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1 Summary

1.1 Executive Summary: Understanding the function of the nervous system constitutes a broad and central challenge of today's biology and medicine. The scale of this challenge is exemplified by the decision of the US government to allocate US\$ 3000 million to an ambitious associative project called Brain Initiative, and by the Human Brain Project, largely funded by the European Union, that has recruited 112 Partners in 24 countries in Europe and around the world to pursue a 10 year global aim of producing rodent and human brain models. Yet despite these efforts the current integration of the structural and functional organization of the brain in physiology and disease remains beyond our grasp. Neuroscience in Chile is a small and emerging discipline, but one with excellent history and worldwide recognition. However, its contributions to improve the quality of life of the population are scarce, both in terms of providing satisfactory treatments to neurological, psychiatric and age related disorders, and to influence other areas such as education and technology. At the Biomedical Neuroscience Institute (BNI) we are generating the capacity to conduct cutting-edge basic Neuroscience to support clinical brain research, education and innovation.

BNI has developed into a trust-based platform that brings together a critical mass of leading basic and clinical neuroscientists along with mathematicians under suitable infrastructure to accomplish world-class scientific research and training. BNI provides a unified vision to explore the organization of the brain under normal physiology and the mechanisms underlying disease from whole organisms to cells. BNI leads Neuroscience in Chile and the region due to: (i) an extensive track record of individual and collaborative research initiatives, (ii) the association to major basic-clinical centers of national and international relevance, (iii) a vast training potential in health science, (iv) a young body of researchers coexisting in a single campus capable of executing the long terms goals of the initiative, and more recently (v) a motivated team of students, investigators, research development professionals, designers and media professionals, capable of reaching the wider community to foster application of discoveries and promote the value of science.

Activities at BNI are focused on integrated and transdisciplinary approaches. Three principles guide its operation: (i) transdisciplinary research, (ii) a bottom-up multi-scale approach to study the function of genes from molecules to behavior in complementary animal models, and (iii) an integrated biomedical strategy to promote high-standard scientific contributions. During 2014 these guiding principles were embraced fully and explicitly by BNI members, organized around interconnected thematic platforms. Through them BNI aims to: (i) establish an international reference centre for the exploration of the 'structure and function of the brain under physiological and pathological conditions', (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 clinicians and the general public.

During this period we have continued to operate as a non-profit organization and the overall structure of the institute has remained unchanged, with approximately 200 people including 24 postdocs, 54 PhD and 23 Master students. Our focus on postdocs and young investigators will significantly impact the institute in the following years. 16 postdocs funded by *Bridge Fellowships* between 2011-2014 (out of 23) have secured Fondecyt grants (70% success). 11 students obtained their undergraduate degrees, Master or PhDs during 2014. 14 students and young investigators have secured positions at other national or international basic or clinical research centers (e.g. international postdocs at UC San Diego, US, and Institut Curie, France). Of note, BNI continues to hold a favorable female:male ratio of 43:57 among its students and postdocs. We continue our commitment to co-mentor students and postdocs, and to collaborate in basic and applied projects. In addition, we have continued to fund pilot-projects, mostly led by young researchers together with

Associate Investigators, to promote interactions and incorporate young investigators to the central activities of the institute. Overall, more than 60% of the Iniciativa Científica Milenio (ICM) funds support common strategic aims.

ICM support represents 27% of the total funds secured by the group of investigators, which total US\$ 4.5 million, showing a successful and coordinated fund raising operation. Other funding sources include: (i) national grants such as FONDECYT (all BNI investigators), CONICYT-USA (C. Hetz, J. Sierralta, A. Couve), and U-Redes (S. Härtel); (ii) medium-size equipment grants (FONDEQUIP) to expand BNI's capacity in automated fluorescence/*Cellomics* imaging for large-scale cellular studies, drug discovery and signaling (C. Hetz), confocal, light-sheet and super-resolution microscopy (L. Leyton, M. Concha, S. Härtel, A. Couve), ultracentrifugation (C. Hidalgo) and computing power (S. Härtel); (iii) international agencies such as Target Validation Award From the Michael J Fox Foundation for Parkinson Research, USA; Frick Foundation Award, for ALS Research, Switzerland (C. Hetz); (iv) Research and Development FONDEF Grants that continue to involve several BNI investigators (C. Hetz, S. Härtel, P. Maldonado and A. Couve); and finally (v) outreach grants such as EXPLORA, INNOVA-CORFO and Fondo Valentín Letelier (A. Couve).

Research lines constitute long-term scientific programs and, therefore, have remained mostly unchanged. During 2014 we published 44 articles, including original studies, reviews and commentaries in journals with broad audiences and high impact factor (>10) such as *Nat Rev Neurosci* (31.6), *Trends Mol Med* (10.2), *Trends in Cell Biol* (12.2), *Mol Cell* (14.2), *Cell Metab* (17.3), *Cell Stem Cell* (23.5), *Nature Chem Biol* (13.2), *Autophagy* (11.4), *EMBO J* (10.7). The average impact factor of 2014 is 7.5, which places us favorable compared to other, similar sized neuroscience institutes in Europe, such as the Helsinki Neuroscience Institute, Finland. BNI investigators and students accumulated more than 89 presentations at national and international scientific conferences. Our first two patents and several brand protections were filed during 2014.

We have continued our weekly investigator meetings, regular seminar series with national and international guests, and our short internal seminars, which have significantly contributed to motivate young investigators and students. We have organized more than 20 scientific events in Chile, which promoted the research and aims of BNI within international speakers and a national audience of thousands of people. We highlight the international conferences, courses and workshops *Optics, Forces and Development; Visualisation and manipulation of signals and forces in developing tissues; Small Brains Big Ideas; and Basic-Clinical Encounters* on aging and schizophrenia, and a regular seminar series with more than 10 national and international guests.

A wide variety of high impact outreach activities were completed during 2014 including lectures, lab visits, web, radio, printed press, and generation of physical and virtual material to reach the general public. We highlight the activities associated to *Mentes Transformadoras*, which included public lectures of 6 distinguished neuroscientists including 3 Nobel Laureates and meetings with other sectors and Chile's president Sebastián Piñera in La Moneda, and *Origin of Animal Form during Development*. During 2014 BNI appeared in the press more than 70 times. To strengthen our program we created an interactive platform, *Loligo* (www.loligo.cl), which now includes *Axon* (short capsules for education), *Dendros* (animated comic and interactive activities) and *Mentes Transformadoras* (16 min documentary).

Associate Investigators and, importantly, students received national and international prizes further demonstrating the quality and commitment of BNI scientists. A formal network based on optics and microscopy generated an international meeting and course with more than 20 international speakers. Additionally, we carried out the third meeting between BNI and a network of Latin American Neuroscience centers and laboratories in Rio de Janeiro (*NeuroSur-III*).

Guided by our transdisciplinary program and intense atmosphere BNI has become a reference center for Neuroscience in Chile and South America.

1.2 Resumen Ejecutivo: La comprensión del sistema nervioso constituye un desafío amplio de la biología y medicina. La magnitud del desafío se ejemplifica por la decisión de EEUU de destinar US\$ 3000 millones a un ambicioso programa llamado *Brain Initiative* y por el *Human Brain Project* financiado por la Unión Europea y que ha reclutado 112 socios en 24 países de Europa y el resto del mundo para producir modelos artificiales de cerebros humanos y de ratón en 10 años. Sin embargo, a pesar de estos esfuerzos, la comprensión de la organización del cerebro en condiciones normales y patológicas sigue fuera de nuestro alcance. La Neurociencia en Chile es una disciplina emergente, aún pequeña pero con una excelente historia de logros y reconocimiento internacional. No obstante, su contribución a mejorar la calidad de vida de la población es escasa, tanto en términos de proveer tratamientos satisfactorios a enfermedades neurológicas, psiquiátricas y del envejecimiento, como en influir otras áreas como educación e innovación. El Instituto de Neurociencia Biomédica (BNI) genera la capacidad de desarrollar Neurociencia básica de frontera para apoyar la investigación clínica del cerebro, la educación y la innovación.

BNI es hoy una plataforma basada en confianzas que atrae a una masa crítica de neurocientíficos básicos y clínicos junto con matemáticos, bajo una infraestructura de punta para realizar investigación científica de nivel mundial y formación de personas. BNI proporciona una visión unificada para explorar la organización estructural y funcional del cerebro y los mecanismos que subyacen a enfermedades, desde los organismos a las células. BNI lidera la Neurociencia en Chile y en la región debido a: (i) una amplia trayectoria de iniciativas de investigación en Neurociencia, (ii) su asociación a los principales centros básico-clínicos, (iii) un vasto potencial en la formación de personas en ciencias de la salud, y (iv) un cuerpo joven de investigadores que coexisten en un único campus capaz de ejecutar los objetivos a largo plazo de la iniciativa, y recientemente (v) un equipo de estudiantes, investigadores, profesionales de innovación, del diseño y de medios audiovisuales, capaces de llegar a la comunidad para aplicar los descubrimientos y promover el valor de la ciencia.

Las actividades en el BNI están enfocadas en aproximaciones integrativas y transdisciplinarias. Tres principios guían esta operación: (i) investigación transdisciplinaria, (ii) un enfoque multi-escala para estudiar la función de genes desde las moléculas al comportamiento en modelos animales complementarios, y (iii) una estrategia biomédica integrada para generar contribuciones científicas de alto estándar y garantizar su transferencia. Durante 2014 estos principios rectores fueron adoptados plena y explícitamente por sus miembros. A través de ellos BNI tiene por objetivo: (i) establecer un centro de referencia internacional para la exploración de la estructura y función del cerebro en condiciones fisiológicas y patológicas, (ii) entrenar a una nueva generación de líderes investigadores y clínicos en un ambiente transdisciplinario único, sólido y vibrante, (iii) producir investigación clínica de alto nivel y transferir su impacto a la sociedad, y (iv) convertirse en un centro de recursos para médicos especializados y el público en general.

Durante este período hemos continuado operando como una organización sin fines de lucro y sin cambios estructurales globales en el Instituto que cuenta con aproximadamente 200 personas, incluyendo 24 postdocs, 54 estudiantes de doctorado y 23 de maestría. Nuestro enfoque en postdocs e investigadores jóvenes impactará el instituto en los años siguientes. 16 postdocs financiados por *Becas Puente* entre 2011-2014 (de un total de 23) han conseguido becas Fondecyt (70% de éxito). 11 estudiantes obtuvieron sus títulos de licenciatura, maestría o doctorado en 2014. 14 estudiantes y jóvenes investigadores han asegurado posiciones en otros centros nacionales o internacionales de investigación básica o clínica (por ejemplo, postdoctorados internacionales en la UC San Diego, EEUU y el Instituto Curie, Francia). BNI mantiene una proporción atractiva de 43:57 mujeres:hombres entre sus estudiantes y postdocs. Continuamos nuestro compromiso de co-dirección de estudiantes y postdocs, y de colaborar en proyectos básicos y aplicados. Además, hemos seguido financiando proyectos piloto, en su mayoría dirigidos por jóvenes, para promover las

interacciones e incorporar nuevos investigadores a las actividades del instituto. Más del 60% de los fondos de la Iniciativa Científica Milenio (ICM) apoyan objetivos estratégicos comunes.

El financiamiento ICM representa el 27% del total de fondos administrados por el grupo de investigadores, que totalizan U\$ 4,5 millones, mostrando una operación exitosa y coordinada de levantamiento de fondos. Otras fuentes son: (i) Fondos concursables nacionales como FONDECYT (todos los investigadores de BNI), CONICYT-EEUU (C. Hetz, J. Sierralta, A. Couve), y U-Redes (S. Härtel); (ii) Fondos para la adquisición de equipamiento mediano (FONDEQUIP) para ampliar la capacidad en microscopía de fluorescencia automatizada/Cellomics, imágenes para estudios celulares a gran escala, descubrimiento de fármacos y vías de señalización (C. Hetz), microscopía confocal, *light sheet* y microscopía de super-resolución (L. Leyton, M. Concha, S. Härtel, A. Couve), ultracentrifugación (C. Hidalgo) y *clusters* computacionales de alta capacidad (S. Härtel); (iii) organismos internacionales como *Target Validation Award* de la Fundación Michael J. Fox para la Investigación de Parkinson, EEUU; *Fundación Frick*, para la Investigación en ELA, Suiza (C. Hetz); (iv) Proyectos FONDEF de I+D que continúan involucrando a varios investigadores BNI (C. Hetz, S. Härtel, P. Maldonado y A. Couve); y, finalmente, (v) las subvenciones de divulgación como EXPLORA, INNOVA-CORFO y Fondo Valentín Letelier (A. Couve).

Las líneas de investigación constituyen programas científicos de largo plazo y se han mantenido sin cambios. Durante 2014 publicamos 44 artículos, incluyendo estudios originales, revisiones y comentarios en revistas de alto factor de impacto (>10), tales como Nat Rev Neurosci (31.6), Trends Mol Med (10.2), Trends in Cell Biol (12.2), Mol Cell (14.2), Cell Metab (17.3), Cell Stem Cell (23.5), Nature Chem Biol (13.2), Autophagy (11.4), EMBO J (10.7). El factor de impacto promedio 2014 es de 7,5, lo que nos sitúa favorablemente en relación a otros institutos de Neurociencia de tamaño similar en Europa, como el Instituto de Neurociencia de Helsinki, Finlandia. Investigadores y estudiantes de BNI acumulan más de 89 presentaciones en congresos científicos nacionales e internacionales. Dos patentes y protecciones de marca se presentaron durante 2014.

