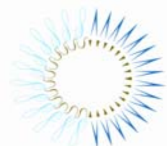
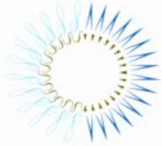


THE PEW CHARITABLE TRUSTS

Latin American Fellows Program *in the* Biomedical Sciences

Below is a list of the 2009 Pew Fellows, in alphabetical order.
Click on a Fellow's name to jump to their full bio below.

Award Year	Full Name	Home Country	U.S. Institution
2009	**Diego Ezequiel Alvarez, Ph.D.**	Argentina	Yale University
2009	**Paulina Cortés-Hernández, M.D., Ph.D.**	Mexico	University of California, Davis
2009	**Verónica Eisner, Ph.D.**	Chile	Thomas Jefferson University
2009	**Ramón A. Jorquera, Ph.D.**	Chile	Massachusetts Institute of Technology
2009	**Andrés Klein, Ph.D.**	Chile	Stanford University
2009	**Kelly Grace Magalhães, Ph.D.**	Brazil	Brigham and Women's Hospital
2009	**João P.B. Monteiro, M.D., Ph.D.**	Brazil	NIAID, National Institute of Health (NIH)
2009	**Facundo Germán Pelorosso, M.D.,**	Argentina	University of California, San Francisco
2009	**Ileana Slavin, Ph.D**	Argentina	The Scripps Research Institute
2009	**Luis Francisco Zirnberger Batista, Ph.D.**	Brazil	Stanford University



Diego Ezequiel Alvarez, Ph.D.

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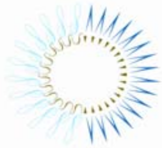
Field: Virology

Research Interest: Dr. Alvarez intends to contribute to the identification and characterization of host factors required for the spread of infection by pathogens. To achieve this he will combine multiple techniques used in the lab such as RNA interference, advanced microscopy and image analysis of human cell lines that are infected with various pathogens. His specific aim will be to determine how pathogens travel from cell to cell inside a host, exploiting the host-cellular architecture to mobilize themselves from infected cells to uninfected cells. These studies will lend new insight into how to stop pathogens from spreading inside a host and will contribute to novel therapeutic targets for some of the worst human diseases related to pathogens.



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Paulina Cortés-Hernández, M.D., Ph.D.

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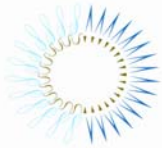
Field: Mitochondrial Dynamics / Cellular Biology

Research Interest:

Human mitochondriadivide by the action of the dyamin related GTPase Drp, which moves between the cytosol and the mitochondrial-surface and assembles into helices that wind around mitochondria to drive membrane constriction and fission. Drp1 interacts with mitochondria through its receptor, Fis1, The yeast ortholog of Drp1 depends on the adaptor protein Mdv1 to bind its mitochondrial receptor and trigger fission. In vertebrates, no adaptors have been found between Drp1 and Fis1. Furthermore, the molecular events that promote and regulate Drp1's targeting, helix nucleation and assembly to divide human mitochondria are not understood. Human Drp1 undergoes several post-translational modifications that may control these events. Mitochondrial fission increases during early apoptosis coinciding with an increment in Drp1's mitochondrial localization, probably through interactions with proteins form the Bcl2 or the endophilin-B family. Understanding how Bcl2 proteins and mitochondrial fission are mechanistically coordinated can lead to novel ways to control the initial stages of apoptosis and the division and distribution of mitochondria.

To unravel the regulation of the human mitochondrial fission machinery and understand how it is coordinated with cellular signaling and apoptosis, I propose experiments aimed at the characterization of Drp1's assembly, molecular contacts and modulation by phosphorylation. The experiments will be conducted in a laboratory that excels at the mechanistic characterization of mitochondrial dynamics.



