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Address	Independencia 1027, Independencia
Telephone(s)	56 (2) 978-6306
Fax	
Web Page	www.bni.cl
Host Institution(s)	Universidad de Chile
Contact Information	
Scientific Contact	Andrés Couve Correa, principal Investigator
Electronic Address	bni@med.uchile.cl

Institute Principal Researcher Name	*Institute Deputy Principal Researcher Name*
Andrés Couve Correa	Claudio Hetz Flores
Principal Researcher's Signature	*Deputy Principal Researcher's Signature*

Index

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. Consequently, the discipline of Neuroscience has expanded worldwide and diversified dramatically in recent decades. Yet the **integration of the structural and functional organization of the brain in physiology and disease continues to remain beyond our grasp.** In Chile thousands of people suffer from neurological and psychiatric disorders with no satisfactory treatment. In addition, the country has experienced a sustained growth in the aged population with concomitant increases in major neurodegenerative and cognitive diseases, but the capacity to conduct clinical brain research sustained by cutting-edge basic Neuroscience is missing.

Tackling this complex issue requires a modern approach grounded on an integrated transdisciplinary strategy. The Biomedical Neuroscience Institute (BNI) constitutes a broad umbrella that brings together a critical mass of leading basic and clinical neuroscientists along with mathematicians under a suitable infrastructure to accomplish world-class scientific research and training. BNI provides a unified vision to explore the dynamic structural and functional organization of the brain under normal physiology and the mechanisms underlying disease from whole organisms to cells. Four particular qualities place BNI in a pivotal position to lead Neuroscience research in Chile and the region: (i) an extensive track record of individual and collaborative research initiatives in Neuroscience, (ii) the association to major basic-clinical centers of national and international relevance, (iii) a vast training potential in health science undergraduate plus Master, PhD in Biomedical Sciences, MD-PhD and MD Specialist programs, and (iv) a young body of researchers coexisting in a single campus capable of executing the long terms goals of the initiative.

BNI operates under three guiding principles: (i) transdisciplinary research with members contributing with complementary expertise in cell and molecular neuroscience, neural development, morphogenesis, neuropathology, behavior, neural systems, clinical research, pharmacology, genetics, and a trademark of productive interactions between Neuroscience and applied mathematics, (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 guaranteeing the transfer of scientific and medical impact to the community. Research at BNI is organized around interconnected thematic platforms. Five platforms explore the relationship between structure and function of the brain, following a bottom up, multi-scale approach. Two transversal platforms integrate the strategy by conducting research and development in applied mathematics/biomedical informatics, and in neuropathology/pharmacological target validation. A clinical research platform strengthens the needed bridge between basic and medical research and promotes the translation of knowledge to and from the clinic. International networks contribute to position the initiative globally.

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 at the interface of basic neuroscience, neuropathology, and quantitative biology, (iii) produce high-standard clinical research and transfer the impact of its research to society by discovering novel diagnostic and therapeutic approaches to improve the life quality of patients with neurological and psychiatric disorders, and (iv) become a resource center for specialized clinical practitioners and the general public.

The long-term goals of BNI align with established national health priorities and with the ICM funding philosophy, which ranks excellence in scientific research and social impact above considerations of direct economic productivity.

1.2 Resumen Ejecutivo

Entender la función del sistema nervioso constituye un reto amplio y central de la biología y la medicina de hoy. En consecuencia, la disciplina de la neurociencia se ha ampliado y diversificado dramáticamente en todo el mundo en las últimas décadas. Sin embargo, **la integración estructural y funcional del cerebro en la fisiología y la enfermedad sigue estando fuera de nuestro alcance**. En Chile miles de personas sufren de trastornos neurológicos y psiquiátricos sin tratamientos satisfactorios. Además, el país ha experimentado un crecimiento sostenido de la población envejecida con un incremento concomitante de las principales enfermedades neurodegenerativas y cognitivas, sin la capacidad de realizar investigación clínica del cerebro apoyada en Neurociencia básica de frontera. La resolución de este problema complejo requiere un enfoque moderno y una estrategia interdisciplinaria integrada. El Instituto de Neurociencia Biomédica (BNI) constituye un paraguas amplio que reúne a una masa crítica de neurocientíficos básicos y clínicos, además de matemáticos, en torno a una infraestructura adecuada para llevar a cabo investigación científica de primera clase y formar nuevos investigadores. El BNI proporciona una visión unificada para explorar la organización dinámica estructural y funcional del cerebro en la fisiología y los mecanismos que subyacen a las enfermedades que lo afectan, tanto a nivel de organismos completos como a nivel celular. Cuatro características sitúan al BNI en una posición central para dirigir la investigación en neurociencia en Chile y la región: (i) una amplia trayectoria de las iniciativas individuales de investigación y de colaboración en Neurociencia, (ii) asociación con los principales centros básico-clínicos a nivel nacional e internacional, (iii) potencial de formación extensa en pregrado en Ciencias de la Salud, Maestría, Doctorado en Ciencias Biomédicas, Programas de Especialidades Médicas y MD-PhD y (iv) un cuerpo joven de investigadores capaz de ejecutar los objetivos de largo plazo de la iniciativa.

El BNI opera bajo tres principios rectores: (i) la investigación transdisciplinaria a distintos niveles: la neurociencia celular y molecular, el desarrollo neuronal, la morfogénesis, la neuropatología, la conducta y los sistemas neuronales, la investigación clínica, la farmacología, la genética y la interacción entre Neurociencia y matemáticas aplicadas, una asociación inédita en Chile, (ii) un enfoque multi-escala para estudiar la función desde los genes y las moléculas a la conducta en modelos animales complementarios, y (iii) una estrategia biomédica integrada para promover la transferencia de las contribuciones científicas y médicas de alto nivel a la comunidad. La investigación se organiza en torno a cinco plataformas interconectadas para explorar la relación entre la estructura y función del cerebro. Dos plataformas transversales integran esta estrategia mediante la investigación y desarrollo en matemática aplicada e informática biomédica, y neuropatología/validación de blancos farmacológicos. Una plataforma de investigación clínica provee el puente necesario entre la investigación básica y médica, y promueve la extensión del conocimiento a la clínica. Redes internacionales posicionan la iniciativa a nivel mundial.

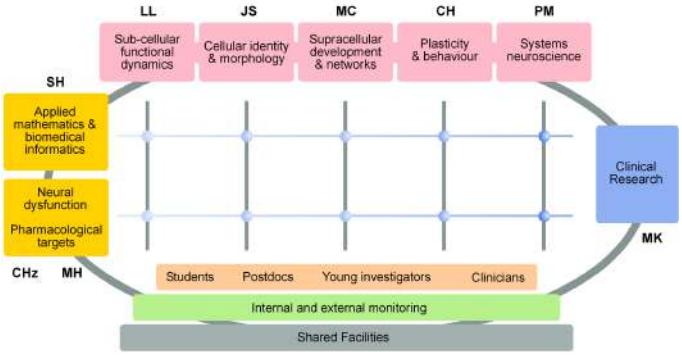
El BNI tiene por objetivos: (i) establecer un centro de referencia internacional para la exploración de la "estructura y función del cerebro tanto en condiciones fisiológicas como patológicas", (ii) capacitar y organizar una nueva generación de investigadores y clínicos en un entorno transdisciplinario único, (iii) producir investigación clínica de alto nivel y transferir las repercusiones de su investigación a la sociedad mediante el descubrimiento de nuevos enfoques diagnósticos y terapéuticos para mejorar la calidad de vida de los pacientes neurológicos o con trastornos psiquiátricos, y (iv) convertirse en un centro de recursos para los profesionales clínicos especializados y el público general. Los objetivos de largo plazo del BNI están en línea con las prioridades nacionales en salud y con la filosofía de financiamiento de la ICM, que sitúa la excelencia en investigación científica y el impacto social por encima de consideraciones directas de productividad económica.

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 eight interconnected thematic platforms. Five 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) (pink). Two transversal platforms foster the collaborative strategy conducting research and development in the fields of applied mathematics and biomedical informatics, and diseases affecting the nervous system and pharmacological target validation (yellow). A clinical research platform strengthens the bridge between basic and medical research, and promotes the translation of knowledge to and from the clinic (blue). BNI's research is supported by students, postdocs, young investigators and young clinicians.



b) Research Lines (RLs):

RL1. Sub-cellular functional dynamics: Neuronal differentiation requires the secretory pathway and the cytoskeleton within neurons and glial cells. 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 used 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 evaluating the role of disease-related genes in common cellular processes leading to neuronal connectivity and synaptic function. The goal is to develop knowledge, expertise and technological approaches to understand the mechanisms by which disease-related genes affect common molecular/cellular/physiological processes involved in neuropathological conditions.