Hemos continuado con reuniones semanales de investigadores, la serie de seminarios con invitados nacionales e internacionales, y nuestros seminarios internos, que han contribuido a motivar a jóvenes investigadores y estudiantes. Hemos organizado más de 20 eventos científicos en Chile, que promueven la investigación y los objetivos de BNI con conferencistas internacionales y llegando a miles de personas. Destacamos las conferencias, cursos y talleres internacionales *Óptica, Fuerzas y Desarrollo; Visualización y Manipulación de Señales y Fuerzas en el Desarrollo; Cerebros Pequeños, Grandes Ideas; y Encuentros Basic-Clinicos sobre envejecimiento y esquizofrenia*, y seminarios regulares con más de 10 invitados nacionales e internacionales. Variadas actividades de difusión de alto impacto se completaron durante el 2014 incluyendo conferencias, visitas a laboratorios, desarrollo web, radio, prensa escrita, y material físico y virtual para público general. Destacamos actividades asociadas a *Mentes Transformadoras*, que incluyeron conferencias públicas de 6 distinguidos neurocientíficos, 3 de ellos Premios Nobel, reuniones con otros sectores y el presidente de Chile, Sebastián Piñera, en La Moneda; y *Origen de la Forma Animal durante el Desarrollo*. Durante 2014 BNI apareció en la prensa más de 70 veces. Para fortalecer nuestro programa creamos una plataforma interactiva, Loligo (www.loligo.cl), que incluye *Axón* (cápsulas para la educación), *Dendros* (comic interactivo) y *Mentes Transformadoras* (documental de 16 min). Investigadores Asociados y estudiantes recibieron premios nacionales e internacionales que demuestran la calidad y el compromiso de los científicos BNI. Una red basada en microscopía y óptica generó una reunión internacional y un curso, con más de 20 profesores internacionales. Además, se realizó la tercera reunión entre BNI y una red de centros y laboratorios de neurociencia de América Latina en Río de Janeiro (*NeuroSur-III*).

Guiados por nuestro programa transdisciplinario y una atmósfera intensa, BNI se ha convertido en un centro de referencia para la Neurociencia en Chile y Sudamérica.

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 4 Adjunct Investigators, 1 Senior Investigator, 24 postdocs, 54 PhD, 23 Master, 75 undergraduate students and technicians and 9 administrative staff. 5 active young collaborators (**Pablo Gaspar, Soledad Matus, René Vidal, Patricio Olguín and Andrea Paula-Lima**) have been recently invited to join as additional Adjunct Investigators in 2015. 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 advisory board. The majority of ICM 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 ICM funds are allocated to operational expenses freely executed by each Associate Investigator within BNI's guiding principles. ICM funding constitutes 27% 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 applications and pilot 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: Intracellular receptor trafficking is controlled by its transport along the dendritic endoplasmic reticulum (ER) (**AC**) (*Valenzuela et al., 2014 J Cell Sci*). A novel subcellular target of ALS-linked SOD1 mutants physically associates with the autophagy regulator Beclin 1, impairing autophagy levels (**CHz**) (*Nassif et al., 2014 Authopagy*). Importantly, ablation of Beclin 1 expression in mice protects against ALS (**CHz**). Further, delivery of active XBP-1 in the brain offers neuroprotection against 6-hydroxydopamine injections (**CHz**) (*Valdés et al., 2014 PNAS*). In cell migration controlled by RhoA GTPases, Rab5 is described to regulate Caveolin-1-dependent Rac1 activation (**LL**) showing that Rab5 is important not only in early endosome trafficking, but also in cell migration (**LL**) (*Díaz et al., 2014 J Cell Sci; Fernández et al., 2014 Mol Cancer*). Computational methods developed by the mathematical platform to analyze cell migration have provided help to study the events involved in this process (**SH**) (*Castañeda et al., 2014 Current Molec Med*). Finally, insulin triggers GLUT4 translocation through ROS activated and IP3 dependent release of calcium from the ER and by lowering the cholesterol, glucose intake is promoted through GLUT4 in adult muscle tissue (**CH**) (*Contreras-Ferrat et al., 2014 J Cell Sci; Llanos et al., 2014 Am J Physiol Endocrin & Metab*). International recognition of the BNI-PIs expertise is evident by invitations to write reviews in important journals (*Cell Stem Cell; Nature Rev Neurosci; Nature Chem Biol; Am J Physiol; Cell Physiol; Sem Cell & Dev Biol; Curr Mol Med; Neurobiol of Aging; Frontiers in Aging Neurosci; Melanoma Research*); editorial comments (*EMBO J; Curr Mol Med*), and a book chapter (*Cell Adhesion Molecules: Implications in Neurological Diseases. Springer*). Additionally, Filamin A was found to physically associate with IRE1 α using a yeast two-hybrid screening, uncovering a novel role of the UPR in cell migration that will be published soon (**CHz/AC**). Other interactions including PDIA6 were discovered using an RNAi screening (**CHz**). This project was complemented with the identification of IRE1 interactions using mass spectrometry to identify novel modulators of stress responses in neurons. Hits are currently being validated in cell culture and also in fly models (**CHz/JS**). BNI participated in numerous meetings and symposia including the XXVIII Annual Meeting of the Chilean Society for Cell Biology; XXXVII Annual Meeting of the Chilean Society for Biochemistry & Molecular Biology and international presentations at the FENS Regional Meeting, Milan, Italy; SEBBM, Granada, Spain; ASCB Annual Meeting, Philadelphia, USA; U. Tartu, Estonia, U. Helsinki, Finland.

RL2. Cellular identity and morphology: We have made progress in all projects:

i) Neural morphogenesis and CTIP1: We have studied this transcription factor, originally identified in a screen for genes involved in neuronal morphogenesis in *Drosophila*, 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. This work is undergoing final revisions prior to publication in *J Neurosci* (**JS/MK**).

ii) CoREST and brain development: Also using *in utero* electroporation in mice we have continued the study of the chromatin-remodeling protein CoREST, focused in novel partners of CoREST. We have identified new partners for CoREST by proteomics that partially explain the phenotype of its downregulation (**MK**).

iii) Transcription network regulated by Hindsight: We have investigated the target genes through which the transcription factor Hindsight (HNT) affects axonal targeting and growth in the optic lobe in *Drosophila*. We have determined that one of the direct targets of HNT is a *Drosophila* homolog of Filamin, Jitterburg, whose knockdown mimics the downregulation of HNT in axonal growth. This study will appear soon in Dev Neurobiol (**JS** and young investigator **P. Olguín**).

iv) Synapse regulation and morphology: Using electrophysiology and microscopy we have studied MAGUK proteins in the formation, function and plasticity of synapses. We demonstrated that DLG proteins are essential for efficient presynaptic neurotransmitter release and localization of Ca²⁺ channels. This work is undergoing final revisions prior to publication in J Neurosci (**JS**).

v) Lactate metabolism and glia-neuron relationship: We have continued the study of a gene originally identified in a loss of function *Drosophila* screen. This gene is a putative lactate transporter that might be essential for viability when expressed in *Drosophila* glial cells (**JS**).

vi) Search for genes associated to motorneuron degeneration: We have continued a modification screen in *Drosophila* to seek for genes that affect the motor phenotype associated to the decrease in the expression of the gene atlastin, directly associated to Hereditary Spastic Paraplegias (HSP) in humans. This is collaboration between two BNI labs and the young investigator **P. Olguín** has obtained support from an International Collaboration CONICYT-USA Grant associated to UMASS (**AC/JS**) and has allowed a short stay of a graduate student (C. De Gregorio) at collaborating labs (V. Budnik, U Mass).

The role of CTIP1 was part of the PhD. thesis of recently graduated student J. Cánovas. Studies on the role of CoREST in neuronal migration and morphogenesis, HNT and the role of Dlg in presynaptic function, the putative lactate transporter and the HSP-model are part of PhD and Ms theses and have been presented as posters in a national and international meetings, winning awards in Denmark and Chile (*Delgado et al.*, best poster in Denmark; *Delgado et al.*, best oral presentation in Chile; *Oliva et al.*, selected for Latin American symposium at the Chilean Neuroscience Society).

RL3. Supra-cellular development and circuits: We have made progress in experimental strategies aimed to dissect mechanisms that direct supra-cellular organization and circuit formation, with special emphasis on *in vivo* approaches using live confocal imaging in genetic model organisms, and in the context of a strong collaborative effort with the BNI-BioMat platform (see RL7), which has help us to implement new methodologies for image tracking and analysis:

(i) Left-right asymmetry in the brain: Through cell tracking and shape analysis in transgenic /mutant zebrafish we revealed that asymmetric positioning of the parapineal nuclei in zebrafish relies on a process of asymmetric evagination of parapineal precursors from the diencephalic roof plate. This process is driven by two main cell behaviors dependent on Nodal signaling: contraction/compaction of a subset of parapineal precursors on the left side and directed intercalation of right-sided precursors towards the left (**MC/SH**).

(ii) Chemokine and Robo-Slit signaling and habenular-IPN connectivity: We demonstrated that habenular neurons internalize Cxcr4b upon exposure to the chemokine Cxcl12 *in vivo*, and that the Robo3 receptor can follow the internalization of Cxcr4b. Combined with previous observations these results allow us to propose a mechanism by which Cxcr4b/Cxcl12 signaling allows early habenular axons to travel across Robo3-mediated repulsive environments and exit the habenula towards the main midbrain targets (**MC/CH**).

(iii) Role of tensile forces in directing cell migration and fate: We performed laser nano-dissection studies to perturb the activity of supra-cellular actomyosin structures and demonstrated that mechanical coupling between embryo progenitor cells and extra-embryonic tissues serves a dual role in development: to direct progenitor cell migration and protect cell fate. Our findings revealed a tissue-guided developmental strategy that secures the correct positioning and specification of progenitor cells in a region of the embryo where they differentiate into a functional tissue/structure (MC/SH).

(iv) Directed cell migration and tissue spreading during embryo morphogenesis: By combining genetic manipulation, *in vivo* imaging, image analysis and mathematical modeling, we demonstrated a novel mechanism of tissue spreading during early embryogenesis, taking advantage of developmental adaptations of annual killifish. This novel mechanism is based on adhesive and rigidity coupling to neighbor extra-embryonic tissue expansion (MC/SH).

(v) Comparative analysis of habenular asymmetry in vertebrates: By performing post-mortem neuroanatomical studies in humans, we demonstrate for the first time that the lateral habenula of humans shows structural asymmetries, with an enlarged left side compared to the right. We also found sexual dimorphisms of habenular shape (MC/SH).

(vi) UPR stress and cell migration: Based on findings linking the UPR stress sensor IRE1 α to cell migration, and its connection with Filamin A, we uncovered a novel role of IRE1 α in cortical neuron migration during the development of brain cortex (MK/CHz). Of note, Filamin A mutations are the major driver of periventricular nodular heterotopia associated with abnormal cell migration in the brain context leading to cognitive impairment.

Based on our contributions, reviews and a dispatch were published on leading journals (*Curr Biol*; *Development*). Results were presented at the *International Symposium Visualization and Manipulation of Signals and Forces in Developing Tissues*, the *Symposium JSPS: Genomic and epigenomic insights into vertebrate regeneration, development and evolution - Xenopus and fish as models*, and the *Third Latin American Zebrafish Network*. Nationally, presentations included the *XXVIII Annual Meeting of the Chilean Society for Cell Biology*, the *XXV Meeting of the Chilean Reproduction and Development Society*, the *Developmental Biology Symposium-Quintay 2014*.

RL4. Plasticity and behavior: Ongoing studies on the role of Ca²⁺ release from the endoplasmic reticulum (ER) mediated by ryanodine-receptor (RyR) channels on hippocampal long-term potentiation (LTP) and structural plasticity, and hippocampal-dependent behavior, CH in collaboration with adjunct investigator **JL. Valdés** and young researchers **A. Paula-Lima/T. Adasme**, generated the following results: i) Selective suppression of RyR activity differentially affected LTP induction depending on stimulation protocol. Theta burst stimulation (TBS) suppressed LTP induction while high frequency stimulation (HFS) prevented sustained LTP, but did not affect the initial fEPSP increase. These findings explain apparent conflicting literature reports contrasting complete TBS-induced LTP suppression by RyR inhibition or prevention of LTP maintenance after HFS without inhibition of its induction. We propose that HFS stimulation generates more robust post-synaptic Ca²⁺ entry signals than TBS, allowing initial LTP stimulation, and that RyR-mediated Ca²⁺ release signals are essential both to maintain long-lasting LTP after HFS and to induce LTP by TBS. The suppression by ryanodine of LTP induction by TBS is likely due to postsynaptic inhibition of RyR-dependent Ca²⁺ signaling pathways; the paired-pulse response remained unaffected but the input-output response was significantly lower. RyR inhibition did not decrease AMPA receptor surface expression. We are currently investigating possible postsynaptic signaling pathways affected by RyR inhibition, which decrease slice excitability and underlie the lack of LTP induction by TBS. ii) BDNF promoted the generation of cytoplasmic reactive oxygen species (ROS) in primary hippocampal neurons, and the antioxidant N-acetylcysteine or selective

inhibition of RyR2 expression by transfection with RyR2 shRNA inhibited RyR-mediated Ca^{2+} release and suppressed BDNF-induced spine remodeling. Moreover, incubation with inhibitors of the Ca^{2+} -dependent ERK kinase MEK or the NADPH oxidase NOX2 suppressed BDNF-induced RyR2 protein increase, while NOX2 inhibition eliminated BDNF-induced spine remodeling. We suggest that BDNF-mediated signaling, which is crucial for synaptic plasticity and spatial memory, entails significant crosstalk between the ROS-sensitive RyR-mediated Ca^{2+} signals and ROS production. iii) In addition, we confirmed that intra-hippocampal injections of abeta peptide oligomers (A β Os) or of anti-RyR2 oligonucleotides decreased RyR2 protein content, without alterations in RyR3 protein levels, and impaired spatial learning. The A β Os-induced decrease in RyR2 mRNA levels in primary hippocampal neurons required mitochondrial ROS generation, but not cytoplasmic ROS production by NOS or NOX. We propose that redox-sensitive RyR2-mediated Ca^{2+} release is crucial for spatial memory processes, and suggest that deficient RyR2-mediated Ca^{2+} signaling contributes to A β Os-induced learning and memory deficits.

We published an invited review on the role of Ca^{2+} release channels in hippocampal-dependent synaptic plasticity, learning and memory (*Paula-Lima et al, Antiox. Redox Signal. 2014*). Additionally, we reported that RyR-mediated Ca^{2+} release underlies iron-induced mitochondrial fission and stimulates mitochondrial Ca^{2+} uptake in primary hippocampal neurons (*San Martin et al., Front Mol Neurosci 2014*). Studies are ongoing to investigate the role of RyR channels in the propagation of intracellular Ca^{2+} waves in dendrites of primary hippocampal neurons (AC/SH/CH). During the reported period, we presented our work in several national and international meetings.