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Verónica Eisner, Ph.D
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Field: Mitochondria and cellular physiology

Research Interest:
The mutual relationship between mitochondrial structure and function is an emerging focus of biology and medicine. In the muscle, the Ca2+-driven contractile activity has to be dynamically matched by energy supply. Both Ca2+ homeostasis and energy metabolism rely on mitochondrial function. Based on recent evidence mitochondrial activity in ATP generation, in Ca2+ handling and even in cell death depends on continuous restructuring of the individual mitochondria in several cell types. Furthermore, Ca2+ the central regulator of muscle contraction emerges as a key signaling molecule in organellar dynamics. However, it has been difficult to study the mitochondrial fusion, fission and positioning in skeletal or cardiac muscle. Excitingly, recent advances in live cell microscopy and in the fluorescent protein technology provide a means to study mitochondrial dynamics and its signaling mechanisms in the muscle. The significance of these studies is further emphasized by the data on the possible mitochondrial contribution to human excitation contraction coupling diseases.
Hypothesis: We propose that mitochondrial morphology and dynamics are controlled by Ca2+ homeostasis in the muscle and become dysregulated and may contribute to tissue injury in genetic defects of the ryanodine receptors (RyRs), including malignant hyperthermia (MH) and catecholaminergic paroxysmal ventricular tachycardia (CPVT) causing mutations.
Aim#1. To evaluate the mitochondrial network continuity in skeletal myotubes and cardiomyocyte primary cultures. **Aim#2.** To test the hypothesis that the augmented Ca2+ release activity caused by RyR mutations alters mitochondrial morphology, fusion/fission and motility dynamics in muscle cells. **Aim#3.** To test the mechanisms of the Ca2+ effect on mitochondrial dynamics under physiological and pathophysiological conditions in the muscle. **Aim#4.** To evaluate the role of the physiological and pathological Ca2+-dependent changes on mitochondria

morphology and dynamics in muscle cells bioenergetics and contractile function. This study will elucidate the possible mitochondrial contribution to human excitation-contraction coupling diseases, by clarifying the fundamental muscle mechanisms of mitochondrial dynamics and its relevance for Ca2+ homesotasis.

Ramón A. Jorquera, Ph.D.

2009 Pew Fellow

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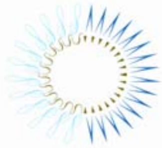
Field: Neurobiology

Research Interest: The computational power of the brain depends on precise synaptic connections that link together billions of neurons. How changes in synaptic function mediate long lasting neuronal plasticity is a key question in modern neurobiology and likely to be important for understanding the pathogenesis associated with human cognitive disorders. Intercellular communication at neuronal synapses occurs on a millisecond timescale and relies on the rapid Ca2+-triggered fusion of neurotransmitter-filled synaptic vesicles at synapses. Following the establishment of the Ca2+ hypotheses for neurotransmitter release by Bernard Katz, there have been a large research effort undertaken to identify the machinery that underlies the transduction of calcium influx to membrane fusion. Like most intracellular membrane trafficking steps, synaptic vesicle fusion requires the assembly of the SNARE complex. The integral membrane synaptic vesicle v-SNARE synaptobrevin and the plasma membrane t-SNAREs syntaxin and SNAP-25 assemble into a four-helix bundle that bridges the synaptic vesicle and plasma membranes. However, fusion via reconstituted SNARE proteins occurs over slow timescales and is Ca2+-independent, contrasting with synaptic transmission, where SNARE assembly and subsequent fusion is rapid and Ca2+-triggered. Synaptic vesicles must also wait in a primed and fusion-competent state for an action potential to trigger Ca2+ influx and fusion. To meet these unique requirements for synaptic transmission, a specific set of synapse-specific regulatory proteins has evolved to act on the SNAREs to make fusion rapid and responsive to Ca2+. These include the synaptic vesicle Ca2+-sensor, Synaptotagmin 1, and the putative fusion clamp, complexin. Here I propose to define how these synapse-specific regulators of SNARE function mediate synaptic vesicle fusion and trafficking in the nerve terminal using *Drosophila* as a genetic system. In particular, I will define how complexin regulates synaptic vesicle fusion and synaptic plasticity, and how it interfaces with Synaptotagmin 1 to generate the unique features of synaptic transmission. Our analysis will combine genetic manipulations available in *Drosophila* with electrophysiological and imaging approaches to characterize how complexin and Synaptotagmin 1 regulate release probability and synaptic plasticity at glutamatergic synapses *in vivo*.