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 Research Teams:

BNI consists of one Principal and nine Associate Investigators, all professors at the FMed, U of Chile, with complementing backgrounds and expertise: A. Couve, PhD, cell/molecular biology of the mammalian neuron; C. Hetz, PhD, cell/molecular biology, genetic manipulation in mice, and neurodegeneration; M. Concha, MD-PhD, neuro-developmental genetics, cellular morphogenesis in zebrafish; S. Härtel, PhD, image processing, biomedical informatics, confocal microscopy, and pattern formation; M. Herrera-Marschitz, MDSci-PhD, neuropharmacology, metabolic insults and neurodegeneration; M. Kukuljan, MD-PhD, neural development and cell physiology; L. Leyton, PhD, cell/molecular biology of neuron-astrocyte communication; P. Maldonado, PhD, neural mechanisms of visual perception and human cognition; J. Sierralta, PhD, cell biology, synaptic physiology in *Drosophila*; H. Silva, MD, psychiatry and clinical research. Additionally, C. Hidalgo and 4 other Adjunct Investigators, 1 Senior Investigator, 5 Young Investigators, 16 postdocs, 51 PhD, 17 Master, 14 undergraduate students, and 51 technicians constitute BNI. Specific strategies to foster interactions include: (i) definition of research line leaders that coordinate efforts and funds within and between 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 between Neuroscience, applied mathematics and clinical research, (v) weekly internal 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. Interaction between young and experienced investigators contributes to strengthen the team's vigor, and the direction by two of the youngest members of the team demonstrates the commitment of the entire team to new ideas and a modern scientific culture. ***See Annex 1.***

3. Scientific and Technological Research

a) Current Status of Research Lines:

Each research 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**). ***See Annex 2.***

RL1. Sub-cellular functional dynamics: Studies completed during this period have partially addressed all three specific aims of this line of research. Key findings obtained are summarized below according to the original specific aims. i) The endoplasmic reticulum (ER) is a highly dynamic network distributed throughout neuronal processes. The morpho-functional organization of this network and the consequences of altered organelle structure in protein trafficking and in human disease have been studied. Recent results have put forward the notion that non-canonical ER trafficking may play an important role in neuronal function and dysfunction (AC/SH). Altered ER functions lead to "ER stress", which triggers adaptive cell responses mediated by proteins like XBP1. Unexpected findings indicate that XBP1 protein deficiency *in vitro* and *in vivo* increases autophagy that protects against Huntington disease. Thus, a gene therapy to target the XBP1 in Huntington *in vivo* has been developed (CHz). The mechanisms underlying the regulation of autophagy were further investigated. BAX inhibitor-1 was described as a new component that connects the response to stress with autophagy (CHz/JS). Moreover, a biological function for a newly discovered protein (GRINA/TMBIM3) in the nervous system as a key stress modulator has been reported (CHz/MC/JS). ii) The study of the role of recently identified proteins in the functional and structural organization of the cytoskeleton has been implemented using genome-wide illumina-microarrays and further qRT-PCR of intra and extra synaptic structural elements in brain samples from patients suffering from schizophrenia. Region specific down regulation of gene products associated to presynaptic vesicles, cytoskeletal proteins, and extracellular matrix proteins have been found (MH). Furthermore, astrocyte-dependent changes in neuronal branching induced by perinatal asphyxia are studied by using primary cultures from asphyxia-exposed animals (MH/LL). iii) Findings on the spatio-temporal activation of signaling molecules downstream of cell adhesion receptors indicate that astrocyte adhesion and migration stimulated by the neuronal protein Thy-1 involve integrin receptor clustering, ATP release, P2X7R activation, calcium entry and activation of downstream effectos such as PKCα and the small GTPases RhoA and Rac1 (LL). Short term stimulation increases RhoA-GTP and cell adhesion; whereas, long-term stimulus results in Rac1 activation and cell migration (LL/SH)). *In vitro* studies with cell lines were extended to primary astrocytes, where these responses were fond to occur only under pro-inflammatory conditions found after injury (LL/MH). In neurons, Thy-1–integrin engagement stops axonal growth and induces retraction of existing processes by signaling mechanisms involving Thy-1 clustering and inhibition of Src (LL/CHz/SH). A consorcium was created between PIs to acquire a compact Olympus FV10i confocal microscope to perform low-to-high maginification analysis of histological sections and live cell imaging of adhesive and migratory process in 4D withtemperature and CO_2 control.

The notion that non-canonical ER trafficking may play a role in neuronal function/dysfunction has been published, *Valenzuela et al., 2011 Mol Cell Neurosci.* Autophagy increased by XBP1 deficiency, its control mechanisms as well as a gene therapy to target the XBP1 in Huntington disease were published in *Vidal et al., 2012 Human Mol Gen, Zuleta et al., 2012 BBRC* and *Castillo et al., 2011 EMBO J.* The function of GRINA in the nervous system was reported in *Rojas et al., 2012 Cell Death Diff.* Region specific down regulation of different gene products of synaptic

elements in schizophrenia brains was published in *Schmitt et al., 2012 Eur Arch Psych Clin Neurosc.* Signaling mechanisms in astrocyte adhesion/migration and neuronal processes growth/retraction have been reported in *Henríquez et al., 2011 J Cell Sci and Herrera-Molina et al., 2012 PLoS ONE*. International recognition of the BNI-PIs expertise are underscored by invitations to write reviews for *Trends in Cell Biol, Nature Rev Mol Cell Biol, Trends in Biochem Sci,* and the edition of a special issue of *Curr Opin Cell Biol.* BNI investigators have been invited to participate in various congresses, meetings and symposia Among them we highlight the *XXV Annual Meeting of the Chilean Society for Cell Biology, Society of Biochemistry and Molecular Biology* and international presentations at *Annual Meeting of the American Society for Cell Biology, Gordon Conference, Key Stone Meeting, FASEB Meeting* in the US and *Cell Signaling Mechanisms* in Merida, México and the *International Neuroscience Winter Conference* in Solden, Austria.

We have purchased an Olympus FV-1000 spectral confocal microscope with a SIM module for simultaneous laser stimulation and an anti-drift mechanism specially designed for live-cell imaging. This major equipment has been placed in a dedicated microscopy suite at the Physiology and Biophysics Program at the FMed. The room was refurbished with a specially designed electrical configuration to protect all microscope components. This state-of-the-art confocal microscope is the first shared equipment of BNI's microscopy facility. Access is guaranteed to all BNI scientists and serves multiple research lines. As stated in our original proposal modern equipment and expertise will contribute to position BNI as a leading center for live-cell imaging and *in vivo* genetic-morphogenetic approaches to reveal the microscopic mechanisms that generate form, structure, and functional organization in the central nervous system.

RL2. Cellular identity and morphology: The central question of how gene expression determines morpho-functional features throughout the development and the lifespan of neurons is being pursued in *Drosophila*, mice and zebrafish. For this research line, the acquisition of an Olympus FV-1000 confocal microscope has been crucial since it is an essential tool that provides the quality and accuracy needed for this type of research. During the period we have made progress in: i) the study of the gene Marlin-1, which we have been able to demonstrate as a critical determinant of neuronal morphology and migration in the cerebral cortex. Specifically, Marlin-1 is required for the establishment of neuronal morphology and the maintenance of an intact Golgi apparatus, is necessary to ensure the availability of a tubulin based molecular motor, namely Kif5, and its depletion results in abnormal pyramidal cortical neuron migration in embryonic mice (AC/MK). ii) In the same system we have demonstrated the importance of the chromatin remodeling protein CoREST in the behavior of progenitors and newly born neurons, and initiated work aimed at understanding the relationship between signal transduction pathways and epigenetic regulation in this system (MK). iii) We have continued the study of CTIP1, a transcription factor that was originally identified in a *Drosophila* screen for genes involved in neuronal morphogenesis. Our results are compatible with a role of CTIP1 in the specification of subclasses of projection neurons in the cerebral cortex (JS/MK). iv) In *Drosophila* we are currently investigating the target genes through which the transcription factor Hindsight affects axonal targeting and growth in the optic lobe (*Oliva and Sierralta, 2010 Dev Biol*). In addition, we are studying the role of MAGUK proteins in the formation, function and plasticity of the synapses by electrophysiology and microscopy. We have demonstrated that DLG proteins are essential for the efficiency of presynaptic neurotransmitter release.

The role of CoREST in neuronal migration has been published in *Cerebral Cortex,* one of the most important journals in the field, recognizing the quality and impact of the work produced at BNI labs (*Fuentes et al., 2011 Cereb Cortex*). The study on Marlin-1 involved two BNI labs and is currently under review (*Vidal et al., 2012 under revision*). Expertise in the field of the role of

MAGUKs in synapse led to an invitation to write a review (*Oliva et al., 2012 Dev Neurobiol*). Additionally, the results on CTIP1 have been presented as posters in an international meeting (*Cánovas et al., 2011 Society for Neuroscience Annual Meeting, Washington*). More recent results in CoREST have been presented as an oral presentation in a national meeting *(Kukuljan, 2011 Chilean Society for Cell Biology Annual Meeting*). The results on MAGUK proteins have been presented in one international meeting (*Astorga et al., 2011 CSHL-Neurobiology of Drosophila Meeting*) and in national meetings (*Molina and Sierralta, 2011 XXV Annual Meeting of the Chilean Society for Cell Biology; Chávez et al. 2011 Chilean Society for Neuroscience Annual Meeting*).

