Keynote Forum
November 29, 2017

Cell Science & Pharmacology 2017

Annual Congress on

Cell Science, Stem Cell Research & Pharmacological Regenerative Medicine

November 29-30, 2017 | Atlanta, USA

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Vincent S Gallicchio

Clemson University, USA

Lithium and stem cells - Advances in stem cell application in clinical medicine

Lithium (Li) salts have been widely used in psychiatry as mood stabilizing agents for 60 years. Li is found in variable amounts in foods, especially grains, vegetables and in some areas, the drinking water. Collectively these sources provide a significant source of the element. Therefore, dietary intake in humans depends on location, type of foods consumed and fluid intake. Traces of Li have been detected in human organs and tissues, leading speculation that the element was responsible for specific functions in the human body. It was not until the 20th century that studies performed in the 1970's and 1990's, primarily in chickens, cows, rats and goats, maintained on Li-deficient diets demonstrated higher mortality, altered reproductive and behavioral abnormalities. Such deficiencies have not been detected in humans; however, studies performed on populations living in areas with low Li levels in water supplies have been associated with higher rates of suicides, homicides and the arrests rate for drug abuse and other violence-based crimes. Li appears to play a significant role in early fetal development as evidenced by high Li levels during the early gestational period. Biochemically, the mechanism of Li action is multi-factorial involving interconnection pathways incorporating enzymes (a potent inhibitor of GSK3β), hormones, vitamins and growth and transforming factors. It clearly can substitute for magnesium as a cation catalyst and at the molecular level it is an effective inhibitor of the Wnt signal transduction pathway. This body of evidence now appears sufficient to label Li as an essential element with the recommended RDA for a 70-kg adult of 1000 µg/day. Of extreme importance for the future is the growing body of evidence indicating Li can be used effectively for the treatment of acute brain injuries, e.g., ischemia and chronic neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, Tauopathies and Huntington's disease. This conclusion is based upon increasing evidence showing Li as important in neurogenesis as well as protecting neurons from neurotoxicity. More than thirty years ago, it was discovered Li influences stem cells derived from bone marrow by increasing their proliferation, thus stem cell numbers are increased in the presence of Li. It is now being well established that Li increases neurogenesis through stimulation of neuronal derived stem cells. This observation has now shown great promise for additional therapeutic implications for this element in clinical medicine in addition to treating psychiatric/mood disorders. Li has now been shown to be an efficacious treatment modality associated with faulty production or damaged blood or nerve cells, in addition to serving as an effective tool to enhance blood stem cell mobilization for transplantation.

Speaker Biography

Vincent S Gallicchio earned his PhD in Experimental Hematology at New York University Medical Center and completed fellowships in Hematology at the Sloan Kettering Institute for Cancer Research and at the University of Connecticut Health Center. He was awarded a diploma in Internal Medicine from the "Vasile Goldis" University of Arad (Romania). He was rated the number one academic biomedical laboratory science researcher in the United States. His rating of 551 was nearly twice that of the next closest professor's score of 285. Additionally, during his leadership, the academic program in Clinical Laboratory Science at the University of Kentucky Medical Center was rated the number one program of its kind among 127 in the nation. His passion for research, a high value placed on excellence, a strong reputation as an esteemed collaborator and a tenacious desire to see a better therapies for human diseases brought to market speak to his overall character.

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Michael Heggeness

The University of Kansas, USA

Quiescent pluripotent stem cells capable of expressing Sox2, Oct4, Klf4 and c-Myc reside within peripheral nerves in adult mammals and can differentiate into cells of all 3 germ layers

We have documented a large population of quiescent stem cells within peripheral nerves. In response to nerve injury, or stimulation with the cytokine BMP2, these cells proliferate and form pluripotent stem cells, expressing Sox2, Klf4, Oct4 and c-Myc (verified by double stain immunohistochemistry and by real time PCR). These are the transcription factors that confer embryonic pluripotency (Cell 126: 663, 2006). We call these cells Nerve Derived Pluripotent Stem cells, or NEDAPS cells. The cells propagate restrictive media and are readily induced to form tissues from all 3 germ layers. We hypothesize they represent the central feature in an important and previously unknown universal pathway for tissue repair. Nerves are nearly ubiquitous in the body. Thus, we believe that nerve injury accompanies virtually any injury and the consequent proliferation of these stem cells occurs locally following essentially any injury representing a previously unknown universal pathway for healing. Data will document induction and successful culture of these unique new pluripotent cells from three mammalian species and demonstrate their directed differentiation into osteoblasts, endothelial cells, primitive neural cells, definitive endoderm and fibroblasts as demonstrated by morphology, immunohistochemical staining and by Real Time-Polymerase Chain Reaction (RT-PCR) data. Stem cell biology is a field that has recently seen an explosion of new work in the last decade, stimulated by the remarkable discovery that induced pluripotent stem cells (iPCs) 4 transcription factors (listed above), most often by the use of retrovirus vectors (Yamanaka, Cell 126: 663, 2006). Such iPCs are being widely studied as possible sources of cells for the treatment of human disease. This work has been hampered by issues of malignant transformation of iPCs and by immune rejection of "non-self" cells. We are aware that previous claims to successful identification of cells with universal differentiation from non-gonadal adult tissue have sadly resulted in some notable and well publicized scandals, involving fabricated data. Confidence in our admittedly unprecedented idea is provided by information from other species. It has long been known that a salamander or starfish can re-grow an entire arm after amputation, but that ablation of the nerve stump will block the regeneration. (Kumar and Brokes Trend. Neurosci 2012 p691). We propose that this new knowledge will also explain vexing clinical problem of impaired wound healing experienced by severely diabetic patients and victims of leprosy. We suggest that in the severe depletion or absence of these newly discovered stem cells due to the neuropathies associated with these illnesses, is the cause of the healing difficulties seen clinically. The other implication of this discovery is that we may now have a straightforward opportunity to obtain individual specific "self-to-self" stem cell treatments based on cells obtained by minimally invasive biopsy of a nonessential peripheral neve of a specific patient in need.

