Neuroprotection Varadero 2015

International Symposium on Neuroprotection

Scientific Program

April 7th – 10th, 2015

Melia Marina Varadero Hotel, Cuba
Dear Colleague,

We are glad welcoming you to Neuroprotection Varadero 2015,

This Meeting will highlight cutting-edge advances from leading basic, clinical and academic topics, as well as regulatory aspects for the development of new therapeutic candidates targeting neurological disorders, such as stroke and neurodegenerative diseases.

This four-day event will be an excellent opportunity to promote the translational nature of modern biomedical and pharmaceutical research, with both scientists and clinicians associated with either drug discovery research or patient care.

We hope the wonderful environment in Varadero will enhance the opportunities for scientific exchange among all the participants to discuss and present the latest important developments in Neuroprotection.
**Neuroprotection Varadero 2015**

**Wednesday, April 8th**

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<td>Deep Phenotyping and Epidemiology In ALS: The Road to Personalized Medicine ? Orla Hardiman (Ireland)</td>
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<td>New evidences of central and peripheral hyperexcitability in patients with ALS Joel Gutierrez (Cuba)</td>
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<td>Bilirubin neurotoxicity and neuroprotection</td>
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<td>10:45 – 11:15</td>
<td>The Role of Periodontitis in Cognitive Function and Ischaemic Stroke</td>
<td>Wenche S. Borgnakke (USA)</td>
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<td>Systemic therapeutic hypothermia in newborns with encephalopathy</td>
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<td>12:15 – 12:45</td>
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Ari Waisman (Germany) |
| 09:30 – 10:00 | Neuroprotection of C-Phycocyanin (c-Pc) and Phycocyanobilin (Pcb) in the context of their general pharmacological properties: concepts that may be underlying  
Majel Cervantes (Cuba) |
| 10:00 – 10:30 | Place of Death in Amyotrophic Lateral Sclerosis: Cuban Experience  
Tatiana Zaldivar (Cuba) |
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Miriam Bucheli (USA) |
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Neuroprotection Varadero 2015

Abstracts

Oral Presentations
BIOMEDICAL RESEARCH AT THE CIGB, HAVANA

Gerardo Guillen Nieto  
*Center for Genetic Engineering and Biotechnology. La Habana, Cuba.*  
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An extensive product pipeline has been built by the Cuban Biotechnology Institutions and by the CIGB. Growing under particular environment with limited resources, the biotechnology is tightly connected with the health system and is driven by a national collaboration instead of competition. The urgency for immediate application of scientific results reinforced the need for expanding collaboration across the sector. Research generated by the CIGB has developed a number of products with significant impact to society. An overview of the achievements including the R&D projects with a strong intellectual property position and the project pipeline comprising several hepatitis related projects will be introduced to the participants.

BUILDING COLLABORATIVE LINKS BETWEEN IRELAND AND CUBA - A TALE OF 2 POPULATIONS.

Orla Hardiman  
*BSc MB BCh BAO MD FRCPI Academic Director, Trinity Biomedical Sciences Institute,  
Professor of Neurology, Trinity College Dublin, Ireland.*  
[orla@hardiman.net](mailto:orla@hardiman.net)
LESSONS LEARNED FROM PRECLINICAL AND CLINICAL STUDIES OF HIGH-DOSE ALBUMIN FOR NEUROPROTECTION IN ACUTE ISCHEMIC STROKE.

Myron D. Ginsberg, MD  Department of Neurology, University of Miami Miller School of Medicine, Miami, Florida, USA 33136
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Objective: To reassess preclinical and clinical-trial investigations of albumin-neuroprotection to understand discrepant outcomes and to discern when pharmacological neuroprotection may be feasible.