RL3. Supra-cellular development and circuits: This platform investigates the supra-cellular transformations of brain morphogenesis leading to the formation of multi-cellular aggregates such as nuclei and layers, and the migration of cells and axonal growth cones during the establishment of neuronal connectivity. During the first year, novel methodologies for 3D confocal visualization and analysis of neuronal morpho-topology in developing GFP-transgenic zebrafish were developed and applied in collaboration with the BNI-BioMat platform (see RL7). In addition, existing methodologies for reverse genetics (morpholino antisense gene knock down, mutant analysis) and cell labeling (*in vivo* electroporation, dye labeling) were consolidated. Finally, staff to maintain adult fish was hired to established a fish facility that aims to provide living specimens for experimental manipulation of this and other platforms. Main results obtained in the collaborative projects during the first year of BNI included:

(i) Asymmetric migration of the parapineal nucleus and the role of Fgf and Nodal signaling (MC/SH): the first event of asymmetry in the zebrafish brain involves a process of nucleogenesis, in which precursors of the parapineal nucleus evaginate asymmetrically from the roof plate to form a 3D rosette-like structure located on the left side of the brain. Fgf is necessary for evagination and nucleogenesis while Nodal imposes a left-sided bias in the evagination process.

(ii) Role of chemokine and robo-slit signaling in establishment of habenular-IPN connectivity (MC/CH): Cxcr4b/Cxcl12-mediated signaling is required for the exit of axons from the habenula to the IPN, through de-sensitising axonal repulsion mediated by robo3b-slit signaling. In the absence of Cxcr4b/Cxcl12 signaling, habenular axons project ectopically, and this phenotype is rescued by abrogation of robo3b in habenular neurons.

(iii) Role of tensile and migratory forces in shaping supra-cellular embryonic structures (MC/SH): opposite mechanical and migratory forces aligned along the anterior-posterior axis establish AP polarity in the laterality organ in zebrafish. Disruption of these forces affects AP polarity and generates misshaped structures.

(iv) Role of differential adhesion and contact inhibition in cell sorting during early morphogenesis (MC/SH): a combination of differential cell adhesion mediated by E-cadherin, and cell contact inhibition of locomotion dependent on N-cadherin regulates the sorting of cells in the early process of epiboly in the fish embryo.

(v) Subnuclear organization of the human habenular complex (MC): the human habenular complex is organized into medial and lateral nuclei as in other mammals, and into several subnuclei that appear well-conserved for the medial subnucleus and divergent in the lateral subnucleus.

The latter appears to result from a relative increase of afferents to the lateral habenula in humans. Projects were in active development during the first year of BNI and project (v) generated a manuscript (*Díaz et al., 2011, J Comp Neurol*). This manuscript is the first description of the habneular subnuclear organization in humans and thus is very timely in the context of recent papers associating the human habenula to the control of negative reward signals, and the association of

habenular disruption in severe depressive conditions. Projects (i) and (ii) are expected to give rise to manuscripts during the second year of BNI, while projects (iii) and (iv) in third year.

Results related to this platform were presented at the national level in the *XXV Annual Meeting of the Chilean Society for Cell Biology*, and at the *III School on Optics and Photonics, Concepción*. At the international level, presentations included the *12th International Conference on Systems Biology 2011*, the *2nd Joint Meeting of the Argentinian Biology Societies*, and the *26th European Cytoskeletal Forum Meeting. ACTIN-BASED MOTILITY: From Molecules to Model Organisms*.

RL4. Plasticity and behavior: The central objective of this research line, conformed by CH, AC and CHz together with their respective teams is to understand how genetic interactions and signaling pathways control long-lasting memories. During this period we have carried out studies on the role of ryanodine-receptor (RyR) calcium release channels on hippocampal long-term potentiation (LTP) and behaviour (contextual fear conditioning) (CH). Preliminary results revealed a complete inhibition of persistent (3 h) LTP induction (theta burst stimulation of Schaffer collateral fibres, fEPSP recorded in the CA1 region) in hippocampal slices preincubated with ryanodine at concentrations that suppress RyR activity. In parallel studies, we have shown that the hippocampal protein content of the RyR2 isoform increases significantly 6 h after a contextual fear conditioning protocol. Additionally, we have found that treatment of primary hippocampal cultures (rat) with non-lethal concentrations of soluble amyloid beta-peptide oligomers (AbOs) induces significant mitochondrial fragmentation that is prevented by NAC, an antioxidant agent that abolishes the stimulation of RyR-mediated calcium release induced by AβOs (*San Martín et al., 2012 Neurodegener Dis, in press*). These soluble oligomers also decrease the mRNA levels of the iron transporter DMT1 (non)-IRE, without affecting DMT1 (+)IRE, and inhibit non-transferrin bound iron uptake (*San Martín et al., 2012 Biometals, manuscript under revision*). An invited commentary in addressing the relevance of RyR2 redox regulation for cardiac function (and presumably for neuronal function, as proposed by us) was published (*Hidalgo and Donoso, 2011 Science*). The commented article published in Science (*Prosser et al., 2011 Science*) is highly relevant to this research line, in which we postulate that RyR redox regulation has a central role in synaptic plasticity. Importantly, the invited commentary for Science highlights the unquestionable recognition of CH as an international leader in her field, confirms that the expertise at BNI is world class, and provides global visibility to the institute.

During the reported period, we presented our work in several national and international meetings, including the *Gordon Conference on Calcium Signaling* and the *8th IBRO World Congress on Neuroscience*.

RL5. Systems Neuroscience: We have initiated a study to determine the neuronal mechanisms related to active sensing. In particular, we are focusing on the rat's vibrissa (whisker) system, recording the neuronal activity for sensory and motor areas to understand the interactions that occur between these areas during perceptual discrimination. We will record activity, both at the population and at the single cell levels from cortical sensory and motor areas simultaneously during the execution of a tactile discrimination task. This will be the first time both cortical areas are recorded simultaneously to explore neuronal interaction during a behavioral task. We will vary the difficulty of the task and examine how the sensory and motor neuronal networks behave as the animal copes with the perceptual challenge. For this project, we have recruited Daniel Rojas, a postdoc who successfully applied for a Fondecyt postdoctoral fellowship.

In addition, two BNI Associated Investigators (HS and PM) initiated a large study that combines basic and clinical aspects. Specifically we are searching for biometrics in patients with

schizophrenia. This pathology is a complex disease in which most of the cognitive activity of the brain is affected. The broad-spectrum of symptoms is thought to derive from a distributed impairment involving many cortical areas and its connectivity rather than a circumscribed deficit. In this project, we are studying a group of diagnosed patients in order to find behavioral, genetic, and electroencephalographic markers for this pathological condition. To this end we have purchased an electroencephalographic system (Biosemi) to record patients at BNI facilities. Acquisition of this shared equipment fulfills a long-term objective of BNI researchers, which was included in the institute's proposal. The study involves the development of a multi center collaborative network, including the Instituto Psiquiátrico Dr. José Horwitz, and two health centers associated to Universidad de Chile: Hospital del Salvador and Clínica Psiquiátrica. We have recruited José Ignacio Egaña MD-PhD, as a BNI-funded postdoctoral fellow to provide an integrated expertise in basic and clinical aspects of the project (see also RL8). Eight abstracts corresponding to preliminary work in the area were presented during 2011.

RL6. Neural dysfunction and pharmacological targets: This transversal platform fosters an *in vivo* genetic/pharmacological/functional approach centered on evaluating the role of disease-related genes in common cellular processes leading to neuronal connectivity and synapse formation. During this past year, we have developed disease models to mimic conditions associated with human pathologies. This involved the establishment of a team for experimental animal manipulation and support (mice and rat) including two veterinaries and one technician, in addition to improve our capacities for working with zebra fish and *Drosophila*. Main results obtained in the collaborative projects during the first year of BNI included:

(i) Genetic manipulation: We have started developing studies and models to investigate pathogenic mechanisms in diseases such as Amyotrophic Lateral Sclerosis (ALS; use of mutant SOD1 and TDP43 transgenic mice), Alzheimer's disease (we are importing APP-PS mutant mice), Parkinson's disease (toxicological and genetic models), spinal cord injury and Huntington's disease. We have been able to develop studies to perform genetic manipulation of the disease models and identify novel targets for therapeutic interventions. For example, CHz has targeted two main transcription factors involved in adaptation to cellular stress using knockout models (i.e. XBP1 and ATF4) and breed them to two Huntington´s disease transgenic mouse models. Using this approach we identified a key component of Huntington´s pathogenesis (*Vidal et al., 2012 Hum Mol Gen, in press*). JS and CHz are currently collaborating to perform a functional screening in the context of Huntington´s disease using fly models and RNAi technology. Similarly, using these genetic tools we established the relative contribution of cellular stress to spinal cord injury. We developed micro-surgery procedures to induce spinal cord injury and then follow partial locomotor recovery. Using this approach, we demonstrated a key role of both ATF4 and XBP1 in this pathological model (*Valenzuela et al., 2012 Cell Death Dis*). Similar studies have been performed in ALS, peripheral nerve degeneration, prion disease, and Parkinson´s disease. We are currently generating new transgenic mice that will be described during the next years.

