS, Arias JL, Galanti N, Ferreira A, (2015),Trypanosoma cruzi Calreticulin Topographical Variations in Parasites Infecting Murine Macrophages, The American Journal of Tropical Medicine and Hygiene
Marriott AL, Rojas-Mancilla E, Morales P, Herrera-Marschitz M , Tasker RA, (2015),Models of progressive neurological dysfunction originating early in life, Progress in Neurobiology		

Category of Publication	MSI Center Members	Reference
ISI Publications or Similar to ISI Standard	Associate Researchers	Barros LF, Sierralta J , Weber B, (2015),How doth the little busy bee: unexpected metabolism, Trends in Neuroscience
		Torres M, Medinas DB , Matamala JM, Woehlbier U, Cornejo VH , Solda T, Andreu C, Rozas P , Matus S , Muñoz N , Vergara C, Cartier L, Soto C, Molinari M, Hetz C , (2015),The Protein Disulfide Isomerase ERp57 Regulates the Steady-State Levels Of the Prion Protein, The Journal of biological chemistry
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		Castillo V , Mercado G , Hetz C , (2015),Gene therapy in Parkinson's disease: targeting the endoplasmic reticulum proteostasis network, Neural Regeneration Research
		Quintanilla ME, Rivera-Meza M , Berríos-Cárcamo P, Cassels BK, Herrera-Marschitz M , Israel Y, (2015),(R)-Salsolinol, a product of ethanol metabolism, stereospecifically induces behavioral sensitization and leads to excessive alcohol intake, Addiction Biology
		Neira-Peña T, Rojas-Mancilla E, Munoz-Vio V , Perez R , Gutierrez-Hernandez M, Bustamante D, Morales P, Hermoso MA, Gebicke-Haerter P, Herrera-Marschitz M , (2015),Perinatal Asphyxia Leads to PARP-1 Overactivity, p65 Translocation, IL-1 β and TNF- α Overexpression, and Apoptotic-Like Cell Death in Mesencephalon of Neonatal Rats: Prevention by Systemic Neonatal Nicotinamide Administration, Neurotoxicity Research
		Israel Y, Quintanilla ME, Karahanian E, Rivera-Meza M , Herrera-Marschitz M , (2015),The "first hit" toward alcohol reinforcement: role of ethanol metabolites, ALCOHOLISM:CLINICAL AND EXPERIMENTAL RESEARCH
		Herrera-Marschitz M , Neira-Peña T, Rojas-Mancilla E, Morales P, Bustamante D, Leyton L , Gebicke-Haerter P, (2015),Short- and long-term consequences of perinatal asphyxia: looking for neuroprotective strategies, Advances in neurobiology
		Diaz-Valdivia N , Bravo D, Huerta H, Henriquez S, Gabler F, Vega M, Romero C, Calderon C, Owen GI, Leyton L , Quest AF, (2015),Enhanced caveolin-1 expression increases migration, anchorage-independent growth and invasion of endometrial adenocarcinoma cells, BMC Cancer
		Wehinger S, Ortiz R, Díaz MI, Aguirre A, Valenzuela M, Llanos P, Mc Master C, Leyton L , Quest AF, (2015),Phosphorylation of caveolin-1 on tyrosine-14 induced by ROS enhances palmitate-induced death of beta-pancreatic cells, Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease
		Cánovas J , Berndt FA, Sepúlveda H, Aguilar R, Veloso FA, Montecino M, Oliva C , Maass JC, Sierralta J , Kukuljan M , (2015),The Specification of Cortical Subcerebral Projection Neurons Depends on the Direct Repression of TBR1 by CTIP1/BCL11a, The Journal of Neuroscience
		Oliva C , Molina-Fernandez C, Maureira M, Candia N, López E , Hassan B, Aerts S, Cánovas J , Olguín P , Sierralta J , (2015),Hindsight regulates photoreceptor axon targeting through transcriptional control of jitterbug/Filamin and multiple genes involved in axon guidance in Drosophila, Developmental Neurobiology
	Quassollo G, Wojnacki J, Salas DA, Gastaldi L, Marzolo MP, Conde C, Bisbal M, Couve A , Cáceres A, (2015),A RhoA Signaling Pathway Regulates Dendritic Golgi Outpost Formation, Current Biology	
Loyola P; Martinez G; Muñoz K; Velasquez J; Maldonado P ; Couve A , (2015),Combining Eye Tracking and Pupillary Dilation Analysis to Identify Website Key Objects. Neurocomputing, Neurocomputing		
	Others	