Andrés Klein, Ph.D.
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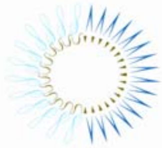
Field: Developmental Biology, Cancer Biology, Neurodegeneration

Research Interest: Niemann Pick type C (NPC) disease is a fatal pediatric neurodegenerative disorder that involves aberrant organelle trafficking and accumulation of free cholesterol within lysosomes. NPC patients have progressive locomotion and cognitive losses, and there is no effective treatment. NPC brains undergo a massive loss of neurons, astrogliosis, and progressive loss of myelin, but the contribution of each brain cell type to the pathology is not known. I plan to address this question by restoring a tagged-Npc1 protein to different neurons, astrocytes, and oligodendrocytes in the Npc1-/- mouse model background. I will use a technology that allows cell-specific and temporal regulation of Npc1-Tag expression. With these new mice I will delineate the sequence of events of the disease and determine when in the progression of the disease the pathology can be rescued. In the second part of my project I will investigate cellular and molecular mechanisms of NPC protein function. Npc1 is a membrane protein found in a subset of endosomes and lysosomes. The vesicular system is very dynamic, allowing communication within neural cells. We know that the absence of Npc1 reduces trafficking of vesicles. We still do not know what information is carried in Npc1 positive vesicles, in neurons or in astrocytes. I will isolate Npc1-positive organelles from the newly engineered mice using anti-tag immuno-magnetic bead precipitation, followed by mass spectroscopy to identify organelle proteins. With this approach I expect to learn about the molecular composition of Npc1-bearing organelles and then study signaling and transport pathways that are altered in NPC disease. In summary, in this project I expect to find important clues for NPC patho-physiology, assessing which cell types matter for the disease, and test the timing of gene therapy that can reverse the disease. The molecular and cellular experiments are directed at learning how Npc1 works in neurons and astrocytes, by identifying proteins that reside in the same compartment as Npc1. The results of both parts of the work will be important for eventually saving lives of NPC patients.



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Latin American Fellows Program in the Biomedical Sciences

Kelly Grace Magalhães, Ph.D.

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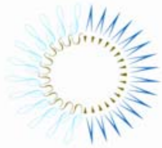
Field: Immunology

Research Interest:

The discovery of CD1 antigen presentation has changed the general view of T cell function by showing that T cells recognize lipid antigens in addition to peptides. Our general hypothesis is that mycobacterial factors may be involved in modulation of host immune response by inducing CD1 antigen processing, inflammasome activation and IL-1 generation. We propose a multidisciplinary approach to determine (I) the mycobacterial compounds that stimulate CD1 induction in human dendritic cells; (II) the mechanisms by which interleukin 1 generated by M. tuberculosis stimulates CD1 expression in human dendritic cell and thereby discover new mycobacterial activators of Tolllike receptors and inflammasome in human dendritic cells. Defining the early molecular events by mycobacterial ligands and inflammasomes regulate CD1 induction may represent an approach to discovering new adjuvants to be used in vaccines and also expands the very concept of "adjuvant" by illuminating mechanisms of both MHC and CD1 expression in dendritic cells.



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Latin American Fellows Program *in the* Biomedical Sciences

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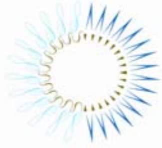
Field: Immunology

Research:

Recent advances in high resolution imaging technology have enabled the direct analysis of immune cell activity in intact tissues and organs in a living host. Using these new methods based on 2-photon microscopy, cell-cell interactions during the process of antigen recognition, the acquisition of effector functions, and the development of humoral responses have been directly observed and analyzed. New information about physical and chemical cues that guide productive immune cell migration and interaction have been revealed, the interface between the innate and adaptive limbs of the immune system has been explored, and the interactions of immune cells and tumors or infectious agents have been visualized. Here, we propose the use of advanced live imaging techniques to study immunological memory, a very important but still incompletely understoof aspect of immunity. The focus will be on $CD4^{+}$ T cells and how their dynamic behavior may differ from naive T cells in secondary lymphoid organs. Using TCR transgenic memory cells generated in vivo and labeled with fluorescent dyes or genetic fluorescent markers including reporters for cytokine gene expression, we will study (i) the general pattern of migration, dynamic behavior, and interaction with antigen-presenting cells, (ii) behavior in the presence of cognate antigens, (iii) dynamics of reactivation, (iv) interaction with lymph node stromal cells, and (v) molecular control of migration and localization. These data will be used to better understand how memory cells give rise to more rapid immune responses, how memory responses interface with those of naïve cells, and how memory cells can be best re-activated to participate in control of tumors and pathogens.



Facundo Germán Pelorosso, M.D.