(ii) Other disease models: In the framework of BNI, we are also investigating the role of the polymerase PARP-1 on the long-term effects produced by perinatal asphyxia, proposing that PARP-1 overactivation is a target for neuroprotection (*Herrera-Marschitz et al., 2011 Neurotox Res*). We have further discussed that inflammation and inflammatory signals are involved in the long-term effects produced by perinatal asphyxia, via a PARP-1-NF-kappaB interaction, leading to translocation of p65, a pro-inflammatory transcription factor. In agreement, p65 is increased by hypoxia, in a region specific manner (*Neira et al., 2012, in preparation*), supporting a role in modulating neuronal networks as a third signaling system of neurotransmission (*Schmitt, et al., 2011 The World Journal of Biological Psychiatry*). The issue was also investigated with primary cultures,

focusing on astrocyte-neuron interaction, developing a model implying chemically-induced hypoxia, focusing on HIF-1alpha, a key transcription factor for cell response to hypoxia, interacting with the DNA-repairing enzymes, such as PARP-1. The studies were performed by Edgardo Rojas-Mancilla, who has been pivotal for the integration of research between MH and LL (*Rojas-Mancilla et al. 2012, in preparation*). Through this interaction we have developed a rat model to study glial scar formation by using fluorescence imaging and panoramic confocal microscopy (*Soto et al., 2011 Chilean Society for Cell Biology Annual Meeting*). Preliminary results have been presented by Soto et al., at the Chilean Society for Cell Biology Annual Meeting. CH has developed models to investigate Alzheimer´s disease at the signaling, morphological, electrophysiological, and behavioral level. She is currently collaborating with CHz in the analysis of stress responses *in vivo* on AD mouse models, and had published their first collaborative article (*Paula-Lima et al., 2011 Antiox Red Sig*).

(iii) Therapeutic strategies: BNI members established collaboration with the biotechnology company Genzyme Corporation. Together they are currently developing Adeno-Associated Viruses (AAVs) for future gene therapy. We have been able to test this method to deliver a transcription factor into the spinal cord of an injury model. This strategy enhanced motor recovery after trauma (*Valenzuela et al., 2012 Cell Death Dis.*). In addition, a new viral-based model was developed for Huntington's using stereotaxic injection of AAVs. This system was used to test a gene therapy to deliver XBP1, which reduced the pathological effects of mutant Huntingtin (*Zuleta et al., Biophys Biochem Res Comm, in press*). These two studies were published in collaboration with two Genzyme scientists. All methods and tools developed for gene therapy and genetic manipulation with this approach are now available to all BNI investigators.

(iv) Studies in Chilean patients: HS and PM initiated a large study that combines basic and clinical aspects searching for biometrics in patients with Schizophrenia. The specific aim is to contribute to improve diagnostics and therapeutics follow-up (See also RL5). We have also developed a large analysis of most Chilean patients affected with Creutzfeldt-Jacob Disease. We have analyzed the CSF of 40 patients and performed the regular diagnostic test based on the detection of 14-3-3 protein. We have investigated the expression pattern of the prion protein and found interesting changes that will help for future diagnostic tests (*Torres et al., PLoS One, submitted*).

(v) Analysis of gene function in complementary animal models: We have performed two studies that combines analysis of gene function not only in cell culture, but also in mice, flies and zebra fish. This type of approach had revealed important new biological functions of genes that are conserved across species. In this line we identified a new regulator of neuronal survival termed GRINA (*Rojas-Rivera et al., 2012 Cell Death Diff, in press*). This study is a collaboration of CHz, MC and JS. We also performed a similar study to uncover a new regulator of the stress response autophagy using mice and fly models (*Castillo et al., 2011 EMBO J*), involving the interaction between CHz and JS.

During this period, CHz received an important award from the North American Spine Society (NASS). Every year NASS awards 2-4 young researchers for their outstanding contribution to understand the causes of spinal cord injury. This is the first time that a Latin American country received this international award. The award contributed with 50.000 USD for the research of the selected laboratory.

RL7. Applied mathematics and biomedical informatics: During the first six months of BNI, the applied mathematics and biomedical informatics research line has formed an interdisciplinary platform (BNI-BioMat) consisting of an image processing specialist (Dr. Mauricio Cerda), a electronics engineer (Felipe Santibáñez) and a bioinformatics engineer (Luis Briones) together with a BNI PhD-student (Jorge Jara) and a post-doc (Omar Ramírez) to study dynamic biological

phenomena on a subcellular, cellular, and supra cellular level. Within this platform, BNI is studying pattern organization in neurons in 2/3D and colocalization in confined sub-cellular compartments to localize/track proteins within sub-cellular organelles. Super-resolution optical fluctuation imaging, SOFI, has been applied in collaboration with Jörg Enderlein's group (Göttingen) to localize $GABA_B$ receptors within subcellular organelles and examine the spatial organization of trafficking in hippocampal neurons (AC/SH). SOFI is being implemented within BNI in the context of the recently formed network for the installation of super-resolution techniques for neuroscience in Latin America. Additionally tracking approaches based on Optical Flow (OF) have been implemented and rigorously tested for the tracking of biological objects to (i) study dendrite branching and axonal wiring [skeletonization algorithms have been implemented to quantify morpho-topological branching in 2/3D, MC/CHz/SH], (ii) model cellular and supra-cellular descriptors for multi-cellular rosette formation based on partial differential equations [active surface models, MC/SH], (iii) develop statistics to study spike trains in multiunit recordings [CH/SH], (iv) model neuronal ensembles to account for activity during natural behavior [MC/AC/CH/SH], and (v) implement mathematical tools for image based tele-analysis within clinical research and diagnostic medicine. Algorithms for remote digital sperm analysis have been implemented and published for clinical trials and testing with one private and one public Chilean hospital. This novel service will be consolidated through the creation of a first technological spin-off, CEDAI Spa, www.cedai.cl.

The article *Performance of Optical Flow techniques for motion analysis of fluorescent point signals in confocal microscope* has been published in a special issue of *Machine Vision and Applications*, and a documented code is being published via the new online journal *IPOL-LA,* a recently created Latin American Section of *Image Processing On Line* in collaboration with laboratories from Uruguay, Argentina, and Brazil. Colocalization routines are constantly improved via open source imageJ plugins through collaborations with international microscopy centers (e.g. University of Sussex). Novel techniques to determine surface properties of 3D biophysical model systems have been published in collaboration with MEMPHYS, Denmark (*A method for analysis of lipid vesicle domain structure from confocal image data' European Biophysical J)* and a quantitative confocal microscopy approach to study the development of 3D architecture of uropathogenic *Proteus mirabilis* Batch Culture Biofilms' has been published in *J of Microbiological Methods*. These and upcoming publications contribute to consolidate BNI-BioMat as an innovative platform for scientific image processing on a national and international level.

Besides numerous contributions of BNI-BioMat members on national and international congresses, symposia, and workshops (many in collaboration BNI-researchers, MC/AC/CH), we emphasize a first contribution towards image based tele-analysis within clinical research and diagnostic medicine presented in the Latin American Association of Investigators in Reproduction Medicine, October 2011, Panama. Image processing technologies and their applications for clinical research and diagnostic medicine are poorly developed in Latin America. Therefore, the mission of BNI-BioMat to contribute with novel methods and imaging technologies from basic science to applied medicine and tele-medical services presents an important landmark.

RL8. Clinical research and capacity building: In this clinical research line we have started the study of patients with borderline personality disorders with the aim to determine genetic polymorphisms associated with impulsivity, aggression and suicidal behavior (HS in collaboration with P. Iturra). In a parallel pharmacogenetic project we have studied several polymorphisms related to serotoninergic system for the prediction of clinical response to selective serotoninergic reuptake inhibitors (SSRI) in borderline personality disorder. The aim is to identify genetic markers for early prediction of anti-impulsive and anti-depressive treatments. Additional studies include the comparison between bipolar II patients and borderline personality disordered patients. The objective

is to determine clinical and genetic differences between these entities that represent a difficult differential diagnoses (HS in collaboration with S. Jerez and J. Villarroel). A manuscript reporting results in this area has been submitted (*Association between neuroticism and polymorphism in the promoter region of the serotonin transporter in borderline personality disorder. Villarroel et al., 2012 Psychiatric Genetics, submitted*).

We have initiated a large study of schizophrenic patients in search of genetic, behavioral and electroencephalographic markers (PM and HS). This project includes patients from Clínica Psiquiátrica (U Chile), Hospital del Salvador (U Chile) and Instituto Psiquiátrico Dr. José Horwitz in Santiago (see also RL 5). Finally we have recruited Rodrigo Nieto MD, a young clinician currently enrolled in a Ph.D. program at FMed to lead a project evaluating the use of the levels of circulating brain-derived neurotrophic factor (BDNF) as a biomarker for cognitive function and clinical response to atypical antipsychotics. Results have been presented at multiple national and international conferences including the LXVI Congreso Chileno de Psiquiatría, Neurología y Neurocirugía, 15th World Congress of Psychiatry, Buenos Aires (Argentina), and European Psychiatry.

b) Publications:

During this funding period BNI members published 6 ISI articles. Their relevance and impact have been described in section 3a. ***See Annex 3***.

Summary table

Category of Publication	MSI Center Members	Number of Publications coauthored by students	Total Number of Publications
ISI Publications	Associate Researchers	3	5
	Other Researchers	0	1
Grand Total		**3**	**6**

c) Other Achievements:

- **Patents:**

Mario Herrera-Marschitz and Yedy Israel, a senior researcher associated to BNI patented a vector and application of a medicine/drug that inhibits the intake of alcohol for prolonged periods, by inhibiting the synthesis of brain catalase or by destroying the product that is generated when brain catalase acts upon ethyl alcohol (License Nº 842-2010; 211,568). Alcoholism and compulsive alcohol consumption are still medical and social challenges waiting for efficient long-lasting treatments. This patent provides a new therapeutic target as well as a mechanism to lessening compulsive drinking. Specific inhibition of brain catalase could generate a reduction of alcohol intake that is virtually complete and lasting at least 50 days.