Category of Publication	MSI Center Members	Reference
SCIELO Publications or Similar to SCIELO Standard	Associate Researchers	
	Others	
Books & Chapters of Books	Associate Researchers	
	Others	
Other Publications	Associate Researchers	Jara-Wilde J, Cerda M , Delpiano J, Härtel S, (2015), An Implementation of Combined Local-Global Optical Flow, IPOL Journal · Image Processing On Line
	Others	

3.5.- Collaborative publications:

Category of Publication	1 researcher		2 researchers		3 researchers		4 or more	
	N°	%	N°	%	N°	%	N°	%
ISI Publications or Similar to ISI Standard	32	88,89%	3	8,33%	0	0,00%	0	0,00%
SCIELO Publications or Similar to SCIELO Standard	0	0,00%	0	0,00%	0	0,00%	0	0,00%
Books and chapters	0	0,00%	0	0,00%	0	0,00%	0	0,00%
Other Publications	1	2,78%	0	0,00%	0	0,00%	0	0,00%
Total of publications	33	91,67%	3	8,33%	0	0,00%	0	0,00%

Annex 4.- Organization of Scientific Events

Scope	Title	Type of Event	City	Country	Responsible Researcher
Internacional	Recent advances in ALS: from discovery to therapies	Seminario	Santiago	Chile	Claudio Hetz Flores
Nacional	Exploring neurogenic niches in the adult brain	Seminario	Santiago	Chile	Andrés Oscar Couve Correa
Nacional	V Encuentro de integración básico clínica: New therapeutic frontiers in neurology	Seminario	Santiago	Chile	Claudio Hetz Flores
Nacional	Vías de señalización intracelular implicadas en la disquinesias inducidas por L DOPA en la enfermedad de Parkinson y mecanismos de neurotoxicidad por drogas de diseño	Seminario	Santiago	Chile	Mario Herrera Marschitz
Nacional	increased neuronal noise is related to the psychosis like effects of 9 - tetrahydrocannabinol	Seminario	Santiago	Chile	Andrés Oscar Couve
Nacional	Relaciones íntimas entre la glia y su axón en programas degenerativos y regenerativos	Seminario	Santiago	Chile	Andrés Couve Correa
Nacional	Plasticidad filogenética en los sistemas sensoriales. algunos ejemplos	Seminario	Santiago	Chile	Andrés Couve Correa
Nacional	A glia to neuron transdifferentiation is required for sex specific learning in c. elegans	Seminario	Santiago	Chile	Andrés Couve Correa
Nacional	Bioquímica a nivel de moléculas individuales: cinética enzimática y motores moleculares	Seminario	Santiago	Chile	Andrés Couve Correa
Nacional	Sinucleína: buscando una función fisiológica	Seminario	Santiago	Chile	Andrés Couve Correa
Nacional	Interacciones nervio glia celular sensorial regulan la capacidad regenerativa en la línea lateral de pez cebra	Seminario	Santiago	Chile	Andrés Couve Correa
Nacional	Regulación de cascadas transduccionales que promueven remielinización en el sistema nervioso central	Seminario	Santiago	Chile	Mario Herrera Marschitz
Nacional	The SUR1 regulated channel and novel treatment for traumatic CNS injury and stroke - Dr. Howard Eisenberg	Seminario	Santiago	Chile	Manuel Kukuljan Padilla
Nacional	Functional organization of synaptic circuits in the thalamo - hippocampal axis	Seminario	Santiago	Chile	Andrés Couve Correa
Nacional	Relating large scale neuronal activity to behaviour: aspects of statistics, analysis and reproducibility - Sonja Grun	Seminario	Santiago	Chile	Pedro Esteban Maldonado Arbogast
Nacional	Charla: Necessity and feasibility of brain - scale simulations: steps in the european Human Brain project - Markus Diesmann	Seminario	Santiago	Chile	Pedro Esteban Maldonado Arbogast
Nacional	Interacción entre estrés y adicción	Seminario	Santiago	Chile	Andrés Couve Correa
Nacional	Enfermedad de Parkinson: prolegómenos, debut y progreso. Roles de señales inflamatorias y fagocitos y células gliales	Seminario	Santiago	Chile	Mario Herrera Marschitz
Nacional	Regulation of proliferation and differentiation in an adult stem cell lineage	Seminario	Santiago	Chile	Andrés Couve Correa
Nacional	The functional organization of axon in health and disease	Seminario	Santiago	Chile	Andrés Couve Correa
Nacional	Neuromodulación de la médula espinal para el mal de Parkinson	Seminario	Santiago	Chile	Andrés Couve Correa
Nacional	La importancia de los embriones de aves para entender la transición dinosaurio - ave	Seminario	Santiago	Chile	Andrés Couve Correa
Nacional	c-abl signaling in Alzheimer disease and other neurodegenerative diseases: projections for drugs searching	Seminario	Santiago	Chile	Andrés Couve Correa
Nacional	Esquizofrenia: de lo cognitivo a lo social	Seminario	Santiago	Chile	Andrés Oscar Couve
Nacional	Breaking symmetry in the brain: from genes to circuits and behaviour	Seminario	Santiago	Chile	Andrés Oscar Couve
Nacional	De la biología del desarrollo al desarrollo tumoral: interacciones entre células y su ambiente	Seminario	Santiago	Chile	Andrés Couve Correa
Nacional	Análisis espectral en EEG	Workshop	Santiago	Chile	Pedro Esteban Maldonado Arbogast
Nacional	Spatio temporal dynamics of sensory processing dysfunction in schizophrenia	Conferencia	Santiago	Chile	Pedro Esteban Maldonado Arbogast