Methods and Results: Studies of high-dose albumin in rodent models of focal cerebral ischemia established consistent neuroprotection (markedly reduced infarct volumes; improved neurobehavior; diminished brain swelling), mediated by many mechanisms (improved perfusion of ischemic core and penumbra; beneficial fatty acid responses; reversal of venular stagnation; improved microvascular perfusion) and supported by literature documenting salutary antioxidant effects and actions on macromolecular transport, oncotic pressure, endothelium, and platelets. Nonetheless, a carefully conducted randomized controlled clinical trial failed to show benefit in patients with acute ischemic stroke. What might account for this discrepancy? Our preclinical studies were conducted mostly in young male rats, in which ischemia was transient (typically, 2 hours) and was produced by an intraluminal filament rather than a blood clot. The lesions were highly reproducible in size and location. By contrast, human subjects in the ALIAS (Albumin in Acute Stroke) Trials were typically older and had thromboembolic strokes that varied in location and extent; 85% received intravenous alteplase (tPA) and ~20% had endovascular thrombolysis. Non-thrombolysed subjects were too few for independent analysis.

Conclusions: Albumin may have failed in clinical trial primarily because a) thrombolysis led to a therapeutic “ceiling” benefit that could not be improved upon by albumin; and b) the overall quality of acute stroke care improved during the trial. Of particular relevance, we have shown experimentally that, while albumin enhances collateral perfusion during ischemia in mouse strains with poorly developed collateral circulation, it has no effect in strains that are already well-collateralized. We speculate that albumin therapy might still have an adjunctive role to play in selected patients with ischemic stroke and poorly developed collaterals.
EPIDERMAL GROWTH FACTOR AND GROWTH HORMONE-RELEASING PEPTIDE-6: COMBINED THERAPEUTIC APPROACH FOR NEURODEGENERATIVE DISEASES.

Authors: Nelvys Subirós Martínez, Héctor Perez Saad, Yaima Rodríguez, Sasha Sánchez, and Diana García del Barco

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Introduction: Considering the multiple pathophysiologic mechanisms involved in neurodegenerative diseases (amyotrophic lateral sclerosis, multiple sclerosis, stroke and others), we sustain the convenience of combined therapy to induce brain protection. Such strategy could allow a concerted blocking of key points of the complex pathophysiology characteristic of neurodegenerative diseases.

Objectives and Methodology: We have developed a therapeutic approach based on the co-administration of EGF+GHRP6 which is in agreement with the principle that successful protection of the central nervous system compels the protection of all the cells thereof.

Results: Some of the pathophysiological phenomena produced during brain damage are targeted by the citoprotective effects of both EGF and GHRP6. The most relevant of these effects act on oxidative stress-induced damage, on mitochondrial dysfunction and on glutamate-induced excitotoxicity. All this properties can explain the salutary therapeutic effects of EGF+GHRP6 co-administration observed in different experimental models of amyotrophic lateral sclerosis, multiple sclerosis and stroke during preclinical evaluations.

Conclusions: The combined therapy of EGF and GHRP6 simultaneously targets different pathophysiologic key points involving not only neurons, but also glial cells and vascular endothelium. In the biology of brain damage, neuroprotection is a limited concept, so it is necessary to think of a more complete praxis involving brain-protection. The results of this work could be considered as an example of therapeutic alternative holistically directed to brain-protection.
There are no disease-modifying drugs for any old age-associated neurodegenerative diseases or stroke. This is at least in part due to the failure of drug developers to recognize that the vast majority of neurodegenerative diseases arise from a confluence of multiple, toxic insults that accumulate during normal aging and interact with genetic and environmental risk factors. Thus, it is unlikely that the current single target approach to drug discovery based upon rare dominant mutations or even a few preselected targets is going to yield useful drugs for these conditions. Therefore, the identification of drug candidates for neurodegeneration should be based upon their efficacy in phenotypic screening assays that reflect the biology of the aging brain, not a single preselected target. We have identified a set of cell-based assays that define molecular toxicity pathways relevant to age-associated neurodegeneration. These include assays for protection against cell death induced by endogenous oxidative stress, energy loss, neurotrophic factor withdrawal and intracellular amyloid beta peptide toxicity. An additional assay for anti-inflammatory activity is also included. We require our drug candidates to work in all of these assays. We identified two polyphenols that were effective in most or all of these assays and used structure activity relationship-driven iterative chemistry to improve their potency and physicochemical properties. We now have several drug candidates that greatly reduce cognitive and other behavioral deficits in multiple animal models of AD and therefore have great potential for the safe and effective treatment of the disease.
TRANSLATION OF PSD95 INHIBITORS FROM MOLECULAR DISCOVERY TO PHASE 3 CLINICAL TRIALS.
Dave Garman\textsuperscript{1}, and Michael Tymianski\textsuperscript{2}
1NoNO Inc., Toronto, Canada, 2Division of Neurosurgery, Toronto Western Hospital, Toronto, Canada
dgarman@nonoinc.ca