- **Congress Presentations:**

During this funding period BNI members attended numerous national and international scientific meetings. The relevance and impact of selected presentations have been described in section 3a.

Summary Table

Type of presentation	National Events [Number]	International Events [Number]
A. Associate Researchers		
Conferences, oral communications, poster communications, others (specify)	45	29
Invited presentations (not included in above row)		
B. Other researchers (Adjunct Researchers, Senior Researchers, Young Researchers, Postdoctoral Researchers and Students)		
Conferences, oral communications, poster communications, others (specify)	2	4
Invited presentations (not included in above row)		

- **Organization of Scientific Events:**

BNI is conducting regular meetings with health professionals whose clinical practices are related to the research areas of the institute. The aim of these meetings is to gain a better understanding of clinical problems in the areas of psychiatry, neurology and geriatrics and evaluate the pertinence of new scientific developments, state-of-the-art technology and collaborative procedures and strategies to provide solutions to these problems by generating productive interactions between basic scientists and clinicians. In addition, by targeting health professionals these meetings provide clinical practitioners a unique opportunity to update their scientific knowledge in Neuroscience. Thus, these events align with two major objectives of BNI: to foster high-standard clinical research and transfer the impact of its research to society, and to become a resource center for health professionals.

Three meetings with different clinical services were conducted during 2011. In each one a BNI scientist presented results from current research projects. These included "The Role of Klotho in the Regulation of Adult Neurogenesis in the Hippocampus" presented by Felipe Salech and A. Couve at the Geriatrics Department Hospital Clínico Universidad de Chile September 14, 2011 (30 participants), "CoREST/LSD1 Control the Development of Pyramidal Cortical Neurons" presented by Manuel Kukuljan at the Pediatric Neurology Department Hospital San Borja, September 15, 2011 (40 participants), and "Research at BNI" presented by A. Couve at the Psychiatry Clinic, Hospital Clínico Universidad de Chile, October 25, 2011 (50 participants). Scientific presentations were followed by a presentation from the clinical service, discussions, evaluation of collaborative alternatives and a social activity to promote the interactions between basic scientists and clinicians. As a result of these events preliminary collaborative initiatives have emerged. BNI investigators are currently collaborating with the team led by Dr. Mónica Troncoso at the Pediatric Neurology Department Hospital San Borja. Preliminary projects include "Genetic causes of hereditary spastic paraplegias in the Chilean population and their impact on cellular function", A. Couve; "Genetic causes of cortical dysplasias in the Chilean population and their impact on supracellular function", M. Kukuljan. BNI has allocated seed funds (U$10,000) to initiate these basic-clinical approaches.

Open BNI seminars have taken place: Prof. Jörg Enderlein, Georg August University in Göttingen, "Stochastic Optical Fluctuation Imaging and Image Scanning Microscopy: The new kids on the block of superrresolution microscopy", July 26, 2011.

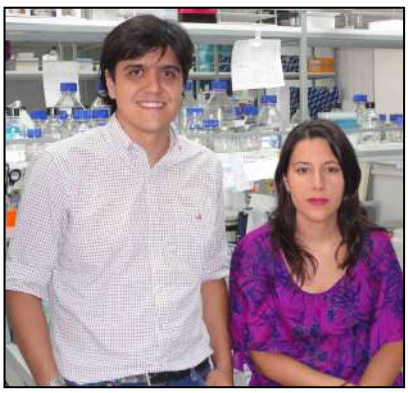
Additionally we have established weekly internal seminars to socialize research lines and translate BNI's cross-disciplinary atmosphere into concrete collaborative projects: A. Couve, September 30, 2011; L. Leyton October 7, 2011; J. Sierralta October 14, 2011; M Concha Octiober 21, 2011; M. Kukuljan November 11, 2011; S. Hartel November 18, 2011; C. Hetz November 25, 2011; H. Silva December 15, 2011; P. Maldonado December 30, 2011. ***See Annex 4.*** *Photograph (right): BNI Associate Investigators during a weekly internal seminar. Cecilia Hidalgo (seated right), currently Adjunct Investigator has actively participated during this period.*

- **Scientific Editorial Boards:**

BNI investigators paticipate 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, Executive Editor), Current Opinion in Cell Biology (CHz, Editor Special Edition 2011), Open Behavioral Sciences Journal (MC, Editor), Amino Acids (MH, Editor in Chief), Neurotoxicity Research (MH, Associated Editor), Journal of Amino Acids (MH, Associated Editor), Biochemical and Biophysical Research Communications (CH, Editor), Developmental Neurobiology (MK, Editor), Frontiers in Neurobiology (MK, Editor), Frontiers in Integrative Neuroscience (PM, Editor). Additionally BNI members are committed to raising the impact of Biological Research, an ISI indexed national journal (CH and LL, Editors).

- **Awards:**

Fernanda Lisbona, a Ph.D. student working in the laboratory of C. Hetz at BNI obtained the L'Oréal UNESCO For Women in Science Award. Importantly, the award is sponsored by CONICYT, the National Commission for Scientific and Technological Research. Annually, L'Oréal and UNESCO recognize two young scientists with a promising future at the doctoral level. They seek to reward female scientists who are developing their Ph.D. thesis in the life sciences and who have excelled in their respective professional areas. This award contributes to demonstrate the quality of young investigators at BNI. It also shows the commitment of BNI in creating equal opportunities for women, and demonstrates that the open-lab atmosphere at BNI stimulates creativity and dedication.



Felipe Salech MD, a Ph.D. student working at BNI obtained the first prize in oral presentations at the XV National Meeting of Geriatrics and Gerontology, August 18-19 2011, Santiago, Chile. Felipe, a young clinician specializing in geriatrics is currently developing his doctoral thesis under the supervision of A. Couve at BNI. The topic of his research is ageing and neurogenesis in mice combining *in vitro* and *in vivo* methodologies in collaboration with C. Hetz. The project fully captures the philosophy of BNI by focusing on a highly relevant topic for human health, it also provides a young clinician the opportunity to develop a project in a basic neurobiology laboratory atmosphere and use the collaborative platforms offered by BNI. Obtaining this award contributes

significantly to establish tangible links with the clinical community, a central goal at BNI. *Photograph (previous page): Felipe and Fernanda, recipients of awards 2011.*

Hernán Silva, BNI investigator was awarded the "Chilean Master of Psychiatry 2011 Prize" given by the Neurology, Psychiatry and Neurosurgery Society of Chile (SONEPSYN) for his role in education and research in the discipline of psychiatry. With his active participation at BNI Dr. Silva has made a significant contribution towards bringing the clinical community closer to the research environment of the institute. Dr. Silva is fully committed to provide a bridge with other medical disciplines related to neuroscience, such as neurology and geriatrics. *Photograph (right): Dr. Hernán Silva, recipient of the 2011 award.*

4. Education and Capacity Building

a) Education and Capacity Building:

This reports covers the first six-month period of BNI and therefore most of the training activity presented here (mainly supervised experimental work) reflects activities ongoing at the start of BNI operation. Nevertheless they conform to the idea, central to BNI, that having laboratories with a high level of research activity provides the only and natural setting for the training of young scientists. Therefore, the role of students at BNI is to become junior researchers in charge of specific projects or parts of projects under the supervision of one or more BNI senior investigators. Special emphasis is being placed on the co-mentorship, which not necessarily translates into formalities, but arises from the daily interactions within laboratories, particularly as the number of shared facilities and technological approaches significantly increased with the start BNI (e.g. shared microscopy facilities, shared EEG equipment, accessible animal models).

As the national system provides growing support (as number of fellowships) to Ph.D. students, our main contribution points towards: i) to provide advanced research opportunities for students already holding fellowships (see research lines) and ii) to provide leverage and bridge support to students and young investigators to complete ongoing projects and to encourage application to other sources of funding, ensuring both estability and continuity as well as competitivity of our students. The specific activities in this respect are described below.

Besides direct experimental research activities, all BNI investigators led or participated in formal teaching activities en graduate and/or clinical training programs during this term. As examples of courses we mention "Neuropharmacology" (MH), "Cellular and molecular neuroscience" (MK, JS, AC), "Medical informatics" (SH). All of them are part of the offer of the graduate school at the F Med, U. Chile. Development of specific initiatives aimed to the training of clinicians and other health-related professions are underway, but they were not formally carried out during the term reported here.

b) Achievements and results:

BNI opened a postdoctoral position award system, aimed at recruiting young investigators able to apply to external funding. A requisite to participate was the application to the FONDECYT postdoctoral grant with a project consistent with BNI goals and philosophy during the following funding round. In the first version of this system six postdoctoral positions were awarded in July 2011 (Tatiana Adasme, Janina Borgonovo, José Egaña, Cecilia Lopez, Gabriela Mercado and Viviana Valdés); four of these young investigators were later awarded FONDECYT grants, therefore bringing additional support to their research lines. Four postdocs are currently funded by

BNI as a result of a second call for applications (José Egaña, Nestor Guerrero, Diego Rojas and Viviana Valdés). In total 16 postdocs are funded through complementary sources at BNI.