2009 Pew Fellow

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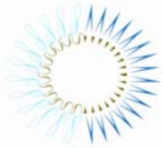
Field: Cancer genetics/ Cancer mouse models

Research Interest: Cancer cells often show a high proliferative rate which results in increased metabolic needs when compared to normal cells. In addition, tumor cells usually develop the ability to increase their glucose intake and their glycolytic rate even in the presence of oxygen. This process, known as the Warburg effect, renders cells resistant to hypoxia and might represent a valuable therapeutic target for cancer treatment. I have obtained preliminary evidence suggesting that loss of Homeobox interacting protein kinase 2 (Hipk2), a gene commonly lost in human tumors, promotes a dramatic change in expression of several enzymes critically involved in glucose metabolism. In particular, Pyruvate kinase m2 (Pkm2) isoform, a putative key regulator of the Warburg effect, is selectively up-regulated by Hipk2 loss. Therefore, in this proposal, I outline my plan to evaluate this potential new role of Hipk2 as a master regulator of cancer cell metabolism. In particular, I plan to further study the effect of Hipk2 loss mRNA and protein expression level on Pkm2 as well as the other potential targets revealed by the preliminary assays. Furthermore, I propose to perform biochemical studies to evaluate the role of Hipk2 on tumor cell growth under low oxygen and glucose conditions, to characterize the possible interaction of Hipk2 with known master regulators of hypoxic metabolism, and, finally, to find new interacting partners of Hipk2 by implementing a relevance network analysis based on available genomic and expression databases derived from different tumor types. The accomplishment of this project will provide new insights into the role of Hipk2 on tumorigenesis and cancer cell metabolism.



Ileana Slavin, Ph.D.

2009 Pew Fellow

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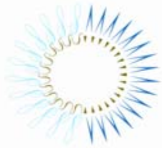
Field: Stem Cells Biology, Cellular and Molecular Biology

Research Interest:

Embryonic stem (ES) cells are pluripotent cells derived from the inner cell mass of the mammalian blastocyst. It has been suggested that microRNAs (miRNA) are coordinately controlled in human embryonic stem cell (hESCs) and, together with epigenetic mechanisms, play critical roles in regulating pluripotence and differentiation. There is a large cluster of 40 miRNAs located downstream of the Maternally Expressed Gene 3 (MEG3), which is an imprinted noncoding gene on human chromosome 14, and its expression is controlled by a Differentially Methylated Region (DMR). Preliminary studies have shown that this MEG3-associated miRNA cluster is strongly downregulated in hESCs, and that the two analyzed CpG sites in its DMR are hypermethylated. These results suggest that these miRNAs may be coordinately repressed in hESCs by hypermethylation, and could be key regulators of pluripotency and differentiation. Moreover, as these miRNAs are also downregulated in some tumors, they may play important roles as tumor suppressor genes in solid tumors.
In order to understand the relationship between expression of this miRNA cluster and epigenetic marks in hESCs, we propose to elucidate the epigenetic mechanisms controlling the expression of the chr14 miRNA cluster, and evaluate whether changes in its expression impacts the maintenance of pluripotence and/or the capacity to differentiate in hESCs. Identification of epigenetic mechanisms that influence the miRNA expression profile in hESCs and differentiated cells is of great importance, particularly those that control the expression of tumor-suppressor genes or oncogenes.



Luis Francisco Zirnberger Batista, Ph.D.

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Field: Telomerase regulation

Research Interest:

The recent generation of induced pluripotent stem (iPS) cells represents a major breakthrough in molecular medicine. With this technique, pluripotent cells are derived directly from a patient's own cells, avoiding the problem of tissue rejection upon transplantation. The ability to re-program somatic cells into an embryonic stem (ES)-like state provides a new and unique tool not only for basic research, but also as a source of cells for clinical use. Although important progress has been made in the last couple of years, the steps that must occur during the re-programming process of somatic cells to iPS cells remain ill-defined. To gain further knowledge on this subject, we propose to determine the regulation of the telomerase complex during the reprogramming process, as well as its importance to the achievement of pluripotency. Also, in a more translational approach, we intent to generate iPS cells from cells isolated from patients with dyskeratosos congenita, a bone marrow failure disease associated with unusual telomere shortening. Together, these studies will greatly inform our understanding of iPS cell reprogramming and provide new insights into a human genetic disease, which together may allow us to correct these genetic defects in dyskeratosis patients.