Objective: The objective of this program is to develop a PSD95 inhibitor for the treatment of acute ischemic stroke in humans. Community acquired stroke is a disorder that affects millions of people each year, but only 3-5% of victims are eligible to receive a drug to reduce the neurological damage from stroke. The FRONTIER trial is a Phase 3 clinical trial currently enrolling in Canada to evaluate the efficacy of NA-1, a novel neuroprotective agent, for the treatment of stroke.

Methods: PSD95 inhibitors were tested in multiple rodent and primate models of stroke to demonstrate their efficacy. The lead PSD95 inhibitor, NA-1, was tested in Phase 1 and Phase 2 human clinical trials to demonstrate its safety and efficacy in the reduction of strokes visible by MRI.

Results: NA-1 was able to reduce the amount of neuronal damage by 50-80% relative to controls in various animal models of ischemic stroke. In the Phase 2 human clinical trial, ENACT, NA-1 reduced the number and volume of strokes in patients undergoing endovascular repair of unruptured and ruptured aneurysms. No significant safety issues were identified, indicating that NA-1 is likely to be safe for administration to subjects with ischemic or hemorrhagic strokes.

Conclusions: NA-1 has been shown to be effective in reducing neuronal damage following strokes in human subjects with demographics similar to the acute ischemic stroke population. Thus, NA-1 development is being continued in a further clinical trial assessing its efficacy in community acquired stroke (FRONTIER).
Wednesday, April 8th

DEEP PHENOTYPING AND EPIDEMIOLOGY IN ALS: THE ROAD TO PERSONALIZED MEDICINE?
Orla Hardiman BSc MB BCh BAO MD FRCPI Academic Director, Trinity Biomedical Sciences Institute,
Professor of Neurology, Trinity College Dublin, Ireland.
orla@hardiman.net

Background
Amyotrophic lateral sclerosis (ALS) is a rare and heterogeneous condition, reflecting a complex interaction between genetic and environmental factors. The established incidence rates of ALS in populations of European extraction is 2.6-3.0/100,000, and at least 24 genes of major effect have been identified of which 4 are important in European populations.

Results
Detailed analysis of our extensively phenotyped population-based register in Ireland demonstrates that ALS is clinically and genetically heterogeneous, with up to 60% of patients exhibiting evidence of cognitive and behavioural impairment. Genotyping of the Irish ALS population indicates that at least 17% of patients harbour variants in known “at risk” genes. Additionally, extensive family aggregation studies, coupled with bioinformatics analysis of publicly available datasets indicate that ALS and some neuropsychiatric conditions may be biologically linked. Spatial mapping of ALS in Ireland demonstrates discreet areas of reduced risk, suggesting that areas of subtle population admixture may alter disease susceptibility.

Conclusions
Careful multimodal clinical, epidemiologic and genetic study of ALS is likely to provide greater clarity regarding disease heterogeneity, and will in turn provide a roadmap for tailored therapeutic interventions based on newly defined disease signatures.
NEW EVIDENCES OF CENTRAL AND PERIPHERAL HYPEREXCITABILITY IN PATIENTS WITH ALS

Joel Gutiérrez, Isván Alvarez, Tatiana Zaldívar, Gloria Lara, Orla Hardiman

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OBJECTIVE:
Various experimental and clinical studies have evidenced central and peripheral nervous system hyperexcitability in patients with sporadic amyotrophic lateral sclerosis (ALS). While brisk tendon reflexes and fasciculations are essential for the clinical diagnosis of ALS the pathophysiological role of nervous system hyperexcitability in ALS (cause or consequence of the disease?) is not yet fully understood. Increased cortical excitability and spinal motor neurons hyperexcitability have been extensively studied but, as happens with motor deficits, hyperexcitability in ALS is a widespread rather than a focal disorder. The present study discloses some other evidences of nervous system hyperexcitability in patients with ALS which have received little or no attention: 1- Decreased habituation of blink reflex responses, 2- Increased facilitation of jaw jerk reflexes and 3- Increased excitability of peripheral motor fibers (assessed with mechanical tapping of peripheral nerves). These signs of hyperexcitability can be clinically explored bed side, without the need of complex technological devices and are not present in some of the disorders that can mimic ALS. Therefore, in the context of patients with suspected ALS, the presence of these clinical signs could represent an additional aid in early diagnosis and monitoring of the disease.
The impressive development of biotechnology over the past decades has provided a wealth of biological products with therapeutic potential in (auto)immune-mediated inflammatory disorders (AIMID; e.g. rheumatoid arthritis, multiple sclerosis, diabetes etc.). However, the translation of promising effects observed in standard animal disease models has been notoriously difficult. This unfortunate situation creates a need for disease models in animals that more closely approximate the human condition, non-human primates for example.