Annex 5.- Education and capacity building

5.1 Capacity Building inside MSI Centers

Tutor	Undergraduated Student			Graduated Students									Total Number per MSI Researcher
				Master			Doctoral			Postdoctoral			
	F	M	T	F	M	T	F	M	T	F	M	T	
Miguel Concha Nordemann	1	0	1	2	0	2	3	2	5	2	3	5	13
Pedro Maldonado Arbogast	0	2	2	3	5	8	3	8	11	0	1	1	22
Lisette Leyton Campos	0	0	0	0	0	0	2	4	6	1	2	3	9
Lisette Leyton Campos	0	0	0	0	0	0	0	1	1	0	0	0	1
Mario Herrera-Marschitz													
Jimena Sierralta Jara	0	0	0	0	1	1	0	1	1	0	0	0	2
Andrés Oscar Couve Correa													
Mario Herrera-Marschitz	1	1	2	1	0	1	3	2	5	0	1	1	9
María Cecilia Hidalgo	0	1	1	2	1	3	1	3	4	1	1	2	10
Steffen Härtel Gründler	0	0	0	1	3	4	2	3	5	3	2	5	14
Claudio Andrés Hetz Flores	0	2	2	2	0	2	0	4	4	4	2	6	14
Jimena Sierralta Jara	0	0	0	0	0	0	2	1	3	0	0	0	3
Andrés Oscar Couve Correa	1	0	1	0	1	1	2	2	4	0	0	0	6
Manuel Kukuljan Padilla	0	0	0	0	0	0	1	0	1	1	1	2	3
Jimena Sierralta Jara	0	1	1	0	0	0	0	0	0	0	0	0	1
Miguel Concha Nordemann	0	0	0	0	0	0	0	1	1	0	1	1	2
Andres Oscar Couve Correa	0	0	0	0	0	0	1	0	1	0	0	0	1
Mario Herrera Marschitz	2	0	2	0	0	0	0	0	0	0	0	0	2
Claudio Andrés Hetz Flores	0	0	0	0	1	1	3	1	4	0	3	3	8
Hernán Silva Ibarra	0	0	0	1	0	1	0	0	0	0	0	0	1
Total	5	7	12	12	12	24	23	33	56	12	17	29	121