RL5. Systems Neuroscience: We have continued a series of studies to determine the neuronal mechanisms related to visual perception and the search for biomarkers in schizophrenia (PM/HS) with 2 postdocs, 6 PhD students, 10 Master's students and 2 engineering undergraduates. We presented 5 national and 5 international meeting abstracts. A novel finding of our EEG studies during natural visual exploration is that event related potentials (ERP) to the onset of visual images differ substantially from evoked visual potential that occur after each eye movement. This finding is significant because most of what we know about visual processes with EEG originates from flash images rather than natural visual behavior. We are currently working on a revised manuscript.

We have continued our characterization of visual behavior during natural exploration. C. San Martin completed her Master's thesis studying eye movement behavior during “top down” cognitive tasks: memory and visual search. We found that the first visual fixation and saccade differ substantially in duration between these two tasks, indicating underlying neural processes that we intent to further explore with EEG. In addition, R. Loyola completed her Master's thesis exploring visual behavior and object perceptions. Spatial aggregation of microsaccades operationally define the visual segmentation of visual objects in a natural scene. We are now preparing manuscripts on these studies. We have also explored the behavior of the pupil in social cognition and 3D perception. G. Varas showed that patients with radimedullar lesions have different pupillary responses during emotional recognitions task, suggesting relevant changes in the autonomic function. A. Campos explored pupil behavior as a marker of visual fatigue. Artificial 3D pictures and movies cause visual problems in a large number of individuals. She showed that fatigue appears to be the consequence of an increased visual process demand of visual disparity, the basis of 3D perception. G. Varas has already graduated and the other MS students will graduate in the coming months.

C. Astudillo completed her Master degree working on the pupillary behavior during natural viewing of emotional images. This work was integrated into our R&D grant (FONDEF IDEA CA12I10061) between BNI members (PM/AC) and J. Velásquez (Instituto Milenio Sistemas Complejos de Ingeniería, ISCI). The aim of the study was to examine eye movement and pupillary dynamics (emotional responses) during the free exploration of web pages. This grant was completed

last year and we are applying for a continuation grant. We have published a book chapter and one journal article has been accepted (*Neurocomputing*). This project has served as substrate for five engineering internships or undergraduate projects (C. Aracena, G. Martínez, J. Jadue, K. Muñoz and S. Madariaga). Importantly, this study has promoted a regular interaction between two Millennium Institutes from distinct, but highly complementary disciplines, a priority strategy for the ICM.

Complementary to these studies we have continued to explore the neuronal mechanisms involved in interoception (**PM**). By recording the activity of the insular cortex in a model of alcohol-addicted rats we have tested whether electrical microstimulation of the vagus nerve modulates craving behavior, which is the basis of a doctoral thesis (C. Ibañez, MD). We found that alteration of the vagus nerve by section, not microstimulation, significantly altered the first consumption of alcohol after re-installation. In addition, PhD student S. Vicencio completed his recordings from the insular cortex of rats while they were exposed to alcohol consumption. We are analyzing the data to confirm that neural activity modulation of the insular cortex participates in drug craving. We expect that C. Ibañez and S. Vicencio will graduate this semester.

During this period, we have continued to combine basic and clinical efforts to study psychiatric patients. A central study involves aims at establishing biometrics for schizophrenic patients (**HS/PM** and young investigator **P. Gaspar**, who has recently accepted a position at the Physiology & Biophysics Program). Specifically, we are studying a group of diagnosed patients in order to obtain behavioral, genetic, and electroencephalographic (EEG) markers for this pathological condition. The study involves the development of a multi-center collaborative network, including the Instituto Psiquiátrico Dr. José Horwitz, and two health centers associated to U Chile (Hospital del Salvador and Clínica Psiquiátrica). JI. Egaña MD, a former BNI-funded postdoctoral fellow, who has been involved in this project is now a Faculty member at the U Hospital. 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. We have set up a new recording facility at the Psychiatric Clinic to avoid bringing patients to the lab.

RL6. Neural dysfunction and pharmacological targets: We have developed projects to address novel disease mechanisms using genetic manipulation in complementary animal models to uncover pathogenic mechanisms in neurological conditions and also test new therapeutic strategies. For example, we have targeted a main component of the autophagy pathway using knockout models (i.e. Beclin 1) and evaluated its function in an ALS transgenic mouse model (**CHz** and young investigators **S. Matus/R. Vidal**). We have identified a key component of ALS pathogenesis that mediates motoneuron loss, possibly due to the control of protein degradation (*Nassif et al., 2014 Autophagy*). This study revealed an unexpected role of autophagy on ALS that was mapped to an abnormal interaction between mutant SOD1 and Beclin 1. This work was highlighted with cover image and involved collaboration with G. Kroemer (France) and B. Levin (US). Using genomic sequencing we have identified novel mutations that may drive ALS currently under study using mouse models (**CHz/S. Matus**). This project received one of the two international awards from the Frick Foundation in Switzerland.

We have also tested novel therapeutic approaches in models of peripheral nerve degeneration and Parkinson's disease (PD) (**CHz/R. Vidal**). These studies included collaboration with Genzyme (US) to generate gene therapy tools to treat diseases. Although growing evidence indicates that endoplasmic reticulum (ER) stress is a hallmark of the disease, its exact contribution to the pathogenic process is not well understood. Here 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 (*Valdés et al., 2014 PNAS*). This survival effect was

associated with preconditioning that resulted in induction of an adaptive ER stress response in dopaminergic neurons of the SNpc but not in other brain regions. In contrast, silencing XBP1 in adult animals triggered chronic ER stress and dopaminergic neuron degeneration. In agreement with this, gene therapy to deliver an active form of XBP1 provided neuroprotection and reduced striatal denervation in animals injected with 6-hydroxydopamine. Our results reveal a physiological role of the UPR in protein homeostasis in dopaminergic neurons that may help explain differential neuronal vulnerability. A new research line has been developed in the area of Alzheimer's disease and gene therapy (**CH/CHz**). We have developed a novel strategy to improve learning and memory by delivering active XBP1 into the hippocampus using AAVs and submitted a publication (**CHz/CH** and Adjunct Investigator **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.

We are currently developing a FONDEF project to generate a novel gene therapy strategy for PD in collaboration with Genzyme. 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** and **R. Vidal**).

Based on our contributions several reviews and editorial comments were published on leading journals (*Nat Rev Neurosci*; *Trends Mol Med*; *Trends Cell Biol*; *Mol Cell*; *Cell Metab*; *Cell Stem Cell*; *Nat Chem Biol*; *Trends Pharmacol Sci*). Importantly, two of these were selected for cover image. This platform is currently developing and establishing new models of neurodegeneration, including transgenic mice of Alzheimer's disease, new models of ALS, and modified animals for stress genes. In collaboration with R. Brown (U Mass) we have identified new mutations that may contribute to ALS and have generated several transgenic lines in mouse, in addition to performing an initial analysis in zebrafish. These studies will be strengthened by a recent 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 (*Herrera-Marschitz et al., 2014*). PARP-1 overactivation leads to NFκB-dependent inflammatory signalling, either by favouring the formation of transcriptionally active subunits of NFκB, and/or by pADPribosylation of p65, the transcriptionally active subunit of NFκB, which is translocated to the nucleus, stimulating the transcription of pro inflammatory cytokines, IL-1β and TNFα. These results were the core of the thesis by Tanya Neira-Pena, and a report will appear in 2015 (*Neira-Pena in press*). We found that HIF-1α is rapidly translocated to the nucleus in neurons and astrocytes. Thus, HIF-1α is an early molecule in the signalling cascade elicited by hypoxia, triggering neuroprotective or deleterious cascades depending upon the intensity of the insult, whenever the metabolic cascade leads to astrocyte reactivity. DNA methylation and histone acetylation are addressed in collaboration with P. Gebicke-Haerter (Mannheim, Germany) and A. Fischer (Göttingen, Germany). Epigenetic changes are investigated on DNA and histone modifications, tentatively on DNA methylation occurring in the promoters of PARP-1, AIF1, and TNF-α, key proteins involved in the long-term effects of perinatal asphyxia. The effect of perinatal asphyxia on CpG-island methylation is investigated in selected brain regions at different ages up to adulthood. We have reported that systemic neonatal nicotinamide treatment prevents the effect of perinatal asphyxia on PARP-1 activity, inflammatory signalling and cell death, supporting the idea that PARP-1 inhibition is a suitable therapeutic strategy (*Neira-Pena in press*). We have also investigated the effect of the HIF-1α inhibitor 3-(5'-

hydroxymethyl-2'-furyl)-1-benzylindazole (YC-1), finding that the treatment prevented the short- and long-term cellular and functional effects elicited by perinatal asphyxia, in tandem with PARP-1 inhibition (Marriott *et al.*, *under review*). 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 2014, 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 computational methods for analysis of dynamic events in cell migration with BNI investigators **MC/SH** (Castañeda *et al.*, 2014 *Curr Mol Med*) and contributed to Liddle *et al.*, 2014 *Chromosome Res* as a result of the Neurosur I meeting in Montevideo 2012. BNI-BioMat member S. Vargas contributed with a publication awarded with a cover image (Busso *et al.*, 2014 *Rep Fert Dev*). In addition, O. Ramírez/**AC** and **CH/SH** continued their long-standing collaborations (Valenzuela *et al.*, 2014 *J Cell Sci*; San Martín *et al.*, 2014 *Front Mol Neurosci*). Former BNI postdoc V. Castañeda continued his FONDECYT postdoctoral fellowship and contributed to Chang *et al.*, 2014 *Comput Meth Prog Bio* with BNI adjunct investigator N. Hitschfeld and **SH**. **SH** also contributed to Limpie *et al.*, 2014 *Acta Trop*. Former BNI-BioMat member and BNI postdoc M. Cerda became an Assistant Professor at the FMed. Former BNI-BioMat members L. Briones and J. Mansilla enrolled in the first International Master Program for Medical Informatics in Latin America at the U Chile 2014 together with 20 graduate students from Latin American Countries (Academic Director **SH**, www.magisterinformaticamedica.cl). BNI-BioMat and associative members continued to foster:

(i) New imaging techniques: Super-resolution Optical Fluctuation Imaging (SOFI), installed in 2013 was coupled to simultaneous 2-channel acquisition for super-resolution co-localization. A new NanoZoomer Whole-Slide Tissue Scanner (Hamamatsu) with fluorescence unit has been installed within a FONDEF project *Microscopía Virtual - Centro de Patología Digital Asistida (CPD)* (**SH**), covered by different national media. A FONDEQUIP project (**MC/SH**) continues the installation of a 4 lens-light sheet microscope in collaboration with U. Kubischek (U Bonn, Ger). In addition, BNI-BioMat member O. Ramírez participated in a FONDEQUIP project to build a laser ablation system coupled to live cell imaging, and **SH** will setup a Data Center at the Medical Faculty.

(ii) High-, mid-, and low-level mathematical-computational methods for microscopic image analysis in combination with high performance computing (HPC): Besides the publications mentioned above we contributed to the Latin American Initiative for reproducible software and code in the field of image processing (IPOL-LA). In this context, we have recently been awarded with a STIC-AmSud Project 'Reproducible Research in Image and Signal Processing' (ReRISiP), which focuses on establishing measures between participating laboratories from Uruguay, Argentina, Chile, Brazil, and France to promote and publish reproducible scientific code and set new ethical standards. Acceleration of existing and novel image processing algorithms was tackled in the regular FONDECYT project *Fast Computational Schemes for the Analysis of Morpho-Topological Data from High Throughput Microscopy* (**SH**), and will also be pursued within the new project 2015-2017 *Image Processing and Physical Models for the Interpretation of Cell Migration with 4-Lens Light Sheet Fluorescence Microscopy*. The application of HPC for high throughput microscopy will be enabled by the new 10Gbps connection to the National Laboratory for HPC (www.nlhpc.cl), within the U-Redes Project *BioMed-HPC: Network for Biologic and Medical HPC* (Director **SH**) that connects the *Campus Norte* of U Chile, the STI, REUNA, and the CMM via dark fiber. During 2015, BNI-members will enjoy a novel infrastructure for big data science at the interface of basic and clinical research with computational science and engineering.

(iii) *R&D of internet assisted services for diagnosis and clinical research*: The *spin-off* for Internet Assisted Medical Services CEDAI SpA (**SH**) is taking final steps towards licensing, and digital pathology is being integrated into remote services for image-based analytics for clinical practices. We continued to host and enroll patient data within the US Latin-American Cancer Research Network-Chile (USLACRN), and to work on the integration of distributed data sources (clinical, pathological, genomic data) in collaboration with postgraduate students of the new Master Program for Medical Informatics mentioned above.

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

(i) *Translational psychiatry in High Risk Psychosis syndromes*: The search for early detection in the prodromal phase of Schizophrenia (SZ) represents one of the most important challenges in SZ research for the next decades. 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. In particular, we are studying a subtype of HRP, called the Attenuated Psychosis syndrome (APS). During 2014, we have successfully recruited 10 subjects who exhibit symptoms compatible with APS and other subtypes of HRP. On those subjects and their first-degree relatives we have collected EEG, blood samples, and MATRICS cognitive assessment. We have been awarded two national grants (FONDECYT and OAIC) to develop these objectives and we have signed agreements with Yale and Columbia U, in order to set tech-transfer and human resource collaborations. The genetic approach is being developed in collaboration with the New York Genomic Center. This line of research represents the starting point of a new laboratory led by young investigator **P. Gaspar** (Translational laboratory lab) in collaboration with two BNI labs (**HS/PM**).

(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 will measure and correlate clinical parameters with BDNF protein and RNA levels in blood, and study 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 worked on establishing a formal relationship with two main partners recruited during 2013: i) 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; and ii) Cancer Center U Chile, who also provided resources in the form of infrastructure, protocols, use of equipment and staff. The formal terms of the collaboration have been drafted by the staff of the Cancer Center, and they will be revised and validated through a legal process. Several items necessary for the functioning of the biobank were acquired through funding from BNI and support from the Department of Psychiatry. A management software purchased in 2013 was launched during 2014 and its main functions are now being used for samples that enter the biobank. Software installation was possible after the acquisition of hardware and the training of 4 administrative staff that are currently managing sample information. Other capacities implemented during 2014 include sample managing and biosafety protocols, as well as the development of informed consents that are currently under review by the local IRB. As for the software, the expansion of its capability, including strengthening the security of the information, will require further training as well as other minor hardware resources.