The common marmoset is a small-bodied Neotropical primate (±350 grams at adult age) that breeds well in captivity. The evolutionary proximity to humans (±35 million yrs) is translated in a high degree of genetic and immunological proximity. Moreover, just like humans, but different from SPF-bred laboratory rodents marmosets live under conventional conditions, where they are exposed to environmental pathogens. These features make the marmoset an exquisite model for translational research into the (immuno)pathogenesis of AIMID. I will review data obtained in a validated preclinical model of the human neuro-inflammatory disease multiple sclerosis (MS), experimental autoimmune encephalomyelitis (EAE) and will discuss the relevance for our understanding of the human disease1.

In brief, we discovered a new pathogenic mechanism that seems relevant for MS, but seems not to exist in SPF rodent EAE models. We postulate that this mechanism is an essential missing link between the animal model and the MS patient.

Reference:

HEALTH SYSTEMS: NEED OF CARE POLICIES. AN APPROACH TO CUBAN EXPERIENCE.
Laura Galeano Zaldivar. Department of Development Economics, Faculty of Economics, Havana University.
lauragz@fec.uh.cu
EXPANDING THE NEUROPROTECTION WINDOW AFTER TBI: TARGETING DELAYED NEUROTOXIC INFLAMMATION

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Objectives: To address the role of persistent neuroinflammation in progressive cell death and tissue damage after TBI, and whether this can be modified late after injury.

Methods: Experimental TBI models were examined in mice subjected to controlled cortical impact (CCI). Animals were followed from 1-12 months after injury, and assessed for behavioral changes and stereological assessment of lesion volume, neuronal cell death and inflammation. Treatments included NADPH oxidase (NOX2) inhibition (pharmacological or genetic), mGluR5 agonist administration, or delayed voluntary exercise.

Results: Progression tissue damage continues through 12 months after CCI, associated with microglial activation (M1 like phenotype) and free radical generation. Trans-membrane components (gp91, p22phox) of NOX2 are chronically up-regulated after injury. GP91 knockout or administration of the NOX2 inhibitor apocynin are markedly neuroprotective, as is the mGluR5 orthosteric agonist CHPG. mGluR5 activation in microglia attenuates NOX2, and central administration of CHPG at 1 month after CCI limits lesion volume expansion and promotes cognitive and motor recovery. Systemic administration of positive allosteric modulators (PAMS) of mGluR5 also inhibits neurotoxic inflammation and promote recovery. Voluntary exercise on a running wheel beginning 5 weeks after CCI attenuates NOX2, neurotoxic inflammation and neurological dysfunction, whereas earlier exercise initiation at 1 week does not.

Conclusions: Experimental TBI leads to chronic progressive neurodegeneration associated with persistent microglial activation, consistent with recent clinical MRI and PET studies. Chronic activation of NOX2 appears to contribute to this neurotoxic inflammation and can be attenuated even weeks after injury through selected molecular targeting or aerobic exercise.
Monoclonal antibodies are biological molecules with great potential for the treatment of autoimmune inflammatory disorders, such as multiple sclerosis (MS), because of their unique capacity to selectively eliminate (physically or functionally) pathogenic cells and molecules. However, despite some successes the translation of promising effects observed in MS animal models into effective treatments for the patient has been notoriously difficult. A major hurdle is the predictive quality of the frequently used MS animal model experimental autoimmune encephalomyelitis (EAE). Our preclinical research in a relevant non-human primate EAE model has shown that the autoreactive T cells that drive progression of neuroinflammatory disease are recruited from a pathogen educated subcompartment of the immune system2, 3. SPF-bred mice lack this T cell compartment and the EBV-infected B cells that are needed for T cell recruitment. We have tested the clinical validity of this novel pathogenic concept using monoclonal antibodies that have been tested with varying success in the clinic, i.e. ustekinumab (anti-IL-12p40), belimumab (anti-BLyS/BAFF) and a clonal variant of ofatumumab, (anti-CD20). The clinical results in the marmoset EAE model seem to replicate the activity in MS and provide insights into the relevance of the new pathogenic mechanism for the human disease.