Annex 5.2. - Short-term Traineeships of MSI students

Student Name	Institution	Country	Advisor	Project Description	Starting Date	Ending Date
Valentina Javiera Muñoz Vio	McGill University	Canada	Dusica Maysinger	PARP-1 inhibition in glioblastome model	01-02-2015	30-04-2015
Estefanie Dufey	University of California, San Francisco	USA	Peter Walter	Role of the ER stress sensor IRE1 in the DNA damage responses	05-10-2015	15-12-2015
Francesca Burgos Bravo	Universidad de California, Berkeley	USA	Dr. Carlos Bustamante	Modern Techniques Single-Molecule Manipulation	21-11-2015	31-12-2015
Julio Torres	Institut du Cerveau et de la Moelle épinière, Paris	France	Dr. Antoni Valero-Cabré	Eye tracking, experiment builder	04-01-2015	27-02-2015
María Graciela Delgado	Universität Kaiserslautern	Germany	Holger Becker	Caracterización de un putativo transportador de acidos monocarboxilicos en Drosophila melanogaster	05-01-2015	21-02-2015
Patricio Ahumada Galleguillos	University College London	England	Dr. Steve Wilson	Correlation between hanular asymmetry and behavior in zebrafish and the importance of cachd-1	29-05-2015	28-07-2015
Aldo Villalón	University College London	Engalnd	Dr. Steve Wilson	Correlation between hanular asymmetry and behavior in zebrafish and the importance of cachd-1	20-05-2015	30-07-2015
Rocio Mayol	Nathan Kline Institute, NY	USA	Antígona Martínez	Analysis of EEG data and eye movements of people affected with schizophrenia	01-09-2015	04-12-2015
Juan José Mariman	The Burke Medical Research Institute, Cornell University, New York	USA	Dylan Edwards	Neuromodulatory interventions (TMS and tDCS) for the study of motor control and learning	01-09-2015	27-09-2015
Daniela Salas	ESPCI- CNRS UMR 8249, ESPCI-ParisTech	France	Zsolt Lenkei	Organization and exportation capacity of the axonal endoplasmic reticulum in hippocampal neurons	30-03-2015	30-06-2015
Hery Urria	Centre de Lutte Contre le Cancer Eugène Marquis, Rennes	France	Eric Chevet PhD	Defining the contribution of the UPR stress sensor IRE1 in tumor and stromal cells to the development of brain cancer	17-09-2015	04-12-2015
Denisse Sepúlveda	University of Kioto	Japan	DR. Kazuhiro Nagata	Role of collagen chaperone HSP47 on the activation of endoplasmic reticulum stress sensor IRE1a	17-10-2015	31-12-2015
Eduardo Pulgar	Institute of Science and Technology - IST	Austria	C.P. Heisenberg	Effect of laser ablation on migration of deep forerunner cells on zebrafish embryo	08-06-2015	03-07-2015

Annex 6.- Networking and other collaborative work

6.1 Networking

Network Name	Network Scope	Researchers				Institutions
		From the Center		External		
		Researchers	Postdocs / Students	Researchers	Postdocs / Students	
NeuroSur	LA	11	0	25	0	Instituto Leloir (Buenos Aires) , Instituto de BioMedicina de Buenos Aires-CONICET-Parter Sociedad Max Planck , INGEBI-CONICET Buenos Aires, Universidad de Buenos Aires, Instituto de Investigación Medica Mercedes y Martín Ferreyra, Universidad Católica de Argentina, Buenos Aires-CONICET, Federal University of Rio de Janeiro, Instituto Oswaldo Cruz, Fundação Oswaldo Cruz, Instituto Pasteur Montevideo, Instituto Clemente Estable, Universidad de la República, Montevideo,
Network for Advanced Microscopy and Quantitative Developmental Biology	I	11	20	8	6	BNI, U. Göttingen, Germany / IST, Vienna, Austria/ U.Bonn, Germany