During 2014 **HS** and young investigators including L. Bustamante, visited the Department of Psychiatry, Columbia U in order to learn about the work of their Genetic Epidemiology Group on the

collection of large samples with massive clinical, biological and genetic information. They extended an invitation to L. Bustamante for a 3 to 6 month stay to acquire further training on their ongoing study. Additionally, a group of 8 people including 3 members of BNI and members of the Cancer Center received training on the administration of the lab management software. Ms. Salinas had further training through her attendance to an international meeting for users of the software.

Currently, biobank infrastructure and protocols are being used by several research projects led by HS and directed by young investigators **P. Gaspar**, L. Bustamante and R. Nieto. The project led by R. Nieto is a collaboration with **CHz/R. Vidal**. The project led by P. Gaspar is a collaboration with **PM**. These projects are part of international collaborations with the New York Genome Center, Columbia University and Yale University.

b) Publications:

During this funding period BNI published 44 articles (42 ISI). Their relevance and impact for each research line have been described in section 3a. *See Summary Table below.*

Summary Table: Publications

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	27	42
	Others	0	0
SCIELO Publications or Similar to SCIELO Standard	Associate Researchers	0	0
	Others	0	0
Books & Chapters of Books	Associate Researchers	0	0
	Others	0	0
Other Publications	Associate Researchers	1	2
	Others	0	0
Total		28	44

c) Other achievements:

• Patents:

BNI hired a part time tech-transfer specialist, Claudio González, who in collaboration with Executive Director P. Cañón established a productive relationship with the central R&D office at U Chile. As a result two patents were filed during 2014*:

1. We registered one genetic treatment method named AAV/XBP1s-HA, which can be used to optimize and improve cognitive, memory and learning abilities. This therapy, still under development, has promising possibilities in human beings and is envisioned as an attractive choice for pathology treatments in relation to memory and mental disorders such as Alzheimer's disease.
2. During the same period a multifunctional manipulator was registered as a utility model that measures brain electrical activity in the mouse. In addition to the exchange standard electrodes currently available in market, this device also allows exchanging of custom-made electrodes for specific necessities, which is innovative relative to other multifunctional manipulators.

* In agreement with current university regulations these patents were filed under U Chile.

• Intellectual property:

During 2014 we continued the process to protect the corporate image of BNI and a number of brands associated to the Institute. Our legal advisor Ms. J. Jiménez has efficiently led this process. In addition to our brand *Dendros*, a web-based interactive platform for education (brand and logo),

which has already been protected through INAPI, other protections that were pursued during 2014 included:

Science and outreach brands:

1. *El Escape de Kai*: an arcade-type video game with Neuroscience content (brand). Approved by INAPI.

2. *Loligo*: an interactive space for audiovisual creativity to promote the value of scientific knowledge (brand and logo). Under final review at INAPI.

3. *Mentes Transformadoras*: a think-tank type platform to promote the value of scientific knowledge (brand and logo). Approved by INAPI.

4. The process for the main brand - *BNI* (neuroscience research institute - brand and logo) - is still in under review.

Commercial brands:

1. *UPRplus*, emerged from BNI lab spin-off, currently under review for protection at INAPI.

2. In addition *CEDAI Spa*, emerged from BNI lab spin-off, will be filed for protection at INAPI in 2015.

• **Congress Presentations:**

During this funding period BNI Associate Investigators and their teams attended, presented their work and organized 89 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: Presentations

Type of Researcher	Type of presentation	National Events	International Events
Associate Researchers	Conferences, oral communications, poster communications, others (specify)	32	28
	Invited presentations (not included in above row)	7	22
Other researchers	Conferences, oral communications, poster communications, others (specify)	0	0
	Invited presentations (not included in above row)	0	0

▪ **Organization of Scientific Events:**

We have continued our weekly Associate Investigator meetings to exchange information of research lines and drive BNI's cross-disciplinary atmosphere into concrete collaborative projects. These meetings have provided the appropriate environment to sustain rich scientific discussions while allowing time to manage and steer the institute.

We have organized regular seminars in topics that combined Neuroscience and medicine, and which involved local and international speakers. The list of seminars included: *Targeting ER proteostasis in glioma* (E. Chevet, U Bordeaux, France); *Arquitectura molecular y modulación por subunidades auxiliares de un canal de K⁺ activado por Ca²⁺ y voltaje* (R. Latorre, CINV, Valparaiso); *Reward system and addiction: what dopamine does and doesn't do?* (C. Di Chiara, Cagliari, Italy); *Dysregulated translational control in brain disorders* (E. Klann, NYU, USA); *Patient-derived stem cells as models for brain diseases* (Mackay-Sim, U-Griffith, Australia); *Robustness in eye development: fishing for new Wnt signaling targets and modulators* (R. Young, RD-CDB, UCL); *Estructura y conectividad de neuronas dopaminérgicas y motoneuronas: una caracterización de neuronas a nivel poblacional e individual* (P. Henny, PUC); *Efectos periféricos del sistema eferente cortico-olivococlear* (P. Délano, U Chile); *Nitric Oxide Signaling in retinal bipolar cells* (O. Schmachtenberg, CINV, Valparaiso); *Difusión en geometrias complejas* (M.L. Cordero, UChile); *Control circadiano y hormonal de la conducta: lecciones de Drosophila* (J. Ewer, CINV, Valparaiso); *Transportadores de cloruro en enfermedades neurosiquiátricas* (P. Rojas, USACH); *Regulación de cascadas transduccionales que promueven remielinización en el SNC* (G.

González, U Cambridge, UK); *Sonic Hedgehog (shh) controls neural stem and precursor cell proliferation through neogenin1: implications in neurogenesis and cancer* (V. Palma, U Chile); *Regulación de los hemicanales formados por conexinas por radicales libres* (M. Retamales, U Desarrollo); *Rol de la histamina cerebral durante los procesos de aprendizaje y memoria* (J.L. Valdés, BNI/U Chile); *Whole genome sequencing: innovation dream or privacy nightmare?* (E. de Cristofaro, UCL, UK); *Cognition in schizophrenia: from neuromodulation to cognitive training* (R. Panizzutti, UFRJ, Brazil).

We organized the 3rd Meeting for Basic-Clinic Encounters (July 30th 2014) on the subject of *Cell Function in Aging and Age-related Diseases*, which had the participation as speakers of C. Hetz (BNI), B. Kennedy, J. Garrison and H. Jasper (Buck Institute, USA), M. Behrens, A. Slachevsky and E. Jaimovich (F Med, U Chile). We organized the 4th Meeting for Basic-Clinic Encounters (November 28th 2014) on the subject of *Schizophrenia* with invited international speaker R. Panizzutti among other national psychiatrists. In addition, we organized the NeuroSur III workshop at the UFRJ of Rio de Janeiro-Brazil (November, 5-7 2014), which gathered speakers from UFRJ-Brazil (R. Lent, R. Panizzutti, E. Volchan, J. Franca), IBCCF-Brazil (C. Hedin-Pereira), IBqM-IBCCF (S. Ferreira), FioCruz-Brazil (W. Savino), Max-Planck B. Aires-Argentina (E. Artz), Pasteur Institute- Uruguay (L. Barbeito), and BNI investigators (see aim of the NeuroSur initiative in Networking).

We co-organized a new version of the international course *Small Brains, Big Ideas* that centered on the value of invertebrate animal research models to understand brain function and behavior. Students from Chile and South America attended the workshop, and a team of national and international neuroscientists led the scientific and outreach activities. In total, more than 50 people were involved. The workshop was a joint effort between BNI and the Millenium Institute CINV.

We organized the International Symposium *Visualization and Manipulation of Signals and Forces in Developing Tissues* together with Quantissue, a network initiative funded by the European Science Foundation (May 12-16 2014). The aim was to promote scientific interactions in the field of morphodynamics of cells and tissues from different perspectives. The symposium congregated 26 speakers from different institutes and universities of Europe (17), US (6) and Chile (3), and attracted over 100 participants from Latin America (66%), US (10%), Europe (23%) and Middle East (1%). Between the attendees, we counted undergrad and grad students, postdocs, as well as young and senior investigators. Such broad spectrum of backgrounds and experiences created a rich environment for scientific exchange. A trans-disciplinary international course, *Optics, Forces and Development* (May 5-16 2014) was organized in parallel to the symposium and exposed a selected group of Latin American students (5 Argentina, 3 Mexico, 2 Brazil, 2 Chile) to theoretical and practical training on microscopic techniques and experimental approaches for the visualization and manipulation of developing tissues given by a staff of 30 teachers/researchers. Overall, the symposium and course were high-quality scientific experiences and a great opportunity to discuss the most recent advances in cell and tissue morphodynamics and strengthen of scientific international networks in a warm and stimulating atmosphere. (Photograph: MC and team at *Visualization and manipulation of signals and forces in developing tissues*).

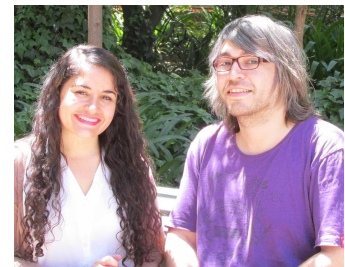


▪ Scientific Editorial Boards:

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). BNI young 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:

BNI investigators received exciting individual awards. G. Delgado, a PhD student working under the supervision of JS received the prize for "Best Oral Presentation" at the XXVIII meeting of the Chilean Society for Cell Biology. Likewise, J. Toledo, a PhD student working under the supervision of AC in close collaboration with SH received the 2nd prize for "Best Scientific Image" in the same conference. This latter prize contributes to recognize the sustained effort of BNI in microscopy and image processing. CH was recognized as one of top 100 women leaders 2014, attending the award ceremony with Chile's current President Michelle Bachelet. This recognition received significant attention from the media, and placed BNI and gender equality at the top of the national agenda. Of special importance, BNI's Associate Investigator MK, MD-PhD, expert in neural development and cell physiology and long-term collaborator of multiple initiatives in Neuroscience was elected Dean of the F Med, U Chile. MK served previously as director of the Graduate School and was part of F Med steering committee. His election as Dean ensures that his previous efforts in coordinating the goals BNI and U Chile, in terms of training and education, acquire special relevance and provides the institute with a solid relationship with the F Med. CHz received relevant national and international recognition. He was selected by *LatinAmericanScience.Org* and *Qué Pasa* magazine as one of the 30 more influencing scientist in Latin America. His research received important grants from high-profile international foundations (Target Validation Award From the Michael J Fox Foundation For Parkinson Research, USA; Frick Foundation Award, Switzerland). Finally his work was highlighted in four covers of high impact scientific journals including *Science Signaling*, *Autophagy*, *Trends in Pharmacological Sciences*, and *Trends in Cell Biology*. (Photographs: (from left to right), MK elected F Med Dean; CH at Top 100 women leaders ceremony; G. Delgado and J. Toledo, recognized at the SBCCH 2014).



4. Education and Capacity Building

a) **Education and capacity building:**

BNI operates in the context of the U Chile, the main 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, 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 program (**JS** Director of the program). 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 (Gottingen, Heidelberg, Magdeburg, Mannheim Institute of Mental Health J5, Germany; Karolinska Institutet, Sweden; Cagliari University, Italy; Jaume I University, Castellon, Spain). The international collaboration has provided a framework for research periods of graduate and associated scientists.

A number of graduate students (>50 students) are receiving full or partial stipends, making possible that they progress and fulfill 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 23 bridge-fellowships with 16 investigators securing a subsequent Fondecyt Postdoctoral Fellowship, constituting an impressive 70% 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 Ph.D. thesis 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

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:

More than 100 students (undergraduate though postdoctoral) are presently associated to BNI. A number of trainees have left the BNI, continuing their careers paths in other national institutions or abroad. The majority of BNI papers are published with students as first authors (27/42 ISI). BNI students participate regularly in national and international meetings, in poster and oral sessions. 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.

It is worth noting that the *First International Master in Medical Informatics* started in 2014 (www.magisterinformaticamedica.cl), academic director **SH**, with 22 students at the F Med U Chile. The Master is implemented within collaboration with Heidelberg University (Ger), and includes the support of four visiting professors per semester, student exchange, and the installation of a double degree in 2015/2016. Within this context, interdisciplinary postgraduate courses such as Image Processing, Biomedicine, or Bioinformatics (among others, see www.magisterinformaticamedica.cl/malla) have been installed for the first time at a regular basis within de F Med and present a novelty in Latin America.

Additionally, two undergraduate students from MIT and one Masters student from Imperial College London worked in BNI labs during 2014 as short-term interns providing evidence for the growing international reputation and impact of the institute.

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 2014 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 Universidad Católica de Chile, U Valparaíso, U A. Hurtado, and U D. Portales. As examples of international careers, JI. Valenzuela, a former graduate student of **AC**, is currently a postdoctoral fellow at the Institut Curie in Paris under the supervision of Franck Perez; and M. Aguilar a former graduate student and young postdoc of **PM** is currently a postdoctoral fellow at U California San Diego. Three have pursued careers in non-academic environments (ACHS, GenyTec LTDA, Centro de Estudios Reproductivos).

d) BNI students participating at international events and initiatives:

Our students and postdocs participate regularly in international conferences, at oral or poster sessions, international training courses, and training periods in the US (U Mass, Harvard, Columbia, McGill) and Europe (Cambridge, SISSA-Italy, Heidelberg, Gottingen, Karolinska Institutet-Stockholm). Particular attention has been given to collaborative initiatives among laboratories of the NeuroSur Network, with students participating at courses organized within the framework of international initiatives (International Neurochemical Society; IBRO, FENS). Furthermore, investigators of the BNI participate as teachers and/or lectures at the referred initiatives.