References:
THE ROLE OF BILIRUBIN IN NEUROPROTECTION AND NEUROTOXICITY

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Objective. Bilirubin has been considered for long time only a waste, and potentially neurotoxic product of the heme catabolic pathway, but more recent data indicate that this tetrapyrrolic compound has also important beneficial effects, in particular against various oxidative stress-mediated diseases. The main objective was to critically review the state of the art in the bilirubin field with focus on its both neuroprotective and neurotoxic effects.

Methods. Data published in the last few decades in journals available in public medical databases, as well as own experimental and clinical data on bilirubin neurotoxicity have been critically reviewed.

Results. Bilirubin neurotoxicity, still being a threat for patients with severe neonatal jaundice or those suffering from Crigler-Najjar syndrome type I, is dependent on its intracellular concentrations, which are in direct relationship with its unbound fraction in the circulation (Bf, bilirubin free). However, mildly elevated systemic concentrations of bilirubin are associated with protection against a whole range of neurodegenerative, psychiatric and autoimmune diseases, such as Alzheimer’s disease, Parkinson’s disease, probably also schizophrenia and neurolupus.

Conclusions. Bilirubin is a typical yin and yang compound, being neurotoxic at very high concentrations, whereas being neuroprotective when only mildly elevated. These novel findings have also therapeutic implications, since modulation of the heme catabolic pathway might substantially affect risk of neurological diseases.

THE ROLE OF PERIODONTITIS IN COGNITIVE FUNCTION AND ISCHAEMIC STROKE

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SYSTEMIC THERAPEUTIC HYPOTHERMIA IN NEWBORNS WITH ENCEPHALOPATHY

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METALLOTHIONEIN: AN ANTIOXIDANT MOLECULE WITH NEUROPROTECTIVE EFFECTS IN TWO MODELS OF CENTRAL NERVOUS SYSTEM DAMAGE.

Araceli Diaz-Ruiz¹, Ivan Santander-Rodea¹, Sandra Orozco-Suarez², Alma Ortiz-Plata³, Marisela Méndez-Armenta³, Patricia Vacio-Adame¹ and Camilo Rios¹.

¹Department of Neurochemistry, National Institute of Neurology and Neurosurgery, Mexico City, Mexico.
²Unit of Medical Research in Neurological Diseases; Mexican Social Security Institute Siglo XXI, Mexico City, Mexico.
³Department of Experimental Neuropathology, National Institute of Neurology and Neurosurgery, Mexico City, Mexico.

Spinal cord injury (SCI) and stroke are world-wide health problems. Therefore, the development of neuroprotective strategies for them is an important goal. Metallothionein (MT) is a small protein with high cysteine content, present both in neurons and glia. Constitutive (MT-III) and inducible (MT-I, MT-II) forms of the protein are expressed after damage. MT is a scavenger of free radicals, mainly hydroxyl radical. The Objective of this study was to characterize the effects of MT by monitoring oxidative damage and apoptosis after SCI or brain ischemia and reperfusion (I/R) in Wistar rats.

Methods: Animals were treated with either vehicle or MT-II at a dose of 10 microg/rat/day, for 3 days, starting MT treatment 3 h after insult. Reactive oxygen species (ROS), lipid peroxidation, the activity of caspases 9 and 3, and histological markers of damage were measured after SCI or I/R. Results showed that animals treated with MT show reduced ROS, lipid peroxidation and a diminution in the activity of caspases 3 and 9, as compared to lesioned animals without treatment. After SCI, we also found a reduced number of cells positive to annexin V and TUNNEL, as compared to the group without treatment. Likewise, animals with I/R and treated with MT-II, showed a better recovery and diminished tissue damage.