NOMENCLATURE:

[Network Scope]

[N] National [I] International [LA] Latin American

Annex 6.2.- Other collaborative activities

Activity Name	Objective	Description	Co-Participants Institutions	Number of Research from the Center	Number of Postdocs / Students from the Center	Number of External Research	Number of External Postdocs / Students	Product	Name of the Center Associate Researchers Participating in the activity
Network in cell and tissue morphodynamics between BNI-Chile, UCL/CDB-UK and IST-Austria	Scientific research activities; Training of young Latin American Scientists, Network Symposium, Network Meeting	To establish a scientific network between BNI and UCL/CDB-UK and IST-Austria to strengthen collaborative research and training of young scientists in cell and tissue morphodynamics	UCL Research Department of Cell and Developmental Biology; Institute of Science and Technology - Austria	3	12	5	25	Training abroad, workshops	SH, MC, CHZ-
Karolinska Institutet	Immunocytochemistry & Neurochemistry	Internships, experimental collaboration	Karolinska Institutet, Prog Mole Clin Pharmacol	1	0	3	0	Internships, experimental collaboration	MHM
Globus Doc Programme, EU	International collaboration: Study of the effects of adenosine receptor ligands on neurobehavioural modifications in a rat model of perinatal asphyxia.	Internships	Universita degli Studi, Cagliari, Italy; Pog Mol Clin Pharmacol, ICBM, Medical faculty, University of Chile	1	0	1	0	Internships	MHM
Identification of neuroprotective compounds from Chilean endogenous plants	Science	Fundacion COPEC-UC is supporting our lab to consolidate a National library of natural compounds derived from Chilean plants to perform a High-throughput screening using the Cellomic platform to identify neuroprotective compounds	Pontificia Universidad Católica de Chile	1	0	1	0		CHZ
Prof. Dr. Sonja Gruen, Juelich Research Centre, Germany	Collaborate for the analysis of electrophysiological recording data in animals.	Collaborative Relationship in order to analyzing data to set characteristics in the neural activity that has been captured in awake animals.	Institute for Advanced Simulation (IAS-6), JARA Brain Institute I, Juelich Research Centre, Germany	1	0	1	0		PM
Dr. Hiroshi Tamura, Osaka University, Japan	Collaborate for the study of neural activity in humans and non humans.	Do joint activities of analysis of registered data in primate non humans and collaborate for the study of the visual psychophysical activity in humans.	Graduate School of Frontier Biosciences Osaka University, Japan	1					PM

Annex 7. – Outreach

7.1. - Outreach activities throughout the period

Event Title	Type of Event	Scope	Target Audience	Date	Country	Region	N° of Student from the Center	N° of Attendees	Duration in days	Participating Researchers	Responsible for the activity
Puerto de ideas	Conferencia	Nacional	Comunidad en General	11-04-15	Chile	Antofagasta		1000	2		Rodrigo Tapia
			Estudiantes Universitarios								
Visita guiada : Penta UC	Otro	Nacional	Estudiantes Secundarios	15-01-15	Chile	Metropolitana de Santiago	5	20	1	Andrés Couve	Vicente Valenzuela, Sergio Vicencio
Debate sobre ley Ricarte Soto: ¿un obstáculo a la investigación científica?	Seminario	Nacional	Servicio Público, Comunidad en General, Industria/Servicios	10-08-15	Chile	Metropolitana de Santiago	20	50	1	Andrés Oscar Couve Correa.	María Graciela Delgado , Roberto Verdugo
Jornada de discusión: ciencia y desarrollo en Latinoamérica	Workshop	Nacional	Comunidad en General, Servicio Público	27-07-15	Chile	Metropolitana de Santiago	30	60	1	Steffen Härtel Gründler.	Steffen Hartel
Visita guiada: colegio Miguel León Prado	Otro	Nacional	Estudiantes Secundarios	20-11-15	Chile	Metropolitana de Santiago	5	25	1	Andrés Oscar Couve Correa.	Rodrigo Tapia
Congreso iberoamericano sobre educación y televisión	Exhibición	Nacional	Estudiantes Secundarios, Estudiantes Universitarios	27-10-15	Chile	Metropolitana de Santiago	6	500	2	Andrés Oscar Couve Correa	Rodrigo Tapia
Charla: la imagen como aliado del aprendizaje	Seminario	Nacional	Comunidad en General	27-10-15	Chile	Metropolitana de Santiago	5	30	1	Andrés Oscar Couve Correa.	Rodrigo Tapia
Jornadas de mediación cultural	Workshop	Nacional	Estudiantes Universitarios	20-10-15	Chile	Metropolitana de Santiago	5	40	1	Andrés Oscar Couve Correa.	Rodrigo Tapia
			Comunidad en General								