Summary Table: Current Position of Students Graduated during 2014 *

Obtained Degree	Academy	Industry and Services	Studies	Research	Other	TOTAL
Undergraduated	0	2	0	1	0	3
Master	1	1	0	2	1	5
Doctoral	2	0	0	1	0	3
Total	3	3	0	4	1	11

* This table does not include postdocs that have pursued careers elsewhere.

5. Networking and other Collaborative Work

a) **Networking:**

During 2014, BNI enhanced national and international association within leading experts in developmental biology, microscopic imaging, Neuroscience, and biomedical informatics. International symposia contributed to strengthen BNI's formal networks.

Network 1. Optics & Microscopy. In May 2014, BNI organized and supported three events to promote this network:

(i) International Course: Optics, Forces & Development, (www.cellmorphodynamics.cl/course2014), organized by **MC/SH**, with 12 students from different Latin American countries and international lectures. The 2-week practical/theoretical course combined optics, microscopic techniques for in vivo 3D visualization and force estimation during cell and tissue development. The course was co-sponsored by QuanTissue (ESF, Europe).

(ii) International Symposium: Visualisation and Manipulation of Signals and Forces in Developing Tissues (www.cellmorphodynamics.cl/symposium2014) organized by **MC** fostered scientific interactions between Latin America and the rest of the world by bringing together 27 lecturers and additional researchers from around the globe interested in morphodynamics of cells and tissues from different perspectives: theory to experiment, molecules to cells, and cells to organisms.

(iii) Open lecture: Origin of Animal Form in Development and Evolution (www.cellmorphodynamics.cl/openlecture2014) organized by **MC** for high school students and the general public at the former national congress building in Santiago, Chile. As before, the event was co-sponsored by QuanTissue (ESF, Europe). (Photograph: **AC**, E. Hamuy, R. Keller, S. Newman, **MC** and F. Dowling in Origin of Animal Form in Development and Evolution at the Ex-Congress Building, Santiago)



The participation of international experts strengthened collaborations and facilitated the development and implementation of advanced microscopic techniques in BNI labs: Light Sheet Microscopy (**MC/SH**, build in 2014/2015), PALM (**AC**, new grant 2014), and Whole Slide Imaging (**SH**, installed 2014).

Network 2. NeuroSur-III: Neuroscience in the Southern Cone

NeuroSur represents a collaborative network strategy between BNI and centers of excellence in Neuroscience working in the American Southern Cone (Chile, Argentina, Uruguay, and Brazil). It involves established senior investigators, young scientific leaders, postdocs and students. The goal of *NeuroSur* is to foster a first class, synergistic hub, addressing relevant topics in Neuroscience across the region. Since the first *NeuroSur* meeting in Montevideo (Uy) in 2012, the strategy has involved two approaches: (i) identification of common research objectives, complementary methodological approaches, up to date techniques, protocols, molecular and biological tools, as well as state of the art equipment, to support the building of a regional (South America) framework of excellence for scientific development and exchange of expertise, and (ii) improving the success rate for securing international funds that support an active scientific network in the region.

We have organized three *NeuroSur* meetings: *NeuroSur-I*, 2012, Montevideo (Uy), jointly organized by Pasteur Institute-Montevideo and BNI; *NeuroSur-II*, 2013, Buenos Aires, (Arg), jointly organized by investigators of Leloir Institute, the Biomedicine Institute of Buenos Aires (CONICET-Argentina-Max Planck Institute-Germany) and BNI. The 2013 program included

scientific presentations of researchers from Chile (BNI), Arg (Instituto Leloir, Pontificia Universidad Católica Argentina, INGEBI and Instituto de Investigación Médica Mercedes y Martín Ferreyra) and Uruguay (Institute Pasteur-Montevideo, Centro Universitario Paysandú and Instituto Clemente Estable). In 2014, *NeuroSur-III*, was organized in Rio de Janeiro (Brazil), jointly with investigators of the Program for Basic and Clinical Neuroscience of the Federal University of Rio de Janeiro, and the Instituto Oswaldo Cruz. The 3rd version enhanced collaborations and continued to promote the interaction between BNI and centers of excellence within all participating countries. After three years of networking a number of topics were addressed: (i) a common *NeuroSur* strategy, (ii) regional scientific and granting policies, and (iii) strategies to increase competitiveness and impact through international macro-initiatives.

As a result of *NeuroSur-I-III*, a collaboration between the laboratories of **AC** (BNI) and **A. Cáceres** (Instituto de Investigación Médica, Córdoba, Arg) has been established and will produce a high impact factor publication in 2015 addressing the formation of Golgi outposts in neurons. Students and teachers participated in microscopy courses. **SH** continued a collaboration with **G. Folle** (*NeuroSur-II* participant) and results have been published (*Liddle et al., 2014 Chromosome Res*). BNI investigators from **SH** lab enhanced collaboration with the Pasteur Institute and Clemente Estable Institute with reciprocal visits of academics and students. In addition, the Pasteur Institute installed a Signal Processing Laboratory (**F. Lecumberry**) in close association with **SH**. In this context, a common STIC_AMSUD project was granted to both labs in addition to collaborators in Argentina, Brazil, and France. The project *Reproducible Research in Image and Signal Processing* (ReRISiP) finances common meetings, courses, and academic exchange in 2015/2016 among all member countries, and addresses the relevant problem of reproducible research, ethics and standards for publication of scientific code within the IPOL and IPOL-LA strategy (www.ipol.im). Further collaborations have been maintained between **MH** and L. Barbeito (Pasteur Institute) through invited lectures in the framework of the IV Diploma on Neuropsychopharmacology (MEDICHI, BNI, Program of Molecular & Clinical Pharmacology, ICBM). (Photograph: BNI members and neuroscientists from Brazil, Uruguay and Argentina in *NeuroSur-III*, Rio de Janeiro).



In summary, *NeuroSur*-meetings have triggered novel associations, networks, and projects between BNI and centers of excellence within and beyond the LA region. BNI will continue its efforts through the organization of a *NeuroSur-IV* meeting in Santiago, Chile, in 2015 in order to coordinate and enhance further steps towards the generation of a robust Latin American network in research and development.

b) Other collaborative activities:

Strong collaborative initiatives not included as formal BNI networks have continued to be promoted by BNI scientists. They have provided additional support for exchange of students, postdocs and expertise with laboratories of Chile, Latin America, US and Europe. During 2014 scientific meetings and collaborative activities contributed significantly to enhance BNI's association to leading researchers and centers.

(i) The international symposium *Small Brains, Big Ideas* (smallbrains.org) organized by **JS** in collaboration with the Millenium Institute CINV gathered international leaders in topics that ranged from micro RNA's, to the formation of neural circuits, to learning in bees, flies, and *C. elegans*. Importantly, the collaboration between two Millenium Institutes aligns with a priority strategy for the Iniciativa Científica Milenio.

(ii) In January 2014 the U-Redes project BioMed-HPC organized its *First Scientific*

Meeting BioMed-HPC with 30 national experts in biomedical data sciences. U-Redes fosters the installation of a 10 Gbps network between the F-Med, REUNA, and the National Laboratory for High Performance Computing (www.nlhpc.cl), and sets a new milestone to propel BNI imaging and data analyses capacities towards new dimensions in size, speed, and connectivity. The meeting enhanced network building in HPC and leads to a new FONDEQUIP project for the installation of the first data center at the F Med.

Other ongoing collaborations have been further pursued: Other ICM Centers (F. Aboitiz, J.L. Valdés), 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), NIH (S. Moss), European Union (S. Wilson), the Harold Leila Mathers Foundation (L. Glimcher), FONDEF (J. Velásquez), FONDECYT (P. Morales, F. Bronfman, L. Bagatolli, R. Kaufman, T. Blanpied, A. Cáceres, C.P. Heisenberg), CONICYT-USA (V. Budnik, R. Brown), and others (G. Kroemer, M. Castro, J. Enderlein, V. Torres, C. González). Network initiatives have been set between BNI associated centers and research Institutions in Latin America and Europe. An agreement with the International Institute of Neuroscience of Natal (Brazil) exists since 2007, including a program of faculty/student exchange. Importantly, R. Fuentes, Director of the Institute in Natal until 2014 recently was recently appointed Assistant Professor at the F Med to lead a new research group in Neuroscience that is expected to collaborate closely with BNI. Networks are also established with the Central Institute of Mental Health J5, Mannheim, Germany, and Karolinska Institutet, Stockholm, Sweden. BNI students have participated in short-term research and traineeship periods as indicated in the advances each of the RLs. Furthermore, BNI has received an increasing number of international students in internship and exchange programs such as MISTI MIT or through their enrollment in graduate programs at U Chile. Together these collaborations consolidate BNI as an international centre of scientific excellence by promoting synergy in partnership.

6. Outreach and Connections with other Sectors

a) Outreach:

During 2014 we developed a variety of outreach activities to promote and strengthen our connections with the general community. From high-school students to business people, we spread our view and passion for science. We executed 29 outreach activities during 2014. Among them we highlight the following:

At the beginning of the year we invited six internationally acclaimed scientists: R. Axel, C. Bargman, T. Maniatis, S. Tonegawa, T. Wiesel and C. Zuker, 3 of them awarded the Nobel Prize in Physiology or Medicine. During a whole day, they lectured to 600 people in the Ex-Congress building in Santiago. Throughout these talks, the general public had the chance to learn about game-changing discoveries in Neuroscience and to value science as a transforming agent for society. We also had the chance to shoot a documentary traveling with them through Patagonia. This short documentary called *Mentes Transformadoras* went online on December 2014 achieving more than 1,400 views in two months (www.loligo.cl). The impact and interest from the general community and the media were outstanding.

(Photographs: Left, speakers from *Mentes Transformadoras* and BNI investigators; right, *Mentes Transformadoras* audience at the Ex-Congress building).



We also organized a second series of lectures at the Ex-Congress in Santiago. This time the subject was *The Origin of Animal Shape*, with two leaders in this area, R. Keller and S. Newman. Again, hundreds of people assisted the event, which was produced in the context of an International Scientific Course: *Optics, Forces and Development*, organized by our Institute, thus providing an excellent strategy to optimize resources. Indeed, during another scientific course organized by our Institute, *Small Brains, Big Ideas*, we also generated a public symposium where M. Freeman (U Mass) lectured to 200 people, mostly high-school students about the use of flies as a model system to understand neurological diseases.

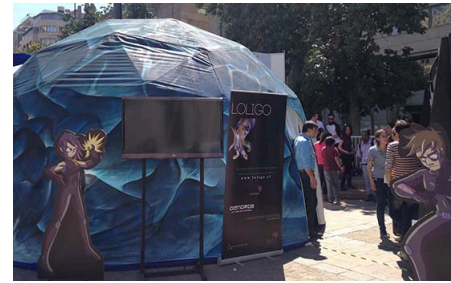
In order to improve our outreach platform we invited D. Liu, director of Biointeractive, Howard Hughes Medical Institute (HHMI). Biointeractive is one of the largest outreach programs in the US with substantial scientific resources for education. Together with D. Liu we organized a seminar in the Planetarium building for more than 200 high-school students and later a seminar for 60 outreach professionals in an entrepreneurship environment.

Apart from these large-scale events, we continued the development of our comic *Dendros*. Our web interactive comic has been a success and we've created a new episode of the story (www.loligo.cl/dendros). We also developed a gaming room based on the characters from *Dendros*, with arcades, pinballs and touch-screen apps. Importantly, during 2014 we designed and built a brain-dome to go on tour with the experience. The brain-dome was launched in October during the National Science Fair (Explora-Conicyt), and in just a couple of days had more than 1,000 visitors. We recorded a video of this event: (www.youtube.com/watch?v=xar9xu3fgfY).

In association with *Las Minas* productions we created a series of 12 short-clips about neuroscience called *Axon*. This series was transmitted online with more than 12,000 views and in Santiago's subway (subTV), where it reached more than a million viewers (www.loligo.cl). We also

established a collaboration with one of our emblematic public school for girls, Liceo 1, and started to work in a project called “Neuro-bug”, where students worked with low-cost EEGs to design an experimental procedure. This new project caught the attention of the media and won the third place in a scientific contest organized by Explora.

Overall we have increased significantly the number of people reached by these activities, and have become a reference center for outreach in the country and abroad. We are now developing strategic alliances with HHMI and the Faculty of Design U Chile to further improve our platform and measure the impact on users.



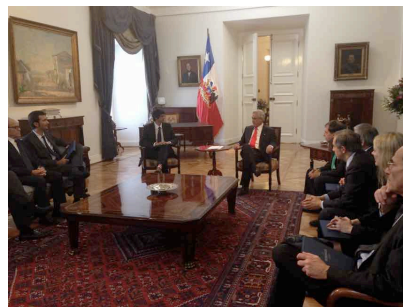
(Photographs: Left, D. Liu from HHMI with students at Planetarium; right, Dendros brain-dome at the National Science Fair, Plaza de la Constitución, La Moneda Palace).

b) Connections with other sectors:

We have established relevant alliances with private and public institutions such as Ilustre Municipalidad de Recoleta, Centro Cultural Palacio La Moneda, Programa EXPLORA-CONICYT Coordinación Norte, US Embassy, and Consejo del Futuro/Senado de Chile. During 2014 we developed a high-impact outreach activity that was held at the Ex-Congress in Santiago, *Mentes Transformadoras* (see *Outreach*). As a result, we were invited to a private meeting with the Chilean President Sebastián Piñera to the Government Palace, La Moneda, together with senators G. Girardi and F. Chahuán to discuss the future of science and technology in Chile. Connections with decision makers have been significantly strengthened since then, especially with Consejo Futuro and Consejo Nacional para la Competitividad y el Desarrollo (CNID). In addition, the event was complemented by a forum, *From Science to Business*, with opinion leaders, entrepreneurs, government officials, business people, university officials, etc, organized in collaboration with Columbia Global Centers at Telefónica (<http://globalcenters.columbia.edu/santiago/content/panel-science-business-watch-livestream>).

We have put additional efforts to connect with the private sector and show our developments in the area of applied research and biotechnology. We organized a discussion panel called *Ciencia de Frontera y Oportunidades de Negocios* at the central office of Carey law firm. Multiple representatives of the Ministry of Economy, CORFO, R&D U Chile and different industries were present at this meeting.