Conclusion: MT is a treatment that reduces secondary damage after SCI and I/R, and it is a good promise for a better treatment of patients, as the protein is a natural human blood component. Supported by CONACYT grant 183667
CHARACTERIZATION OF THE NEUROPROTECTIVE MECHANISMS OF DAPSONE
Camilo Rios\textsuperscript{1}, Araceli Diaz-Ruiz\textsuperscript{1}, Jorge Flores-Hernández\textsuperscript{2}, Pavel Montes-de-Oca\textsuperscript{1}, Alma Ortiz-Plata\textsuperscript{3}, Penélope Aguilera\textsuperscript{3}.
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\textsuperscript{1}Department of Neurochemistry, National Institute of Neurology and Neurosurgery. Mexico City, Mexico.
\textsuperscript{2}Instituto de Fisiología, Benemérita Universidad Autónoma de Puebla, Puebla, Mexico.
\textsuperscript{3}Departments of Experimental Neuropathology and cerebrovascular diseases, National Institute of Neurology and Neurosurgery. Mexico City, Mexico.

According to the WHO, there are 15 million of patients suffering from Stroke every year. Five million of them die and other 5 million live with permanent disability. dapsone is currently in use for Leprosy. We discovered a neuroprotective effect of dapsone in animal models of brain ischemia. Recently, we finished a Phase-II clinical trial using dapsone to treat patients with ischemic Stroke. From that study, we concluded that dapsone, administered within the 12 h after brain infraction, was able to increase the number of patients without sequels (Rankin scale 0) from 8.9\% (Placebo group) to 25\%. **Objective:** To characterize the mechanism of neuroprotection exerted by dapsone. **Methods:** We employed 2 models of damage: Culture cells exposure to N-Methyl-D-Aspartate agonist of glutamate receptor, and a model of spinal cord injury (SCI) by contusion. The former was employed to test the hypothesis that dapsone is potential antagonist of the NMDA receptor. The latter was used to characterize the anti-inflammatory effects of the drug. **Results:** NMDA-induced Calcium influx to cells (rat cortical cells and neuroblastoma cells), was reduced by 30-40\% in the presence of micromolar concentrations of Dapsone, as recorded by Fluo-4 live cells fluorescence, and patch clamp recording. This antagonistic effect was dose-dependent. Dapsone dose tested (25 mg/Kg), administered 3 h after SCI to rats reduced significantly the arrival of both neutrophils and macrophages to the site of lesion. **Conclusion:** Dapsone is acting both as an NMDA-receptor antagonist and an anti-inflammatory drug. Supported by CONACYT grant 183667.
Th17 cells are critically involved in the development of autoimmune disease, but the mechanism for that is not clear. In our lab, we use techniques of conditional gene targeting to study the function of these cells. In my talk, I will discuss the need for cytokine signaling for the development of pathogenic Th17 cells. Furthermore, I will show how the transcription factor IRF-4 and RORt regulate the development of these cells. In addition, I will discuss the topic of gut microbiota and their role in autoimmunity.

In the gut, as with the skin and lung, the immune system is constantly exposed to the local bacteria. A steady state exists between these bacteria, termed microbiota, and the immune system, each influencing the other. It was previously shown that specific microbes are involved in the generation of Th17 cells in the gut, and that the presence of some bacterium species in the gut can influence the development of autoimmunity. By using mice lacking the expression of IL-17, we discovered the counter influence of Th17 on the microbiota. We found that the absence of IL-17 affects the composition of the gut microbiota, and that this change in the bacterium species present in the gut results in different susceptibility to autoimmunity. Our studies reveal that some bacteria species in the gut are not involved only in the development of effector T cells, but suggests that they may also regulate the development of suppressive immune cells.
NEUROPROTECTION OF C-PHYOCYANIN (c-Pc) AND PHYCOCYANOBILIN (Pcb) IN THE CONTEXT OF THEIR GENERAL PHARMACOLOGICAL PROPERTIES: CONCEPTS THAT MAY BE UNDERLYING

Pentón-Rol G¹, Marín-Prida J¹, Lagumersindez-Denis N², Cervantes-Llano M¹, Muzio L¹, Bergami A¹, Furlan R¹, Fernández-Masso JR¹, Nazabal-Gálvez M¹, Llópiz-Arzuaga A¹, Herrera-Rolo T¹, Véliz-Rodriguez T¹, Polentarutti N¹, Raíces-Cruz I¹, Valenzuela-Silva C¹, Teixeira MM¹, Pentón-Arias E¹.