Event Title	Type of Event	Scope	Target Audience	Date	Country	Region	N° of Student from the Center	N° of Attendees	Duration in days	Participating Researchers	Responsible for the activity
Cientificas por un dia	Otro	Nacional	Estudiantes Secundarios	13-10-15	Chile	Metropolitana de Santiago	8	16	6	Mario Herrera Marschitz.	Esteban Palacios
Visita guiada: colegio Puerto Paz	Otro	Nacional	Estudiantes Secundarios	14-08-15	Chile	Metropolitana de Santiago	8	30	1	Claudio Hetz , Mario Herrera-Marschitz	Valentina Muñoz, Vicente Valenzuela
Visita guiada: Ecole polytechnique federale de Lausanne EPFL	Otro	Internacional		09-07-15	Chile	Metropolitana de Santiago	30	60	1	Andrés Couve , Claudio Hetz	Pamela Valdés
Function, plasticity and development of specific brain synapses	Seminario	Internacional	Estudiantes Universitarios	09-07-15	Chile	Metropolitana de Santiago	30	60	1	Andrés Oscar Couve Correa, Claudio Andrés Hetz Flores.	Pamela Valdés

7.2. - Products of outreach

Name of Product	Product Objective	Target Public	Type of Product"	Scope
Digital register of the 5th Meeting for Basic-Clinic Encounters	Spread the content of the meeting between attendees and promote joint collaborations	Comunidad Científica. Estudiantes de Postgrado. Industrias / Servicios.	Other	National
8th chapter of interactive comic Dendros	To continue the story of Dendros and contribute to science education	Estudiantes Secundarios. Estudiantes de Educación Primaria. Comunidad en General.	Other	National
5th Meeting for Basic-Clinic Encounters (October: New frontiers in neurology)	Acercar la ciencia básica con la ciencia aplicada y generar redes de colaboración nacionales e internacionales en neurociencias.	Comunidad Científica. Profesores Universitarios. Estudiantes Universitarios.	Other	National
Bulletin	Spread the content of the meeting between attendees and promote joint collaborations	Comunidad Científica. Profesores Universitarios. Estudiantes de Postgrado. Estudiantes Universitarios. Comunidad en General. Industrias / Servicios.	Bulletin	National
Updated data baase	Update BNI data base	Comunidad en General. Comunidad Científica.	Data Base	National
Exhibition of room Dome Brain Dendros through differents places in Chile	Bring to different regions of Chile the Dome Brain and its content, with the aim of expanding science education	Comunidad en General. Estudiantes de Educación Primaria. Estudiantes Secundarios.	Other	National

7.3.- Articles and Interviews

Type of Media and Scoupe	Local / Regional		National		International		Total
	N° Interviews	N° Articles	N° Interviews	N° Articles	N° Interviews	N° Articles	
Written	0	4	2	49	0	1	56
Internet	2	3	1	30	2	1	39
Audiovisual	0	0	15	1	0	0	16
Total	2	7	18	80	2	2	111

Annex 8. - Connections with other sectors:

Activity	Type of Connection	Type of Activity	Institution Country	Agent Type	Economic Sector
Technology contract	Industria	Desarrollo de Proyecto	Chile	Industria	Otro