A second activity aimed to directly support students has been the allocation of funds to support (stipend or partial stipend) students in each of the eleven labs constituting BNI, which has allowed the completion of projects and smoothed transitions, besides supporting students in programs not receiving additional fellowship support. Direct BNI support, as full stipends or complements, was awarded to 31 students. In total 14 undergraduate, 17 Masters and 51 Ph.D. students are funded through complementary sources at BNI. ***See Annexes 5.1 and 5.2.***

c) **Destination of Students:**

As this report covers only the first six months of activity, the number of students finishing their training at BNI is small and is mainly the outcome of the previous activity of the labs. Nevertheless, in the spirit of the institute, there is a trend of alumni to stay in research and/or pursue more advanced training. "Other" outcomes, which are expected to constitute an stable proportion of the destination of BNI trainees is the professional activity in health-related areas, consistent with BNI definitions and our placement in the main FMed in Chile.

Summary Table*:*

Obtained Degree	Academy	Industry and Services	Studies	Research	Other
Doctoral				2	
Master			1	2	
Undergraduate			1	1	1
TOTAL			**2**	**5**	**1**

5. Networking and Other Collaborative Work

a) Networking:

During 2010 BNI researchers interacting through the Millenium Nucleus of Neural Morphogenesis (NEMO) applied for international collaborative funds to the Deutsche Forschungsgemeinschaft (DFG) together with German scientists mostly from the Georg August University in Göttingen. As part of the competition for "DFG Initiation and Enhancement of Bilateral Cooperation" € 20.000 were obtained to cover a bilateral meeting in Santiago and € 9.000 for three research stays in Germany. With these initial funds the formal network NEMO Scientific Network (NSN) was established. NSN is an international collaborative platform that creates a well-focused and strongly interactive alliance of Chilean and German scientists that fosters an integrated *in vivo* genetic-morphogenetic approach to reveal the microscopic mechanisms that generate form, structure, and functional organization in the central nervous system. NSN includes a wide range of expertise from cellular physics, cellular and developmental neurobiology, genetics and microscopic imaging. The goal of this trans-disciplinary platform is to uncover genetic and molecular networks, and associated cell/tissue behaviors that encompass the morphological and functional organization of the brain. The "Initiation Phase" of the network (January to December 2010), included the application and planning of a first meeting. The "Cooperation Phase" (January to December 2011), included an open symposium and a workshop that took place in Santiago (January 2011). It also included the exchange of students and investigators. In this context, during July 2011 Prof. Jörg Enderlein from Göttingen, an expert in the development of new methods of single molecule fluorescence spectroscopy and super-resolution imaging and their application to complex biological systems, visited BNI labs in Chile, was invited speaker in a BNI seminar and was special guest in a formal social activity with BNI researchers. Additionally, between July and October 2011 two young investigators from BNI, Omar Ramírez, Ph.D. and Felipe Santibáñez travelled to Göttingen to train in Super-resolution Optical Fluctuation Imaging (SOFI), a super-resolution microscopy technique developed by Prof. Enderlein, that Omar and Felipe are currently implementing at BNI. Plans for 2012 include a second meeting and strengthening the network with additional funds recently obtained by BNI from the ICM Network Funds competition. At BNI we consider that NSN is an important step towards becoming an international reference centre for *in vivo* genetic/morphogenetic investigations of brain morphogenesis and function. ***See Annex 6.*** *Photograph (right): Felipe Santibañez and Omar Ramírez.*

b) Other Collaborative Activities:

Other individual and shared collaborative initiatives from BNI members have established a multidisciplinary collaborative network with leading academic and research institutions worldwide. Individual initiatives have involved the exchange of personnel and expertise with laboratories in the US, Europe and Latin America, funded by DAAD-CONICYT (C.P. Heisenberg), FONDAP-CEMC, PBCT-Research-Rings (A. Maas, C. Best, C.P. Heisenberg, G. Randall), NIH (S. Moss), HFSPO (S. Kindler), European Union (S Wilson), and The Harold Leila Mathers Foundation (L Glimcher), and FONDECYT (L. Bagatolli, R. Kaufman, T. Blanpied) among others. During 2011 these network connections were consolidated through short-term traineeships by BNI students Álvaro Álvarez

(U Queensland, Australia), Gabriela Martínez (Harvard School of Public Health, USA), Jorge Jara (U Heidelberg, Germany) and Pamela Valdés (Ecole Polytechnique Fédérale de Lausanne, Switzerland). Broader network initiatives have also been set between BNI associated centers and research Institutions in Latin America and Europe. For example, a network agreement between CENI and the International Institute of Neuroscience of Natal (Brazil) exists since 2007, including a program of faculty/student exchange between Brazil and Chile.

6. Outreach and Connections with Other Sectors

a) Outreach:

A specific aim for the first period of BNI was to initiate and strengthen actions to promote the institute's visibility. To this end we have created the BNI logo. The image is a colorful representation of a human brain and spinal cord. Three colors represent the multiple disciplines converging at BNI. The interwoven and winding colored lines add a layer of dynamism to the silhouette, an essential component of BNI research. Lines can be traced to individual cells but they also outline the entire system, emphasizing that multiscale integration is a trademark of BNI research. All researchers at BNI are strongly focused on neuroscience, but we all recognize and use the power of genetics, thus a DNA double-strand was included as an integral component of the nervous system. Additionally, the institute's website is under construction, but a summary of activities can already be accessed at the temporary site (www.bni.cl). *Insert (above): the BNI logo.*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Formal outreach activities of BNI will start during 2012. However, BNI members are constantly and actively engaged in communicating science to the general public. Importantly written, internet, television and radio interviews appeared during this period to promote the birth of the institute. *Inserts: press clippings from "El Mercurio".*

In addition, BNI members socialized the institute initiative and philosophy with authorities of the Institute of Biomedical Sciences (September 21, 2011; 15 participants), with authorities of the Faculty of Medicine (September 29, 2011) and with students, postdocs and BNI staff (October 20, 2011; 80-100 participants).

Importantly, during 2011 Miguel Concha participated in a lecture series for the general public entitled "Forms of Reality" at Centro de Estudios Públicos (CEP), an influential think tank engaged in disseminating the principles of a free and democratic society. His talk "The Forms of Life" was received with enthusiasm by an audience of students of wide interest (September 22, 2011; 30-40 participants). ***See Annex 7.*** *Photograph (right): Miguel Concha and Ernesto Rodríguez, Advisory Board Member, CEP.*

7. Administration and Financial Status

a) Organization and administration:

The institute is currently applying for "legal person status" according to MSI guidelines. During 2011 the eleven associate investigators constituted a temporary directory. Paola Cañón, Ph.D. was hired as Executive Director. An independent administrative office was established temporarily at the Program of Physiology and Biophysics at the Faculty of Medicine, U Chile. This office is currently constituted by Ana Timmermann, who has extensive expertise in accounts managing and Millenium funds, and Johanna Jiménez, an undergraduate law student who is contributing with her expertise as assistant to Dr. Cañón and Mrs. Timmermann. A computer expert, Jorge Mansilla was hired to provide technical support to BNI labs and administrative staff. Two teams of graphic designers (led by Nicolás Vasquez and Rodrigo Tapia) and journalists (Inés Llambías Comunicaciones) were hired to generate BNI's corporate image and promote its activities and achievements. *Photograph (right): Paola Cañón, Ana Timmermann, Johanna Jiménez and Jorge Mansilla.*

Category	Female	Male	TOTAL
Assistant & Technicians	22	19	41
Administrative Staff	8	2	10
TOTAL	**30**	**21**	**51**

b) Financial Status:

See Annexes 8.1, 8.2 and 8.3.

8. Annexes

Annex 1.- Institute Researchers

1.1.- Associate Researchers

Full Name	Research Line	Nationality	Gender	Date of birth	Profession	Academic Degree	Affiliation	Current Position	Relation with Center
Couve Correa, Andres Oscar	1, 2, 3, 4, 7, 8	Chilean	M	23-10-68	Biologist	D	University of Chile	Associate Professor	1
Hetz Flores, Claudio	1, 4, 6, 8	Chilean	M	24-03-76	Biotechnology Engineering	D	University of Chile	Full Professor	2
Concha Nordemann, Miguel Luis	1, 2, 3, 7, 8	Chilean	M	06-03-66	Medicine	D	University of Chile	Full Professor	2
Härtel Gündel, Steffen	1, 3, 5, 6, 7	Germany	M	24-11-68	Physical	D	University of Chile	Assistant Professor	2
Herrera-Marschitz, Mario	1, 3, 6, 8	Chilean	M	25-06-44	Medicine	D	University of Chile	Full Professor	2
Kukuljan Padilla, Manuel	2, 3, 7, 8	Chilean	M	08-08-63	Medicine	D	University of Chile	Full Professor	2
Leyton Campos, Lisette	1, 3, 6	Chilean/Swiss	F	22-07-59	Biochemist	D	University of Chile	Associate Professor	2
Maldonado Arbogast, Pedro Esteban	5, 7	Chilean	M	30-04-60	Biologist	D	University of Chile	Associate Professor	2
Sierralta Jara, Jimena Alejandra	2, 3, 7	Chilean	F	12-09-62	Biochemist	D	University of Chile	Associate Professor	2
Silva Ibarra, Hernán	5, 7, 8	Chilean	M	01-07-49	Physician	D	University of Chile	Full Professor	2