(Photographs: Left, President S. Piñera with speakers from *Mentes Transformadoras*, senators G. Girardi and F. Chahuán, and CHz and AC from BNI in La Moneda Palace; right, AC, K. Trusich (Subsecretary of Economy), G. Carey and CHz at *Ciencia de Frontera y Oportunidades de Negocios*).



We also participated in the workshop *El Desafío de Emprender y Desarrollar Tecnologías para el Sector Salud: Una Oportunidad Emergente* organized by UDD Ventures and Programa de Mejoramiento Institucional (PMI-UDD) where a discussion session was developed to evaluate business opportunities in the biomedical area. We have also continued the development of research interactions with the Biotech Company Genzyme Corporation from the US through a FONDEF grant. We have also met with officials from the US Embassy searching for projects that could be potentially supported by the US Navy. In addition, two BNI members (**AC/CH**) were nominated for the Presidential Commission on Science and Technology to help guide the country's future in social and economic development. During 2014 we also formally requested the incorporation of five new adjunct investigators. Among them **S. Matus** and **R. Vidal** represent a new private initiative, *Neuounion Biomedical Foundation*, where **CHz** is a member of the board of directors. Finally, BNI has invested significant resources to consolidate a biobank of human samples from Chilean patients through an alliance with the F Med, U-Cancer and the Psychiatric Clinic.

7. Administration and Financial Status

a) Organization and administration:

BNI continued to operate 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 2014. 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). As a consequence of the elections for Dean and the nominations for new Director of R&D at the F Med the constitution of the Board will be revised during the next funding period. P. Cañón, who excelled in her role as Executive Director left BNI on December 2014. She is now an executive officer at CORFO. Her departure provides and opportunity to restructure the institute to accommodate the growing research, education and innovation demands. Her role in 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 will be covered by more than one professional during 2015 allowing the institute to define specific work profiles and responsibilities, and thus tackle the growing opportunities with a long-term vision. The Executive Office is additionally constituted by A. Sanguinetti, a reporter who focuses on web, social networks and press activities to connect with the public and high-school students in particular, J. Jiménez, a young lawyer who provides legal assistance, and R. Tapia, BNI's artist in residence who has acquired increasing responsibilities and established our successful outreach program *Dendros* as a national reference in scientific communication and impact. The Grant Management Office is constituted by A. Timmermann, who has extensive expertise in Millenium funds, S. Carrasco and K. Miranda assistant accountants, and J. Mansilla, informatics expert. Mrs. Timmerman monthly financial reports to the Ministerio de Economía have been spotless. A graphic design team led by N. Vasquez and journalists led by I. Llambías have contributed to consolidate BNI's corporate image and promote its activities. These central BNI staff work closely with administrative and technical personnel distributed among the 11 research groups. *See Summary Table below.*

Summary Table Organization and Administration

Category	Female	Male	TOTAL
Assistant & Technicians	23	17	40
Administrative Staff	10	6	16
TOTAL	33	23	56

b) Financial Status:

Summary Table Outcome Structure

Item	Operative	Networks	Outreach	TOTAL 2014
Honoraria researchers & personnel	352,405,061	-	-	352,405,061
Tickets and travel expenses	43,583,239	34,096,504	15,580,412	93,260,155
Materials and supplies	96,061,489	-	6,712,036	102,773,525
Goods and equipment	77,527,384	-	99,990	77,627,374
Infrastructure	9,792,857	-	-	9,792,857
Administratives expenses	48,896,126	-	-	48,896,126
Publications and subscriptions	2,279,308	-	3,647,827	5,927,135
Consultancies	21,000,000	-	13,531,000	34,531,000
Overhead	31,615,861	-	-	31,615,861
Others	4,349,086	-	-	4,349,086
Total	687,510,411	34,096,504	39,571,265	761,178,180

Annexes

Annex 1.-

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	Medicine	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 Gründler	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	Physical	D	University of Chile	Assistant Professor	2
Pedro Esteban Maldonado Abogast	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	Medicine	D	University of Chile	Full Professor	2

1.2 Young Researchers

There is no register in this section

1.3 Senior Researchers

Full Name	Research Line	Nationality	Gender	Date of birth	Profession	Academic Degree	Affiliation	Current Position	Relation with Center
Yedy Israel Jacard	RL1. Sub-cellular functional dynamics.	Chilean	M	19-09-39	Biochemist	D	University of Toronto	Full Professor	2

1.4 Others

Full Name	Research Line	Nationality	Gender	Date of birth	Profession	Academic Degree	Affiliation	Current Position	Relation with Center
Jose Luis Valdes Guerrero	RL1. Sub-cellular functional dynamics. RL3. Supra-cellular development and circuits. RL6. Neural dysfunction and pharmacological targets. RL8. Clinical research .	Chilean	M	16-12-75	Biologist	D	University of Chile	Assistant Professor	2
Nancy Hitschfeld Kahler	RL7. Applied mathematics and biomedical informatics.	Chilean	F	24-03-76	Science Computer	D	University of Chile	Associate Professor	2
Jaime Ortega Ocampo	RL7. Applied mathematics and biomedical informatics.	Chilean	M	16-10-67	Mathematic	D	University of Chile	Associate Professor	2
Adrian Ocampo Garces	RL4. Plasticity and behavior. RL7. Applied mathematics and biomedical informatics.	Chilean	M	21-10-65	Medicine	D	University of Chile	Associate Professor	2

<u>NOMENCLATURE:</u>		
[Gender] [M] Male [F] Female	[Academic Degree] [U] Undergraduate [M] Master [D] Doctoral	[Relation with Center] [1] Full time [2] 2

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. Yedy Israel Jacard . Mario G.G. Herrera-Marschitz Muller. Jose Luis Valdes Guerrero.	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 Drosophila, 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 Drosophila 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.	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 Robot/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. Yedy Israel Jacard . Manuel Kukuljan Padilla. Mario G.G. Herrera-Marschitz Muller. Jose Luis Valdes Guerrero.	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. Adrián Ocampo Garces.	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.	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. Yedy Israel Jacard . María Cecilia Hidalgo Tapia. Jose Luis Valdes Guerrero.	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 assemblies 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. Adrian Ocampo Garces. Nancy Hitschfeld Kahler. Jaime Ortega Ocampo.	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. Yedy Israel Jacard . 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 ICM)

Category of Publication	MSI Center Members	Reference
ISI Publications or Similar to ISI Standard	Associate Researchers	Mardones P, Dillin A, Hetz C, (2014),Cell-nonautonomous control of the UPR: mastering energy homeostasis, Cell metabolism
		Hetz C, Medinas DB, (2014),Protein homeostasis: Modeling UPR adaptive responses, Nature Chemical Biology
		Couve A, Hetz C, (2014),RESETEting ER proteostasis: selective stress pathway hidden in the secretory route. , The Embo Journal
		Matus S, Bosco DA, Hetz C, (2014),Autophagy meets fused in sarcoma-positive stress granules, Neurobiology of Aging
		Matus S, Valenzuela V, Hetz C, (2014), A new method to measure of autophagy flux in the nervous system, Autophagy
		Rojas-Rivera D, Hetz C, (2014),TMBIM protein family: ancestral regulators of cell death, Oncogene
		Valenzuela JI, Jaureguierry-Bravo M, Salas DA, Ramírez OA, Cornejo VH, Lu He, Blanpied TA, Couve A., (2014),Transport along the dendritic endoplasmic reticulum defines the trafficking modality for GABAB receptor, Journal of cell science
		Couve A, Kittler JT, (2014),Preface. Trafficking of organelles and proteins in the nervous system., Seminars in cell & developmental biology
		González C, Couve A, (2014),The axonal endoplasmic reticulum and protein trafficking: cellular bootlegging south of the soma, Seminars in cell & developmental biology
		Paula Lima AC, Adasme T, Hidalgo C, (2014),Contribution of ca(2+) release channels to hippocampal synaptic plasticity and spatial memory: potential redox modulation., Antioxidants & Redox Signaling
		Contreras-Ferrat A, Llanos P, Vásquez C, Espinosa A, Osorio-Fuentealba C, Arias-Calderon M, Lavandero S, Klip A, Hidalgo C, (2014),Insulin elicits a ROS-activated and an IP3-dependent Ca2+ release, which both impinge on GLUT4 translocation., Journal of cell science
		Dufey E, Sepúlveda D, Rojas-Rivera D, Hetz C, (2014),Cellular Mechanisms of Endoplasmic Reticulum Stress Signaling in Health and Disease, American journal of physiology. Cell physiology
		Duran-Aniotz C, Martinez G, Hetz C, (2014),Memory loss in Alzheimer's disease: Are the alterations in the UPR network involved in the cognitive impairment? , Frontiers in aging neuroscience
		Campos G, Schmidt-Heck W, Ghallab A, Rochlitz K, Pütter L, Medinas DB, Hetz C, Widera A, Cadenas C, Begher-Tibbe B, Reif R, Günther G, Sachinidis A, Hengstler JG, Godoy P, (2014),The transcription factor CHOP, a central component of the transcriptional regulatory network induced upon CCl4 intoxication in mouse liver, is not a critical mediator of hepatotoxicity, Archives of toxicology
		Dejeans N, Manié S, Hetz C, Bard F, Hupp T, Agostinis P, Samali A, Chevet E, (2014),Addicted to secrete – novel concepts and targets in cancer therapy, Trends in molecular medicine
		Hetz C, Mollereau B, (2014),Disturbance of endoplasmic reticulum proteostasis in neurodegenerative disease, Nature Reviews. Neuroscience
		Matus S, Medinas DB, Hetz C, (2014),Common Ground: Stem Cell Approaches Find Shared Pathways Underlying ALS, Cell Stem Cell
		Vidal RL, Matus S, Bargsted L, Hetz C, (2014),Targeting autophagy in neurodegenerative disease, Cell metabolism
		Nassif M, Valenzuela V, Rojas-Rivera D, Vidal R, Matus S, Fuentealba Y, Kroemer G, Levine B, Hetz C, (2014),Pathogenic role of Beclin 1/BECN1 in the development of amyotrophic lateral sclerosis, Autophagy
		Valdes P, Mercado G, Vidal RL, Molina C, Parsons G, Court FA, Martínez A, Galleguillos D, Schneider BL, Hetz C, (2014),Control of dopaminergic neurone survival by the unfolded protein response transcription factor XBP1, Proceeding of the National Academy of Science of the United States of America (www.pnas.org)
		Groenendyk J, Peng Z, Dudek E, Fan X, Mizianty MJ, Dufey E,Urra H, Sepulveda D, Rojas-Rivera D, Lim Y, Kim DH, Baretta K, Srikanth S, Gwack Y, Ahnn J, Kaufman RJ, Lee SK, Hetz C, Kurgan L, Michalak M, (2014),Interplay Between the Oxidoreductase PDIA6 and microRNA-322 Controls the Response to Disrupted Endoplasmic Reticulum Calcium Homeostasis, Science Signaling
		Reig G, Pulgar E, Concha ML, (2014),Cell migration: from tissue culture to embryos. , Development (Cambridge, England)

Category of Publication	MSI Center Members	Reference
ISI Publications or Similar to ISI Standard		Signore IA, Concha ML, (2014),Genetics: a common origin for neuronal asymmetries? , Current biology: CB.
	Associate Researchers	Castañeda V, Cerda M, Santibáñez F, Jara J, Pulgar E, Palma K, Lemus CG, Osorio-Reich M, Concha ML, Härtel S, (2014),Computational methods for analysis of dynamic events in cell migration. , Current Molecular Medicine
		Cárdenas A, Kong M, Alvarez A, Maldonado H, Leyton L., (2014),Signaling pathways involved in neuron-astrocyte adhesion and migration., Current molecular medicine
		Leyton L, Torres VA, Quest AF, (2014),Editorial: Signaling in cell migration and disease., Current molecular medicine
		Aguilar-Guzmán L, Lobos-González L, Rosas C, Vallejos G, Falcón C, Sosoniuk E, Coddou F, Leyton L, Lemus D, Quest AF, Ferreira A, (2014),Human survivin and Trypanosoma cruzi calreticulin act in synergy against a murine melanoma in vivo., Plos one
		Díaz J, Díaz N, Leyton L, Torres VA, Quest AF, (2014), Molecular mechanisms implicated in Caveolin 1 dependent Rab5 activation, migration and invasion of metastatic cancer cells., Cancer Cell & Microenvironment
		Fernández JG, Rodríguez DA, Valenzuela M, Calderon C, Urzúa U, Munroe D, Rosas C, Lemus D, Díaz N, Wright MC, Leyton L, Tapia JC, Quest AF, (2014),Survivin expression promotes VEGF-induced tumor angiogenesis via PI3K/Akt enhanced β -catenin/Tcf-Lef dependent transcription., Molecular cancer
		Díaz J, Mendoza P, Ortiz R, Díaz N, Leyton L, Stupack D, Quest AF, Torres VA, (2014),Rab5 is required in metastatic cancer cells for Caveolin-1-enhanced Rac1 activation, migration and invasion., Journal of cell science
		Lobos-Gonzalez L, Aguilar-Guzmán L, Fernandez JG, Muñoz N, Hossain M, Bieneck S, Silva V, Burzio V, Sviderskaya EV, Bennett DC, Leyton L, Quest AF, (2014),Caveolin-1 is a risk factor for postsurgery metastasis in preclinical melanoma models., Melanoma Reseach
		Quintanilla ME, Rivera-Meza M, Berrios-Cárcamo PA, Bustamante D, Buscaglia M, Morales P, Karahanian E, Herrera-Marschitz M, Israel Y, (2014),Salsolinol, free of isosalsolinol, exerts ethanol-like motivational/sensitization effects leading to increases in ethanol intake, Alcohol Journal
		Rivera-Meza M, Quintanilla ME, Bustamante D, Delgado R, Buscaglia M, Herrera-Marschitz M, (2014),Overexpression of hyperpolarization-activated cyclic nucleotide-gated channels into the ventral tegmental area increases the rewarding effects of ethanol in UChB drinking rats., Alcohol, clinical and experimental research
		Herrera-Marschitz M, Neira-Pena T, Rojas-Mancilla E, Espina-Marchant P, Esmar D, Perez R, Muñoz V, Gutierrez-Hernandez M, Rivera B, Simola N, Bustamante D, Morales P, Gebicke-Haerter PJ, (2014),Perinatal asphyxia: CNS development and deficits with delayed onset, Frontiers in neuroscience
		Karahanian E, Rivera-Meza M, Tampier L, Quintanilla ME, Herrera-Marschitz M, Israel Y, (2014),Long-term inhibition of ethanol intake by the administration of an aldehyde dehydrogenase-2 (ALDH2)-coding lentiviral vector into the ventral tegmental area of rats., Addiction biology
		Urta H, Hetz C, (2014),A novel ER stress-independent function of the UPR in angiogenesis. , Mollecular Cell
		Liddle P, Lafon-Hughes L, Di Tomaso MV, Reyes-Ábalos AL, Jara J, Cerda M, Härtel S, Folle GA, (2014),Bleomycin-induced γ H2AX foci map preferentially to replicating domains in CHO9 interphase nuclei. , Chromosome Research
		Chang V, Saavedra JM, Castañeda V, Sarabia L, Hltschfeld N, Härtel S, (2014),Gold-standard and improved framework for sperm head segmentation. , Computer Methods and Programs in Biomedicine
		Busso D, Oñate-Alvarado MJ, Balboa E, Castro J, Lizama C, Morales G, Vargas S, Härtel S, Moreno RD, Zanlungo S, (2014), Spermatozoa from mice deficient in Niemann-Pick disease type C2 (NPC2) protein have defective cholesterol content and reduced in vitro fertilising ability., Reproduction, fertility, and development.
		Sanmartín CD, Paula Lima AC, Garcia A, Barattinni P, Hartel S, Núñez MT, Hidalgo C, (2014),Ryanodine receptor-mediated Ca(2+) release underlies iron induced mitochondrial fission and stimulates mitochondrial Ca(2+) uptake in primary hippocampal neurons. , Frontiers in molecular neuroscience
		Liempi A, Castillo C, Cerda M, Droggett D, Duaso J, Barahona K, Hernández A, Díaz-Luján C, Fretes R, Härtel S, Kemmerling U., (2014),Trypanosoma cruzi infectivity assessment in "in vitro" culture systems by automated cell counting., Actatropica
		Torres M, Matamala JM, Duran-Aniotz C, Cornejo VH, Foley A, Hetz C, (2014),ER stress signaling and neurodegeneration: At the intersection between Alzheimer's disease and Prion-related disorders., Virus research