9.1 Total incomes:

Funds	Accumulated incomes last year [\$]	2015 Incomes		Total Incomes to 2015 [\$]
		Amount [\$]	Percentage of resources used by the center [%]	
MSI	3,282,755,687	900,620,000	114	4,183,375,687
Anillo-Conicyt	223,387,675	168,112,500	75	391,500,175
Explora	40,000,100	-	0	40,000,100
Fondap	726,200,012	61,000,000	8	787,200,012
Fondecyt	1,611,630,094	514,968,000	100	2,126,598,094
Fondef	753,513,113	185,993,934	50	939,507,047
Fondequip	199,968,655	356,203,000	100	556,171,655
Fundación para Investigación	21,910,000	26,737,000	100	48,647,000
Innova Corfo	47,159,642	-	0	47,159,642
Mecesup	50,000,000	50,000,000	100	100,000,000
Otro	2,415,310	125,919,840	100	128,335,150
Otro - U-Redes	212,200,001	-	0	212,200,001
Otro International	528,296,605	186,713,457	100	715,010,062
Otro-Conicyt	162,277,100	158,900,000	100	321,177,100
TOTAL	7,861,713,995	2,735,167,731		10,596,881,726

9.2 Outcome structure

ITEM	Accumulated expenses to last year [\$]	2015 Expenses [\$]				Total expenses to 2015 [\$]	%
		Operative	Networking	Outreach	Total		
Honoraria Researchers& personnel	1,164,997,826	417,416,063	-	-	417,416,063	1,582,413,889	45%
Tickets and travel expenses	212,978,093	31,110,473	-	3,920,900	35,031,373	248,009,466	7%
Materials/supplies	352,722,903	115,388,064	-	91,593	115,479,657	468,202,560	13%
Goods and equipment	344,047,567	49,249,573	-	176,808	49,426,381	393,473,948	11%
Infrastructure	65,792,857	315,823,373	-	-	315,823,373	381,616,230	11%
Administrative expenses	155,295,623	52,171,053	-	-	52,171,053	207,466,676	6%
Publications and subscriptions	7,740,025	4,050,000	-	4,110,492	8,160,492	15,900,517	0%
Consultancies	69,326,114	10,350,000	-	8,312,493	18,662,493	87,988,607	2%
Overhead	53,172,600				0	53,172,600	2%
Insurance costs		2,922,852	375,718	629,469	3,928,039	3,928,039	0%
Legal personality expenses					0	0	0%
Others	83,412,847	3,191,780	-	-	3,191,780	86,604,627	2%
Total Expenses (\$)	2,509,486,455	1,001,673,231	375,718	17,241,755	1,019,290,704	3,528,777,159	100%

9.3 Financial accounting

ITEM	2015 [\$]				TOTAL TO 2015
	Operative	Networking	Outreach	Total [\$]	
Income	802,620,000	9,000,000	29,000,000	840,620,000	4,183,375,687
Outcome	1,001,673,231	375,718	17,241,755	1,019,290,704	3,561,274,339
Annual balance	-199,053,231	8,624,282	11,758,245	-178,670,704	622,101,348