1.2.- Young Researchers

Full Name	Research Line	Nationality	Gender	Date of birth	Profession	Academic Degree	Affiliation	Current Position	Relation with Center
Morales Retamales, Paola	6	Chilean	F	18-11-66	Biologist	D	University of Chile	Associate Professor	2
Bustamante Cadiz, Diego	6	Chilean	M	11-03-52	Biochemist	M	University of Chile	Associate Professor	2
Gebicke-Haerter, Peter	6	German	M	26-04-47	Biologist	D	Mannheim, DE	Professor	2
Paula-Lima, Andrea	4, 6	Brazilian	F	20-11-77	Pharmaceutics	D	University of Chile	Assistant Professor	2
Sánchez Vergara, Gina	4, 6	Chilean	F	11-12-54	Biochemist	D	University of Chile	Assistant Professor	2

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	6	Chilean	M	19-04-39	Biochemist	D	University of Chile	Full Professor	2

1.4.- Others

Full Name	Research Line	Nationality	Gender	Date of birth	Profession	Academic Degree	Affiliation	Current Position	Relation with Center
Hidalgo Tapia, Cecilia	4, 6	Chilean	F	10-06-41	Biochemist	D	University of Chile	Full Professor	2
Hitschfeld Kahler, Nancy	7	Chilean	F	20-11-60	Science Computer	D	University of Chile	Associate Professor	2
Ocampo Garcés, Adrián	4, 5	Chilean	M	21-10-65	Medicine	D	University of Chile	Assistant Professor	2
Ortega Palma, Jaime	7	Chilean	M	16-10-67	Mathematic	D	University of Chile	Associate Professor	2
Valdés Guerrero, José Luis	4	Chilean	M	16-12-75	Biologist	D	University of Chile	Assistant Professor	2

NOMENCLATURE:

[Gender]
[M] Male [F] Female

[Academic Degree]
[U] Undergraduate [M] Master [D] Doctoral

[Relation with Center]
[1] Full time [2] Part time

Annex 2.- Research Lines

Nº	Line Research	Objective	Description	Researcher	Discipline	Starting Date	Ending Date
1	Sub-cellular functional dynamics	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.	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 (Marlin1) 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.	Miguel Concha, Andrés Couve, Steffen Härtel, Mario Herrera-Marschitz, Claudio Hetz, Lisette Leyton	6, 25, 59, 61, 63, 65, 143	28-06-11	
2	Cellular identity and morphology	To understand how gene expression determines morpho-functional features throughout the development and the 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 combine 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 (Marlin1).	Miguel Concha, Andrés Couve, Manuel Kukuljan, Jimena Sierralta	61, 63, 65	28-06-11	
3	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 brain function.	Here we combine the use of genetic approaches in GFP-transgenic zebrafish and in hippocampal organotypic cultures with in vivo 3D confocal visualization and analysis of neuronal structure and function to study: (i) the cellular mechanisms that control adhesive, tensile and polarity changes leading to cell migration, formation of cell sheets and brain nuclei, and wound healing, (ii) the genetic and morphogenetic mechanisms that guide axonal growth cones and establish neuronal connectivity in vivo, focused on Wnt/PCP, FGF, Chemokines and Robo/Slit, and neurogenesis in hippocampal circuits, and (iii) the dynamic configuration and functional correlate of neuronal circuits using optogenetic probes and in vivo electrophysiology. This strategy provides a contextual view of the mechanisms that drive form, supra-cellular structure and neuronal circuit development, revealing general principles of brain organogenesis and function.	Miguel Concha, Andrés Couve, Steffen Härtel, Mario Herrera-Marschitz, Manuel Kukuljan, Lisette Leyton, Jimena Sierralta	6, 25, 59, 61, 63, 65, 67, 72, 110, 143	28-06-11	
4	Plasticity and behavior	To understand how genetic interactions and signaling pathways control long-lasting memories.	We have established methodologies to study the role of ryanodine-receptor (RyR) dependent Ca2+ 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 Ca2+ 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 assembles, and (iii) their behavioral correlates.	Andrés Couve, Claudio Hetz, Cecilia Hidalgo	61, 65, 73	28-06-11	

Nº	Line Research	Objective	Description	Researcher	Discipline	Starting Date	Ending Date
5	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 recordings, local field potentials, and electroencephalographic recordings 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, Pedro Maldonado, Hernán Silva	6, 25, 59, 73, 120, 143	28-06-11	
6	Neural dysfunction and pharmacologic al 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 Amyotrophyc 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, Mario Herrera-Marschitz, Claudio Hetz, Lisette Leyton, Cecilia Hidalgo	65, 6, 25, 59, 143, 67, 72, 110, 61, 73	28-06-11	
7	Applied mathematics and biomedical informatics	To uncover novel neural processes based on mathematical models that reveal morpho-functional 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 sub-cellular compartments and fosters new approaches to: (i) localize/track proteins within sub-cellular organelles, (ii) study dendrite branching and axonal wiring, (iii) model cellular and supra-cellular descriptors for multi-cellular rosette formation based on partial differential equations, (iv) develop statistics to study spike trains in multiunit recordings, (v) model neuronal assembles to account for activity during natural behavior, and (vi) implement mathematical tools for image based tele-analysis within clinical research and diagnostic medicine.	Miguel Concha, Andrés Couve, Steffen Härtel, Manuel Kukuljan, Pedro Maldonado, Jimena Sierralta, Hernán Silva	6, 25, 59, 61, 56, 67, 73, 143	28-06-11	
8	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 Amyotrophyc lateral sclerosis (ALS) and Parkinson's, (iii) genetic comparison of patients with bipolar disorders, and (iv) autism spectrum disorders and alterations of neural development.	Miguel Concha, Andrés Couve, Mario Herrera-Marschitz, Claudio Hetz, Manuel Kukuljan, Hernán Silva	61, 63, 65, 67, 72, 110, 120	28-06-11	

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

3.1.- ISI Publications or Similar to ISI Standard

3.1.1.- Associate Researchers:

1. Valenzuela JI, Jaureguiberry-Bravo M, **Couve A** (2011). Neuronal protein trafficking: Emerging consequences of endoplasmic reticulum dynamics. Mol Cell Neurosci. 48(4):269-77.
2. **Hetz C**, Martinon F, Rodriguez D, Glimcher LH (2011). The Unfolded Protein Response: Integrating Stress Signals Through the Stress Sensor IRE1{alpha}. Physiol Rev. 91(4):1219-43.
3. Díaz E, Bravo D, Rojas X, **Concha ML** (2011). Morphologic and immunohistochemical organization of the human habenular complex. J Comp Neurol. 519(18):3727-47.
4. Castillo K, Rojas-Rivera D, Lisbona F, Caballero B, Nassif M, Court FA, Schuck S, Ibar C, Walter P, **Sierralta J**, Glavic A, **Hetz C** (2011). BAX inhibitor-1 regulates autophagy by controlling the IRE1α branch of the unfolded protein response. EMBO J. 30(21):4465-78.
5. Schlapp G, Scavone P, Zunino P, **Härtel S** (2011). Development of 3D Architecture of Uropathogenic Proteus mirabilis Batch Culture Biofilms - A Quantitative Confocal Microscopy Approach. J Microbiol Methods 87(2):234-40.

3.1.2.- Other researchers:

1. **Hidalgo C**, Donoso P (2011). Cell signaling. Getting to the heart of mechanotransduction. Science 333(6048):1388-90.

3.2.- Collaborative publications

Category of Publication	1 researcher		2 researchers		3 researchers		4 or more researchers	
	Nº	%	Nº	%	Nº	%	Nº	%
ISI Publications or Similar to ISI Standard	5	83.33	1	16.66				
SCIELO Publications or Similar to SCIELO Standard								
Books and chapters								
Other Publications								
Total of publications	5	83.33	1	16.66				

3.3.- ISI Publications or Similar to ISI Standard

Published before formal initial funding date of the institute (28 Jun 2011) with BNI affiliations

1. Woehlbier U and **Hetz C** (2011). Modulating stress responses by the UPRosome: A matter of life and death. Trends in Biochem Sci (TiBS) 36:329-37.
2. Matus S, Glimcher LH, and **Hetz C** (2011). Protein folding stress in neurodegenerative diseases: a glimpse into the ER. Curr Op. Cell Biol. 23:239-52.
3. **Hetz C** and Glimcher LH (2011). Protein homeostasis networks in physiology and disease. Curr Op. Cell Biol. Editorial Overview. 23:123-5.
4. Rodriguez D, Rojas D, and **Hetz C** (2011). The Endoplasmic Reticulum Gateway of Death. Biochimica et Biophysica Acta (BBA) - Molecular Cell Research. 1813:564-74.
5. Barrientos SA, Martinez NW, Yoo S, Jara, JS, Zamorano S, **Hetz, C**, Twiss JL, Alvarez J, Court FA (2011). Axonal degeneration is mediated by the mitochondrial permeability transition pore. J. Neurosci. 31:966-978.
6. Vidal R, Caballero B, **Couve A** and **Hetz C** (2011). Converging pathways in the occurrence of endoplasmic reticulum (ER) stress in Huntington's disease. Curr. Mol. Med. 11:1-12.

3.4.- Other Publication

Published before formal initial funding date of the institute (28 Jun 2011) with BNI affiliations

1. Torres M, Encina G, Soto C and **Hetz C** (2011). Abnormal calcium homeostasis and protein folding stress at the ER: a common factor in familial and infectious Prion disorders. Commun Integr Biol. 4: 258 - 261.