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C-Pc, the biliprotein conferring color to the blue-green algae *Spirulina platensis* (Sp) and Pcb, its colored tetra-pyrorlic prosthetic group and the active ingredient responsible for most of the pharmacological properties attributed to Sp and C-Pc, have been shown to share a wide range of activities with therapeutic potential, mainly verified in vitro or in animal models, but starting to slowly seep into the clinical setting. This presentation deals with the neuroprotective properties of these components and their correlation with more general concepts possibly underlying these and other actions of clinical interest described for the crude algae preparations, the purified biliprotein (C-Pc) and their pharmacologically active functional group (Pcb) from extractive or synthetic sources. Some observations on the superior performance of C-Pc compared to Pcb, are not surprising if the apoprotein moiety is considered as the preserving envelope of the prosthetic group, indicating that in the future the interactions between these structures must be better characterized. C-Pc and/or Pcb neuroprotective effects have been evidenced in acute monophasic and chronic progressive Experimental Autoimmune Encephalomyelitis (EAE) rat and mouse models, in a global I/R ischemia model in gerbils, in a focal I/R ischemia in retina and chronic cerebral hypo-perfusion model in Wistar rats and on isolated mitochondria from brain exposed to neurotoxic agents, preventing cellular death.
Our group at CIGB, together with the excellent assistance of colleagues from other collaborating centers, has been able to show that C-Pc and Pcb show a potent capacity of preventing or limiting the extension of injuries to the central nervous system (CNS) of different nature, which may derive from entities so distant from each other as a vascular occlusion and an internal pathological process such as multiple sclerosis (MS). Moreover, during the last two decades, a large number of pharmacological properties have been described for Sp, C-Pc and Pcb, most of them (but not all) for all three, meaning that they ultimately depend on Pcb, which are those we are concerned with in this presentation. These are the vast majority of the properties described for Sp, but there are cases in which they do not depend exclusively on Pcb, since the role of the C-Pc protein subunits is also relevant for certain actions, such as keeping the stability, integrity and proper ionization state of the active functional group. It can be easily understood that although the well-known anti-oxidant or reactive oxygen species (ROS) scavenging capacity of these active principles is important, it cannot solely explain the diversity of processes claimed to be modified such as inflammation, atherosclerosis, immune modulation, cytoprotection, cancer, etc., for which reason, other basic mechanisms are also expected to be involved. Our group has provided evidence on other mechanisms such as the induction of regulatory T cells subsets and the modulation by C-Pc of the differential expression of genes involved in mechanisms for the regulation of signal transduction, transport of protein, synaptic transmission, immune processes, apoptosis, re-myelination and gliogenesis.
PLACE OF DEATH IN AMYOTROPHIC LATERAL SCLEROSIS: CUBAN EXPERIENCE.

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Background: There are several studies about place of death, and whole agree this topic is considered an important indicator of quality of end-of-life care. Death in the usual place of residence is associated with the presence of family and friends, comfort and a feeling of control. One additional element being highlighted as increasingly important to the concept of a 'good death' is identifying patients' preferences for how wish to be cared for at the end of their lives and where they wish to die. This is a cultural concept, and not only related with quality of health care at the end of life.

Institute of Neurology and Neurosurgery in Cuba, has the experience, since October 2005, with the differentiated clinical attention to ALS patients. Referrals are received from throughout Cuba for diagnostic confirmation.

Aim: Identify where the place of death more preferred by ALS patients and families is.

Methodology: Death data in ALS patients which received follow up in a multidisciplinary attention clinic, were resumed, in the period 2008-2013.

Results: Variables obtained for each record included age at death, sex, color of skin, and place of death. Mean age of death was 61 +/- 10 SD. 77 patients died with ALS diagnosis, home death was more frequent in older patients, mean age 65 and in younger patients was more frequent place of death in hospital, mean age 59. P0.035.