9.4 Intercambio

Researchers traveling abroad

Tipo Investigador	Name	Activity	Stay [Days]	Country to travelling	Entidad que financia (Milenio/Externo/Mixto)
Principal Investigator	Andrés Couve	Tsukuba Global Science Week 2015	7	Japan	External
Principal Investigator	Andrés Couve	Janelia Farm		USA	External
Principal Investigator	Andrés Couve	Institut Curie		France	External
Associated Investigator	Pedro Maldonado	Brazilian Society for Neuroscience and Development	5	Brazil	Milenio
Associated Investigator	Pedro Maldonado	44th Annual Meeting of the Society for Neuroscience	7	USA	External
Associated Investigator	Miguel Concha	Research Visit Londres and Viena	11	United Kingdom - Austria	External
Associated Investigator	Miguel Concha	VII International meeting of the latin american society for developmental biology	4	Brazil	External
Associated Investigator	Cecilia Hidalgo	AD/PD 2015: International Conference on Alzheimer's and Parkinson's Diseases	7	France	External
Associated Investigator	Cecilia Hidalgo	Gordon Research conferences	8	USA	External
Associated Investigator	Cecilia Hidalgo	L Congress of the Brazilian Society of Psychology	6	Brazil	External
Associated Investigator	Cecilia Hidalgo	25th International for Neurochemistry (ISN) and Asian Pacific Society for Neurochemistry (APSN) Biennial Meeting, Cairns, Australia	8	Australia	External
Associated Investigator	Mario Herrera-Marschitz	9th World Congress of the International Brain Research Organization (IBRO)		Brazil	External
Associated Investigator	Mario Herrera-Marschitz	International Society for Neurochemistry: Latin American School of Advanced Neurochemistry		Uruguay	External
Associated Investigator	Mario Herrera-Marschitz	VII Neurotoxicity Meeting		Spain	External
Associated Investigator	Hernan Silva	World Federation of Societies of Biological Psychiatry 2015 Congress		Greece	External
Associated Investigator	Hernan Silva	Update en Neuropsicofarmacología. Colegio Latinoamericano de Neuropsicofarmacología (CLANP) y Asociación Ecuatoriana de Psiquiatría.		Ecuador	External
Associated Investigator	Hernan Silva	6th Paraguayan congress for Psychiatry		Paraguay	External
Deputy Investigator	Claudio Hetz	KIA International Award		Iran	External
Deputy Investigator	Claudio Hetz	ER proteostasis disturbances in neurodegenerative diseases		France	External
Deputy Investigator	Claudio Hetz	Research Visit Switzerland		Switzerland	External
Deputy Investigator	Claudio Hetz	ICGEB meeting		Argentina	External
Deputy Investigator	Claudio Hetz	Research Visit USA		USA	External
Associated Investigator	Lisette Leyton	2015 Cell Biology ASCB Annual Meeting	7	USA	External
Associated Investigator	Lisette Leyton	School of Neurobiology	15	Argentina	External
Associated Investigator	Jimena Sierralta	56 th Drosophila Research Conference		USA	External
Associated Investigator	Jimena Sierralta	Neurobiology of Drosophila		USA	External

Reserchers traveling from abroad

Name Researcher	Nationality	Activity	Stay [Days]	Country from traveling	Funding (Milenio, External, Mixed)
Martin Raff	Canadian	BNI Advisory Board	2	United Kingdom	Milenio
Jeremy Henley	British	BNI Advisory Board	3	United Kingdom	Milenio
Claudio Soto	Chilean	BNI Advisory Board	3	USA	Milenio
Robert Brown	American	International Workshop “Recent advances in ALS, from discovery to therapies”	2	USA	Milenio
Mathew Rasband	American	BNI Seminar	3	USA	External
Emery Brown	American	Seminar/Workshop	3	USA	External
Daryl Bosco	American	International Workshop	3	USA	Mixed
Fen-Biao Gao		International Workshop	3	USA	External
Fernando Pitossi	Argentinian	5 th Clinical Encounter	3	Argentina	Milenio
Bernard Schneider	Swiss	5 th Clinical Encounter	3	Switzerland	Mixed
Antígona Martínez	Brazilian	BNI Seminar	3	USA	External
Ralph Schneggenburger	Swiss	BNI Seminar	7	Switzerland	External
Richard Poole	British	BNI Seminar	2	United Kingdom	External
Steven Wilson	British	BNI Seminar	2	United Kingdom	External
Markus Diesmann	German	BNI Seminar	3	Germany	External
Sonia Grün	German	BNI Seminar	3	Gernamy	External
Margaret Fuller	American	BNI Seminar	2	USA	External
Rosario Moratalla	Espanien	BNI Seminar	3		External
Trinidad Herrero	Espanien	BNI Seminar	3		External
Howard Eisenberg	American	BNI Seminar	3	USA	External
Luis Bagatolli	Uruguayan	Jornada de Discusión: Ciencia y Desarrollo en Latinoamérica	7	Denmark	External