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	Leyton L, Hagood JS, (2014), Thy-1 modulates neurological cell-cell and cell-matrix interactions through multiple molecular interactions, Advances in neurobiology
		Nieto R, Silva H, Kukuljan M, Rojas C, Armijo A, Nachar R, González A, Castañeda CP, Montes C, Aguirre C, Meneses J, Medina S, Salinas V. , (2014), Relation between BDNF Serum levels and matrices consensus cognitive battery performance in patients with schizofrenia, Official Journal of Biological Psychiatry(Supplement)
	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	39	88,64%	3	6,82%	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	2,27%	1	2,27%	0	0,00%	0	0,00%
Total of publications	40	90,91%	4	9,09%	0	0,00%	0	0,00%

Annex 4.- Organization of Scientific Events

Scope	Title	Type of Event	City	Country	Responsible Researcher
Internacional	Optics, Forces and Development: Scientific Meeting	Workshop	Santiago	Chile	Miguel Luis Concha Nordemann
Internacional	Small Brains Big Ideas	Workshop	Santiago	Chile	Jimena Sierralta Jara
Internacional	Visualisation and manipulation of signals and forces in developing tissues	Otro	Santiago	Chile	Miguel Luis Concha Nordemann
Internacional	NeuroSur: Workshop	Workshop	Rio de Janeiro	Brasil	Andrés Oscar Couve Correa
Nacional	Whole Genome Sequencing: innovation dream or privacy nightmare	Seminario	Santiago	Chile	Andrés Oscar Couve Correa
Nacional	Estructura y conectividad de neuronas dopaminérgicas y motoneuronas: una caracterización de neuronas a nivel poblacional e individual	Seminario	Santiago	Chile	Andrés Oscar Couve Correa
Nacional	Efectos periféricos del sistema eferente cortico-olivococlear	Seminario	Santiago	Chile	Pedro Esteban Maldonado Abogast
Nacional	Difusión en geometrias complejas	Seminario	Santiago	Chile	Andrés Oscar Couve Correa
Nacional	Control circadiano y hormonal de la conducta: lecciones de Drosophila	Seminario	Santiago	Chile	Jimena Sierralta Jara
Nacional	Regulación de los hemicanales formados por conexinas por radicales libres	Seminario	Santiago	Chile	Andrés Oscar Couve Correa
Nacional	Patient-derived stem cells as models for brain diseases	Seminario	Santiago	Chile	Lisette Leyton Campos
Nacional	Glial Cell Development and function in drosophila	Seminario	Santiago	Chile	Jimena Sierralta Jara
Nacional	Rol de la histamina cerebral durante los procesos de aprendizaje y memoria	Seminario	Santiago	Chile	Jose Luis Valdes Guerrero
Nacional	Sonic Hedgehog (shh) controls neural stem and precursor cell proliferation through neogenin1: implications in neurogenesis and cancer	Seminario	Santiago	Chile	Andrés Oscar Couve Correa
Nacional	Dysregulated translational control in Brain disorders	Seminario	RM	Chile	Claudio Andrés Hetz Flores
Nacional	Dysregulated translational control in Brain disorders	Seminario	RM	Chile	Claudio Andrés Hetz Flores
Nacional	Reward System and addiction: What dopamine does and doesn't do ?	Seminario	RM	Chile	Mario G.G. Herrera-Marschitz Muller
Nacional	4to Encuentro de integración básico clínica: Cognition in schizophrenia: From Neuromodulation to cognitive training	Seminario	RM	Chile	Hernán Silva Ibarra
Nacional	3er Encuentro de Integración básico clínica: Cell Function in aging and age related disease	Seminario	Santiago	Chile	Andrés Oscar Couve Correa
Nacional	Arquitectura molecular y modulación por subunidades auxiliares de un canal de K+ activado por Ca ²⁺ y voltaje	Seminario	Santiago	Chile	Andrés Oscar Couve Correa
Nacional	Proteostasis impairment in age-related disorders affecting the nervous system	Conferencia	RM	Chile	Claudio Andrés Hetz Flores
Nacional	Transportadores de Cloruro en enfermedades neuropsiquiátricas	Seminario	RM	Chile	Andrés Oscar Couve Correa
Nacional	Nitric oxide signaling in retinal bipolar cells	Seminario	RM	Chile	Andrés Oscar Couve Correa
Nacional	Targeting ER proteostasis in glioma	Seminario	RM	Chile	Claudio Andrés Hetz Flores

Annex 5.- Education and capacity building

5.1 Capacity Building inside BNI

Tutor	Undergraduated Students		Graduated Students						Total
			Master		Doctoral		Postdoctoral		
	F	M	F	M	F	M	F	M	
Miguel Luis Concha Nordemann	3	1	2	1	3	5	2	3	20
Pedro Esteban Maldonado Abogast	0	2	3	5	0	5	0	4	19
Lisette Leyton Campos	0	0	0	0	3	5	1	2	11
Lisette Leyton Campos Mario G.G. Herrera-Marschitz Muller	0	0	0	0	0	1	0	0	1
Jimena Sierralta Jara Andrés Oscar Couve Correa	0	0	0	1	0	1	0	0	2
Mario G.G. Herrera-Marschitz Muller	2	2	2	1	3	4	0	1	15
María Cecilia Hidalgo Tapia	0	0	2	2	1	1	1	1	8
Steffen Härtel Gründler	0	1	2	1	2	2	0	4	12
Claudio Andrés Hetz Flores	2	3	1	2	3	4	7	6	28
Jimena Sierralta Jara	0	1	1	0	1	1	0	0	4
Andrés Oscar Couve Correa	0	0	1	1	3	4	1	0	10
Manuel Kukuljan Padilla	0	0	0	0	0	1	1	0	2
Hernán Silva Ibarra	0	0	0	0	0	0	0	1	1
Total	7	10	14	14	19	34	13	22	133

Annex 5.2.- Short-term Traineeships of MSI students

Student Name	Institution	Country	Advisor	Project Description	Starting Date	Ending Date
Gonzalo Rivera	Cambridge University	England	Shrivas Chennu	Learning analysis tools on EEG data from patient in minimal consciousness	01-01-14	04-04-14
Cristian De Gregorio	University of Massachussets, Med School	USA	Jimena Sierralta, Andrés Couve	Learn and perform EM in Drosophila axons	10-10-14	20-12-14
Jonathan Wimmer	SISSA (Scuola Internazionale Superiore di Studi Avanzati)	Italy	Mathew Diamond	Learning analysis tools on data from the rats vibrissa system	03-08-14	28-09-14
Julio Torres	Harvard Medical School	USA	Alvaro Pascual-Leone	Learning analysis tools on data from TMS	23-06-14	04-07-14

Annex 6.- Networking and other collaborative work

6.1 Networking

Network Name	Network Scope	Network Participants				Institutions
		From the Center		External		
		Researchers	Postdocs / Students	Researchers	Postdocs / Students	
Network in cell and tissue morphodynamics between BNI-Chile, UCL/CDB-UK and IST-Austria	Internacional	3	0	0	0	
Neurosur	Internacional	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,

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
International Course Workshop "Optics, Forces & Development"	Science	To establish a scientific network between BNI and two international centres of excellence (UCL/CDB-UK and IST-Austria) with the aim of potentiating collaborative research and training of young scientists in the field of cell and tissue morphodynamics, using state-of-the-art in vivo imaging techniques and trans-disciplinary approaches that integrate biology, mathematics and informatics		16	2	10	10		Miguel Luis Concha Nordemann. Steffen Härtel Gründler.
Maysinger Dusica	Scientific collaboration	Nanoparticles of PARP siRNA as therapeutics tool for model of perinatal asphyxia	Department of Pharmacology, McGill University, Montreal - Canada	1	1	1	1	Thesis & Research Stay	Mario G.G. Herrera-Marschitz

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
Gaetano Di Chiara	Scientific collaboration	Dopamine modulation of addiction	University of Cagliari, Cagliari-Italy	1	0	1	0	Publications, Experiments	Mario G.G. Herrera-Marschitz Muller.
Tomas Hokfeltd	Scientific collaboration	Perinatal asphyxia, Dopamine innervation of neurogenic niches (hippocampus and subventricular area), and secretogone pathways	Karolinska Institutet, Stockholm-Sweden	1	0	1	1	Publications	Mario G.G. Herrera-Marschitz Muller.
Marcelo Kogan	Scientific collaboration	Nanoparticles of PARP siRNA as therapeutic tool for model of perinatal asphyxia	Chemical and Pharmaceutical Sciences Faculty, University of Chile	1	1	1	1	Thesis	Mario G.G. Herrera-Marschitz Muller.
Peter Gebicke-Haerter	Scientific collaboration	Perinatal asphyxia and epigenetics	Institute of Health, Manheinn, Germany	1	0	1	0	Publications, Experiments	Mario G.G. Herrera-Marschitz Muller
International Course: Small Brains, Big Ideas	Science and outreach	This is a theoretical and practical international course that trained latinamerican graduated students in several invertebrate models. The course had 25 students 19 of them international including students from Colombia, , Argentina and Brazil. 8 invited professor from UK, USA and Argentina together with 5 chilean professors gave lectures and directed the laboratories assisted by six TAs from US, and Chile. The course will be repeated every other year.	Centro Interdisciplinario de Neurociencia de Valparaíso (CINV), UMASS medical School, IBRO, CONICYT	1	5	14	32	10 lectures, 8 practical sessions, 14 scientific Conferences, 1 outreach conferences	Hernán Silva Ibarra.
Primer Encuentro Científico BioMed-HPC 2014	Conectividad	Conocer proyectos de investigación, I & D, y educación vigentes que requieren el uso de HPC 2014 Definir estrategias de colaboración y futuros proyectos entre los miembros de U-Redes BioMed-HPC Definir estrategias de capacitación, cursos y simposios de U-Redes BioMed-HPC	REUNA-STI-GOCCHI-CMM-OMICS-ICBM-ESP-CITC-NLHPC-BNI-FOUCH-CCTV / Internacionales: Instituto Pasteur Brow University y GIGA	1	4	40		40, Scientific conference	Steffen Härtel Gründler.
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		1			Claudio Andrés Hetz Flores.
Assist with all aspects of data acquisition, processing and analysis of EEG	Scientific collaboration	Technical support of the project	Department of Psychiatry, Columbia University	1				1, Fondecyt 2014	

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
La matrix y otras películas sobre el cerebro y realidad virtual: ciencia o ficción?	Conferencia	Nacional		13-08-14	Chile	Metropolitana de Santiago		100	1	Pedro Esteban Maldonado Abogast.	
Discursos Científicos: Explorando mundos ocultos para encontrar nuevos medicamentos	Conferencia	Nacional	Estudiantes Secundarios Estudiantes Universitarios	02-10-14	Chile	Metropolitana de Santiago		200	1	Andrés Oscar Couve Correa.	Andres Couve
Reunión anual Iniciativa Científica Milenio	Foro	Nacional	Servicio Público	05-12-14	Chile	Metropolitana de Santiago		61	1	Andrés Oscar Couve Correa. Claudio Andrés Hetz Flores.	Andres Couve, Claudio Hetz
Mentes Transformadoras	Seminario	Internacional		06-01-14	Chile	Metropolitana de Santiago		750		Lisette Leyton Campos. Miguel Luis Concha Nordemann. Steffen Härtel Gründler. Claudio Andrés Hetz Flores. Andrés Oscar Couve Correa. Jimena Sierralta Jara. María Cecilia Hidalgo Tapia. Pedro Esteban Maldonado Abogast. Mario G.G. Herrera-Marschitz Muller. Manuel Kukuljan Padilla.	Andres Couve