Conclusions: It is remarkable, the study about several factors related with place of death in order to improve counseling about End of life to patients and caregivers.
BIOETHICAL CONSIDERATIONS FOR VULNERABLE PATIENT POPULATIONS IN INTERNATIONAL STUDIES
Miriam E. Bucheli, PhD Department of Neurology, University of Massachusetts Medical School, USA; YACHAY EP, Ecuador
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Historically, Latin America has been far behind North America, Western Europe and Asia in scientific output, but for the period 1996-2008, Scopus publication data indicate that Latin America and Asia were the fastest growing producers of such output. Throughout Latin America, much scientific output has historically been due to international collaborations, especially with developed countries. In general, Latin American scientists publish more papers with U.S. collaborators than with those from any other country.

Minority populations are of special interest as research subjects, based on their varying genetic and linguistic backgrounds, extreme range of environmental conditions in which they live, and environmental exposures. This creates a classical ethical problem, in which scientists from the dominant population -and their foreign collaborators- study a minority population who are distinct from the majority in language, appearance, customs and/or ancestry, and who are in a lower socio-economic status. Another related issue is that of trust in the scientific community, which has been sadly lacking in minority communities in the U.S. and elsewhere in Latin America. Solutions to address these problems are to have no group under-represented in the scientific workforce, as well as, the creation of community liaisons and training in the issues of research ethics by ethically trained scientists that can encourage community involvement.

With the growth of scientific research in Latin America, training in biomedical research ethics must seek to prepare scientists to do research or to collaborate in international research that can satisfy grant agencies, plus government, university, and industrial regulations.
# List of Participants

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The CIGB Biomedical Research Direction is pleased to announce as part of the series of events on OMICS and Bioinformatics the International Meeting **OMICS Varadero 2015** which will be held on October 27th-30th in Varadero, Cuba.

The Meeting will cover topics such as bioinformatics and statistical methods for genomic and proteomic research, technologies for OMICS data generation, cancer genomics, mass spectra data processing and computational proteomics, next Generation Sequencing: RNASeq, ChipSeq, DNA methylation, data management and analysis, metagenomics; personalized medicine: selection of drug-response markers, translational biomarkers, epigenetics, integrative OMICS data analysis, genomic technology and methodology development and system biology based bioinformatics software development.

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The CIGB's Direction of Biomedical Research invites you to attend **Basic Wound Healing Varadero 2016**, an *International Meeting on basic aspects of physiological and pathological cutaneous healing* which is going to be held on Oct 25-28, 2016.

The Meeting will gather some of the world's top researchers and specialists in these hot topics and is intended for clinicians and scientists interested on the cellular and molecular mechanisms of cutaneous tissue repair.

**Major clinical conditions to be addressed:** Basic science of burn injury, diabetic foot ulcers and pressure ulcers.

I- Epithelial response to injury.
II- Dermal response to injury.
III- Immuno-inflammatory cells response in wound healing.
IV- Growth factors and stem cells in wound healing.

We cordially invite you to be part of these exciting meetings. For more information please visit [http://biomed.cigb.edu.cu](http://biomed.cigb.edu.cu)
**LEGEND**

**BEACH**
7. Beach of the hotel

**RESTAURANTS**
8. - El Pilar / Buffet
   - Don Ernesto / Latin
   - Don Peperoni / Italian
   - Casa Burguete / Gourmet
   - Bana / Oriental
   - Islas en el Golfo / Ice cream parlor
9. El Pescador / Beach grill
10. Habana / Snack bar (pool)

(*) As Reference

**BARS**
11. - Fiesta / Lobby Bar / Piano Bar
    - Cojimar / Beers Bar
    - Daiquiri / Ron Bar

12. - Vuelta Abajo / Cigar Bar
13. - Ambos Mundos / Appetizers bar
14. - El Mojito / Aquabar
15. - Chiringuito / Beach Bar
16. - La Velas / Pool Bar - Apartments
17. - Tierra española / Tapas bar

(*) As Reference

**FAMILIES**
16. Kids club

**MEETING ROOMS**
17. Convention Center

**YHI SPA**
18. YHI-Spa / Gym / Beauty Parlor

**WEDDINGS**
19. Wedding gazebo

**THE LEVEL**
20. Reception Desk and Lounge Bar La Vigia