Annex 4.- Organization of Scientific Events

Scope	Title	Type of Event	City	Country	Responsible Researcher
National	1st Meeting with clinical and health professionals	Seminar and discussion groups	Santiago	Chile	A Couve
National	2nd Meeting with clinical and health professionals	Seminar and discussion groups	Santiago	Chile	M Kukuljan
National	3rd Meeting with clinical and health professionals	Seminar and discussion groups	Santiago	Chile	A Couve

Annex 5.1.- Capacity Building inside MSI Centers

MSI RESEARCHER	NUMBER												TOTAL NUMBER PER MSI RESEARCHER		
	Ungraduate students			Graduate students						Postdoctoral					
				Master			Doctoral								
	F	M	T	F	M	T	F	M	T	F	M	T	F	M	T
A Couve	1	1	**2**	1		**1**	3	2	**5**	1		**1**	6	3	**9**
C Hetz	2	1	**3**	1	2	**3**	4	3	**7**	4	4	**8**	11	10	**21**
M Concha	2		**2**	1	1	**2**	3	6	**9**	1	1	**2**	7	8	**15**
S Härtel	1		**1**	1	1	**2**		1	**1**				2	2	**4**
M Herrera-Marschitz								1	**1**					1	**1**
C Hidalgo							2	1	**3**				2	1	**3**
M Kukuljan							2	2	**4**	1		**1**	3	2	**5**
L Leyton	1	1	**2**				3	5	**8**				4	6	**10**
P Maldonado				2	5	**7**	1	7	**8**		3	**3**	3	15	**18**
J Sierralta	1	3	**4**	2		**2**		2	**2**				3	5	**8**
H Silva											1	**1**		1	**1**
A Couve, J Sierralta								1	**1**					1	**1**
M Kukuljian, H Silva								1	**1**					1	**1**
L Leyton, M Herrera-Marschitz								1	**1**					1	**1**
TOTAL	**8**	**6**	**14**	**8**	**9**	**17**	**18**	**33**	**51**	**7**	**9**	**16**			**98**

Annex 5.2.- Short-term Traineeships of MSI students

Student Name	Institution	Country	Advisor	Project Description	Starting Date	Ending Date
Alvarez Martínez, Alvaro	University of Queensland	Australia	Justin Cooper-White	To determine the role of P2X7 receptor in Thy-1-induced focal adhesion formation and/or maturation, as well as its role in PKC alpha activation	11-10-11	31-12-11
Jara Wilde, Jorge	University of Heidelberg	Alemania	Karl Rohr	Segmentation and morpho-topological characterization of 3D structures in time series from fluorescence microscopy images of high resolution	01-09-11	23-12-2011
Martinez, Gabriela	Harvard School of Public Health	USA	Laurie Glimcher	In Dr. Laurie Glimcher's laboratory at Harvard School of Public Health, Boston USA, She is developing part of aim 1 of her doctoral thesis related to cloning of the kif17 promoter region, after She will measure the activation of the transcription factor XBP1 in this region using the luciferase assay. Within this context, She is learning and developing the technique of chromatin immunoprecipitation to assess the direct binding of XBP1 in this region	26-09-11	29-02-12
Ramírez González, Omar	University of Göttingen	Alemania	Jörg Enderlein	Study of the structure of the endoplasmic reticulum in dendrites of hippocampal neurons cultured rat, using super resolution microscopy SOFI	25-07-11	25-09-11
Santibañez Leal, Felipe	University of Göttingen	Alemania	Jörg Enderlein	Study of the structure of the endoplasmic reticulum in dendrites of hippocampal neurons cultured rat, using super resolution microscopy SOFI	01-08-11	28-10-11
Valdés, Pamela	Ecole Polytechnique Fédérale de Lausanne	Switzerland	Bernard Schneider	Evaluation of the XBP-1 role in a genetic model of Parkinson Disease. We are testing the possible protective role of targeted XBP-1 overexpression through adenoassociated virus (AAVs) in the S.Nigra of a rat model of PD. This genetic model has been well characterized in Dr. Aebisher's lab	22-08-11	14-02-12

Annex 6.- Networking and other collaborative work

6.1.- Networking

Network Name	Network Scope	Network Participants				Institutions
		[Number]				
		From the Center		External		
		Researchers	Postdocs/Students	Researchers	Postdocs/ Students	
NEMO Scientific Network (NSN)	I	6	2	7	2	University of Chile University of Göttingen

NOMENCLATURE:
[Network Scope]
[N] National [I] International [LA] Latin American

Annex 7.- Outreach

7.1.- Outreach activities throughout the period

Scope	Title of the Event	Type of Event	Date	Place Region	Target Audience
Nacional	BNI socialization	Seminar	20-10-11	Faculty of Medicine, University of Chile, Santiago	University student and general comunity
Nacional	Presentation of BNI to the Council of the Faculty of Medicine	Seminar	29-09-11	Faculty of Medicine, University of Chile, Santiago	General comunity
Nacional	CEP Conference and conversation	Seminar	22-09-11	CEP (Centro de Estudios Públicos), Santiago, Chile	Student and general comunity
Nacional	Presentation of BNI to the ICBM	Seminar	21-09-11	Faculty of Medicine, University of Chile, Santiago	General comunity

7.2.- 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	-	1	2	5	-	-	**8**
Internet	-	-	2	-	-	-	**2**
Audiovisual	-	-	1	-	-	-	**1**
TOTAL	1	1	5	5	-	-	**11**

Annex 8.1.- Total incomes

Funds	2011 Incomes		Total incomes to 2011 [$]
	Amount [$]	Percentage of resources used by the Center [%]	
MSI	506.885.666	100	506.885.666
FONDECYT (AC) 1100137	48.300.000	40	48.300.000
FONDECYT (CHz) 1100176	101.430.000	1	101.430.000
FONDECYT (MC, SH) 1090242	43.470.000	10	43.470.000
FONDECYT (SH) 1090246	17.974.845	0	17.974.845
FONDECYT (MH) 1080447	48.300.000	10	48.300.000
FONDECYT (CH) 1100052	91.770.000	10	91.770.000
FONDECYT (LL) 1110149	48.300.000	0	48.300.000
FONDECYT (MK) 1090281	38.640.000	10	38.640.000
FONDECYT (PM) 1090101	20.865.600	30	20.865.600
FONDECYT (JS) 1090272	43.470.000	10	43.470.000
FONDECYT (YI/MH) 1095021	48.300.000	0	48.300.000
FONDECYT (Paola Morales & MH) 11070192	48.300.000	0	48.300.000
FONDAP 1501006 (CH, LL, CHz)	676.200.000	12	676.200.000
ANILLO-CONICYT ACT 66 (PM)	169.050.000	15	169.050.000
HHMI (MC) 55005940	46.851.000	10	46.851.000
FIRCA NIH-USA (AC)	10.626.000	25	10.626.000
FIRCA NIH-USA (LL)	46.368.000	0	46.368.000
CONICYT/DAAD No 1378-09529	9.660.000	0	9.660.000
ICGEB, Italy (CHz)	31.395.000	0	31.395.000
DFG (MC, AC, SH, CHz, JS, MK)	9.660.000	100	9.660.000
Mh-Marschitz Foundation, Stockholm, Sweden	4.830.000	0	4.830.000
Micheal J Fox Foundation For Parkinson Research, USA (CHz)	60.375.000	2	60.375.000
ALS Association, USA (CHz)	36.225.000	0	36.225.000
Guillermo Puelma Foundation	2.415.000	100	2.415.000
Genzyme, USA (CHz)	28.014.000	0	28.014.000
FONDEF (SH) D07I1019	49.930.608	0	49.930.608
TOTAL [$]	**2.287.605.719**		**2.287.605.719**

Exchange rate: US$ 1 = $ 483

Annex 8.2.- Outcome structure

ITEM	2011 Expenses [$]				Total expenses to 2011 [$]	%
	Operative	Networking*	Outreach*	Total		
Honoraria Researchers	51.200.000			51.200.000	51.200.000	16,35
Honoraria students and other personnel	101.673.000			101.673.000	101.673.000	32,46
Tickets and travel expenses	12.864.267			12.864.267	12.864.267	4,11
Materials/supplies	45.011.446			45.011.446	45.011.446	14,37
Goods and equipment	66.269.020			66.269.020	66.269.020	21,16
Infrastructure	7.000.000			7.000.000	7.000.000	2,23
Administrative expenses	17.899.057			17.899.057	17.899.057	5,71
Publications and subscriptions	-			-	-	
Consultancies	700.000			700.000	700.000	0,22
Overhead	10.629.668			10.629.668	10.629.668	3,39
Insurance costs	-			-	-	
Legal personality expenses	-			-	-	
Others	-			-	-	
Total Expenses [$]	313.246.458			313.246.458	313.246.458	100

**during this period, the institute did not received additional funds from MSI for networking or outreach.*

Annex 8.3.- Financial accounting

ITEM	2011 [$]			Total [$]
	Operative	Networking*	Outreach*	
Income	506.885.666	-	-	506.885.666
Outcome	313.246.458	-	-	313.246.458
Annual balance	193.639.208	-	-	193.639.208

**during this period, the institute did not received additional funds from MSI for networking or outreach.*