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
Science to business	Workshop	International	Industrias / Servicios Servicio Público	07-01-14	Chile	Metropolitana de Santiago		60	1	Miguel Luis Concha Nordemann. Steffen Härtel Gründler. Claudio Andrés Hetz Flores. Andrés Oscar Couve Correa. Manuel Kukuljan Padilla. Jimena Sierralta Jara. Pedro Esteban Maldonado Abogast. Mario G.G. Herrera-Marschitz Muller.	Andres Couve
Ciclo de charlas de verano EDV: Neurociencia, astronomía e Internet	Conferencia	Nacional	Estudiantes Secundarios Estudiantes Universitarios	08-01-14	Chile	Metropolitana de Santiago		60	1	Claudio Andrés Hetz Flores.	Claudio Hetz
Campamento científico KIMLU	Conferencia	Nacional	Estudiantes Universitarios Estudiantes Secundarios	15-01-14	Chile	Valparaíso		40	1	Andrés Oscar Couve Correa.	Andres Couve
Seminarios del CINV	Conferencia	Nacional	Estudiantes Universitarios	26-03-14	Chile	Valparaíso		100	1	Jimena Sierralta Jara.	Jimena Sierralta
Dendros 2.0	Conferencia	Nacional	Estudiantes Universitarios Estudiantes Secundarios	16-04-14	Chile	Metropolitana de Santiago		200	1	Andrés Oscar Couve Correa.	Andres Couve
The endoplasmic reticulum and protein trafficking in dendrites and axons	Conferencia	Nacional	Estudiantes Universitarios	16-04-14	Chile	Metropolitana de Santiago		40	1	Andrés Oscar Couve Correa.	Andres Couve

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
Discursos Científicos: Open Lecture: El Origen de la Forma Animal en la Evolución y Desarrollo	Conferencia	Nacional	Estudiantes Universitarios Estudiantes Secundarios	15-05-14	Chile	Metropolitana de Santiago		400	1	Miguel Luis Concha Nordemann.	Miguel Concha
"El cerebro y los misterios de la percepción"	Conferencia	International	Estudiantes Secundarios	19-06-14	Chile	Metropolitana de Santiago		60	1	Pedro Esteban Maldonado Abogast.	Pedro Maldonado
Seminario de educación científica	Exhibición	Nacional	Estudiantes Universitarios	07-08-14	Chile	Metropolitana de Santiago		120	1	Andrés Oscar Couve Correa.	Andres Couve
¿Están las nuevas tecnologías cambiando el cerebro?	Conferencia	Nacional	Estudiantes Universitarios Estudiantes Secundarios	25-07-14	Chile	Metropolitana de Santiago		100	1	Jimena Sierralta Jara.	Jimena Sierralta
Foro Santiago High Tech: Neuronas espejo: expresión de lo colectivo	Seminario	Nacional		28-08-14	Chile	Metropolitana de Santiago		40	1	Pedro Esteban Maldonado Abogast.	Pedro Maldonado
El cerebro y el lenguaje	Conferencia	Nacional	Estudiantes Universitarios Estudiantes Secundarios Comunidad en General	15-10-14	Chile	Metropolitana de Santiago		30		Pedro Esteban Maldonado Abogast.	Pedro Maldonado
¿Como vemos lo que vemos? la ciencia de los sentidos"	Conferencia	Nacional	Estudiantes Secundarios	25-08-14	Chile	Metropolitana de Santiago		300	1	Pedro Esteban Maldonado Abogast.	Pedro Maldonado
Lanzamiento cápsulas axón y charla El cerebro una estructura en constante cambio	Conferencia	Nacional	Estudiantes Universitarios Estudiantes Secundarios	28-08-14	Chile	Metropolitana de Santiago		120	1	Andrés Oscar Couve Correa.	Andres Couve

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
Bienestar en animales de laboratorios	Conferencia	Nacional	Estudiantes Secundarios	04-09-14	Chile	Metropolitana de Santiago		80	1	Manuel Kukuljan Padilla.	Manuel Kukuljan
Explorando mundos ocultos para descubrir nuevos medicamento	Conferencia	Nacional	Estudiantes Universitarios	02-10-14	Chile	Metropolitana de Santiago		80	1	Andrés Oscar Couve Correa.	Andres Couve
Discursos Científicos: Entendiendo enfermedades neurológicas con ayuda de las moscas	Conferencia	Internacional	Estudiantes Universitarios Estudiantes Secundarios Comunidad en General	06-10-14	Chile	Metropolitana de Santiago		200		Jimena Sierralta Jara.	Jimena Sierralta
"Innovar y Emprender en Salud: Una oportunidad emergente"	Foro	Nacional	Industrias / Servicios Servicio Público	13-11-14	Chile	Metropolitana de Santiago		100	1	Andrés Oscar Couve Correa.	Andres Couve
Visita guiada por los laboratorios BNI	Exhibición	Nacional		13-11-14	Chile	Metropolitana de Santiago		25	1	Claudio Andrés Hetz Flores. Pedro Esteban Maldonado Abogast.	Claudio Hetz, Pedro Maldonado
XV Congreso Nacional de Explora Conicyt	Workshop	Nacional	Estudiantes Secundarios	27-11-14	Chile	Metropolitana de Santiago		300	1	Andrés Oscar Couve Correa.	Andres Couve
Ciencia de frontera y oportunidades de negocios	Foro	Nacional	Industrias / Servicios Servicio Público	11-12-14	Chile	Metropolitana de Santiago		60	1	Andrés Oscar Couve Correa. Steffen Härtel Gründler. Claudio Andrés Hetz Flores.	Andres Couve
Getting the Public to love science	Conferencia	International	Estudiantes Universitarios	03-10-14	Chile	Metropolitana de Santiago		80	1	Andrés Oscar Couve Correa.	Andres Couve
Domo Cerebro	Exhibición	Nacional	Estudiantes Secundarios Estudiantes Universitarios Comunidad en General	06-10-14	Chile	Metropolitana de Santiago		3000	1	Andrés Oscar Couve Correa.	Andres Couve

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
Registro audiovisual simposio Cellmorphodynamics	Otro	International	Estudiantes Universitarios	12-05-14	Chile	Metropolitana de Santiago		100		Miguel Luis Concha Nordemann.	
Documental Mentes Transformadoras	Otro	International	Comunidad en General	31-12-14	Chile	Metropolitana de Santiago		1000		Andrés Oscar Couve Correa.	

7.2.- Products of outreach

Name of Product	Product Objective	Target Public	Type of Product	Scope
Data Base	Considerando los intereses de nuestras actividades, se creo una importante base de datos que permite enviar la información del BNI de manera dirigida. La base de datos contiene contactos del sector privado y público. Además de líderes científicos y políticos, todos actores que pueden aportar a la construcción de la difusión de la cultura científica.	Comunidad en General.	Otro	Internacional
Segunda temporada Dendros	Se realizó el segundo capítulo del comic interactivo Dendros, un viaje por el cerebro, que estuvo dedicado a Parkinson. Además se agregaron pestañas informativas en los capítulos que permiten la interacción con amigos virtuales y redes sociales.	Estudiantes Secundarios. Comunidad en General.	Otro	Nacional
Historieta impresa Dendros, un viaje por el cerebro	Se imprimieron 2000 copias del comics "Dendros un viaje por el cerebro", las que fueron repartidas a los estudiantes en charlas, ferias científicas y actividades de extensión. Todo con el objetivo de entregar material entretenido a los jóvenes y puedan encantarse con la ciencia	Estudiantes Secundarios. Comunidad en General.	Otro	Nacional
Domo cerebro y carpa exterior	En el marco de la Feria de la tecnología de Conicyt, se presentó el Domo – cerebro, que expuso la sala de videojuegos “Dendros: un viaje por el cerebro” en la Plaza de la Constitución, ofreciendo una inolvidable experiencia que espera motivar a los asistentes con la neurociencia y la tecnología. El domo cerebro, cuenta con una capa externa que fue pintada por un importante grafitero, que simula el cerebro.	Estudiantes Secundarios. Comunidad en General.	Otro	Nacional
Cápsulas educativas DENDROS	Las capsulas educativas buscan responder preguntas sobre el sistema nervioso. Los actores son Kay y Reymi, los que en formato de dibujo animado abordan el tema del Parkinson y memoria. Un proyecto piloto dedicado a estudiantes de educación media. Las capsulas puedes encontrarlas en el canal Youtube Dendros TV	Estudiantes Secundarios. Comunidad en General.	Guión de TV o Película	Nacional
Newsletter	Con el objetivo de divulgar lo que se está haciendo dentro del BNI, se crearon newsletter bimensuales, donde se informaron las principales noticias, actividades e investigaciones de los investigadores asociados. El newsletter fue subido a las web y también distribuido por mail a más de mil receptores	Estudiantes Universitarios. Comunidad en General.	Otro	Nacional

7.3.- Articles and Interviews

Type of Media and Scope	Local / Regional		National		International		Total
	N° Interviews	N° Articles	N° Interviews	N° Articles	N° Interviews	N° Articles	
Written	0	0	1	31	0	1	33
Internet	0	0	1	19	0	1	21
Audiovisual	0	0	16	2	0	1	19
Total	0	0	18	52	0	3	73

Annex 8.- Connections with other sectors:

Activity	Type of Connection	Type of Activity	Institution Country	Agent Type	Economic Sector
Foro: Ciencia de Frontera y oportunidades de negocios	Instituciones Públicas o Privadas	Otra	Chile	Instituciones Públicas o Privadas	Actividades empresariales
3er Encuentro de Integración básico clínica: Cell Function in aging and age related disease	Instituciones Públicas o Privadas	Otra	Chile	Instituciones Públicas o Privadas	Medicina y salud humana
The UPRosome: novel regulatory checkpoints and physiological outputs.	Instituciones Públicas o Privadas	Desarrollo de Proyecto	Chile	Instituciones Públicas o Privadas	Otro
Targeting the ER stress sensor PERK for the treatment of Parkinson's disease	Otra	Desarrollo de Estudio	Estados Unidos de America	Otra	Medicina y salud humana
A role of ER stress in wild-type SOD1 misfolding: A model for sALS?	Otra	Desarrollo de Proyecto	Estados Unidos de America	Otra	Medicina y salud humana
Defining the function of protein Disulfide Isomerases in ALS	Otra	Desarrollo de Proyecto	Estados Unidos de America	Otra	Medicina y salud humana
Defining the role of the Unfolded Protein Response in Alzheimer's Disease	Otra	Desarrollo de Proyecto	Estados Unidos de America	Otra	Medicina y salud humana
Identification of neuroprotective compounds from Chilean endogenous plants	Instituciones Públicas o Privadas	Desarrollo de Proyecto	Chile	Instituciones Públicas o Privadas	Otro
Gene therapy strategy to target the unfolded protein response in ALS	Instituciones Públicas o Privadas	Desarrollo de Proyecto	Estados Unidos de America	Instituciones Públicas o Privadas	Otro
Functional study of the IRE1a interactome in cell migration and cancer.	Instituciones Públicas o Privadas	Desarrollo de Proyecto	Francia	Instituciones Públicas o Privadas	Otro
Foro: Science to business	Instituciones Públicas o Privadas	Otra	Chile	Instituciones Públicas o Privadas	Actividades empresariales
UPRplus: A novel gene therapy to treat Parkinson's disease	Instituciones Públicas o Privadas	Desarrollo de Proyecto	Chile	Instituciones Públicas o Privadas	Otro
Neuronal network initiative: Understanding selective neuronal vulnerability in neurodegenerative diseases.	Instituciones Públicas o Privadas	Desarrollo de Proyecto	Chile	Instituciones Públicas o Privadas	Otro

9.1 Total incomes:

Funds	Accumulated incomes to last year [S]	2014 Incomes		Total incomes to 2014 [S]
		Amount [S]	Percentage of resources used by the Center [%]	
MSI	897.821.000	2.451.618.021	100	3.349.439.021
FONDEF	453.581.066	991.332.000	10	1.444.913.066
FONDECYT	667.470.000	2.036.227.500	50	2.703.697.500
CONICYT - Anillo	54.337.500	-	50	54.337.500
CONICYT - Otro	149.617.000	60.000.000	50	209.617.000
CORFO - Otro	47.159.449	93.000.000	100	140.159.449
FONDAP	50.000.000	700.000.000	10	750.000.000
Fundación para Investigación	21.910.000	-	50	21.910.000
Otro	249.968.655	27.500.000	30	277.468.655
Otro - U-REDES	212.199.021	489.855.000	10	702.054.021
Otros Fondos Internacionales	253.708.106	507.398.000	50	761.106.106
TOTAL	3.057.771.797	7.356.930.521		10.414.702.318

9.2 Outcome structure

Item	Accumulated expenses to last year [\$]	2014 Expenses [\$]				Total expenses to 2014 [\$]	%
		Operative	Networks	Outreach	Total		
Honoraria researchers and research personnel	812.592.765	352.405.061	-	-	352.405.061	1.164.997.826	46,4
Tickets and travel expenses	119.717.938	43.583.239	34.096.504	15.580.412	93.260.155	212.978.093	8,5
Materials and supplies	249.949.378	96.061.489	-	6.712.036	102.773.525	352.722.903	14,1
Goods and equipment	266.420.193	77.527.384	-	9.999	77.627.374	344.047.567	13,7
Infrastructure	56.000.000	9.792.857	-	-	9.792.857	65.792.857	2,6
Administrative expenses	106.399.497	48.896.126	-	-	48.896.126	155.295.623	6,2
Publications and subscriptions	1.812.890	2.279.308	-	3.647.827	5.927.135	7.740.025	0,3
Consultancies	34.795.114	21.000.000	-	13.531.000	34.531.000	69.326.114	2,8
Overhead	21.556.739	31.615.861	-	-	31.615.861	53.172.600	2,1
Others	79.063.761	4.349.086	-	-	4.349.086	83.412.847	3,3
Total	1.748.308.275	687.510.411	34.096.504	39.481.274	761.178.180	2.509.486.455	100,0

9.3 Financial accounting

ITEM	2014 [\$]				TOTAL TO 2014
	Operative	Networking	Outreach	Total [\$]	
Income	802.621.000	35.000.000	60.000.000	897.621.000	1.795.242.000
Outcome	687.510.411	34.096.504	39.481.274	761.088.189	1.522.176.378
Annual balance	115.110.589	903.496	20.518.726	136.532.811	273.065.622