Speaker Biography

Michael Heggeness completed his PhD at UC San Diego in membrane biology and a postdoc at Rockefeller University in Virology. He received his MD from the University of Miami. After a residency in Orthopaedic Surgery, he completing a fellowship in Spine Surgery at the University of Toronto. He then joined the faculty at Baylor College of Medicine where he became Chairman of Orthopaedic Surgery in 2004. He moved take the Orthopaedic Surgery Chair at University of Kansas in Wichita in 2013. He has 84 publications and 4 issued patents.

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Woodring E Wright

UT Southwestern Medical Center, USA

The creation of artificial lungs from decellularized tissue

Lung failure is a major health problem, both in genetic disorders such as cystic fibrosis and following environmental insults in diseases such as emphysema and idiopathic pulmonary fibrosis. The restricted availability of histocompatible human lungs for transplantation is often a rate limiting factor for treatment. Transplanting both lungs increases patient long-term survival, but the shortage of lungs makes this controversial since it halves the number of recipients. This problem would be solved by being able to create two lungs for each patient. Lung transplantation is further complicated by chronic transplant rejection; after receiving a transplant a patient must be on immune-suppressing drugs for the rest of their lives even after tissue matching. This long term immunosuppression has significant side effects and allows only <20% of recipients to survive more than 10 years after transplantation. We will avoid both immunological and availability problems by using a patient's own bronchial epithelial and endothelial cells to create two lungs. Previous approaches to populating decellularized lungs with bronchial epithelial and endothelial cells have met with only limited success. The introduced cells differentiated rapidly, producing only small foci of normal appearing alveolar or conducting airway histology, widely separated from other foci containing capillaries. We are overcoming these limitations by a variety of interventions to temporarily block differentiation and stimulate both proliferation and migration. Some of these approaches use chemical reagents, while others exploit oncogenes. Many oncogenes are known to block differentiation and stimulate both migration and proliferation. In preliminary experiments, we are introducing them and simply analyzing their effects on colonization of the decellularized lungs. In later experiments, these oncogenes will be under the control of inducible promoters or in cre-lox excisable constructs. All constructs will contain herpes-virus TK suicide cassettes, so that any cells that escaped excision by cre could still be eliminated by treatment with ganciclovir if they began to proliferate excessively. Ultimately, we hope to be able to create transplantable lungs on demand without any need for ongoing immunosuppression.

Speaker Biography

Woodring E Wright received his BA degree, Summa Cum Laude, from Harvard University in 1970, a PhD under the direction of Dr. Leonard Hayflick in 1974 and an MD from Stanford University School of Medicine in 1975. Following a Post-doctoral fellowship at the Pasteur Institute in Paris, France with Dr. Francois Gros, he joined the faculty at Southwestern Medical School in Dallas, Texas in 1978, where he is now Professor of Cell Biology and Southland Financial Corporation Distinguished Chair in Geriatric Research. He has been the recipient of the Lyndon Baines Johnson Research Award of the American Heart Association, a Research Career Development award from the NIH, a Merit Award from the National Institute on Aging, an AlliedSignal Award for Research on Aging, the Hayflick Award from American Aging Association and an Ellison Medical Foundation Senior Scholar Award. He is on the Scientific Advisory Board of the Buck Institute on Aging. He is the author of more than 200 scientific publications and holds 15 US patents, with an additional eight pending.

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Namrita Lall

University of Pretoria, South Africa

Green solutions for skin-ageing

South African plants were selected for investigation on the basis of their traditional uses for skin-disorders. South Africa has a wealthy supply of plants (about 23,500 species of higher plants) together with a high degree of endemicity (36.6%), of which 4000 plant taxa are ethno medicinally used and approximately 500 species are used in traditional medicine by an estimated 70% South Africans on a regular basis. The country has huge potential in identifying novel compounds to treat many diseases. Ethanolic and fermented extracts were prepared and their anti-ageing potential was evaluated by means of elastase inhibition. The results showed significant elastase-inhibition for three samples compared to the positive control, ursolic acid, a known inhibitor, with the ability of the extracts to inhibit 50% of the enzyme (IC50) at concentrations of 79.09 µg/ml, 83.92 µg/ml and 50.59 µg/ml for the ethanolic samples of *Annona senegalensis* (leaves) (ASL), *Annona senegalensis* (bark and twigs) (ASB) and *Persicaria senegalensis* (PS) respectively. All three samples were then evaluated for their *in vitro* cytotoxic potential against the human keratinocyte cell line and were found to exhibit no cytotoxicity at the highest concentration tested (400 µg/ml). Further studies then investigated the anti-inflammatory propensity of the extracts by measuring their ability to inhibit a crucial enzyme involved in the inflammatory process, cyclooxygenase-ii. The results indicated the best inhibition of this enzyme to be for PS, with an IC50 of 2.27 µg/ml, followed closely by ASL (3.51 µg/ml) and ASB (5.02 µg/ml). Superoxide has been identified as one of three main free radicals implicated in the activation of the ageing pathway and as such the scavenging capacity of these extracts was also evaluated. The results again revealed the best activity by PS (27.22 µg/ml), followed then by ASB (43.29 µg/ml) and ASL 70.38 µg/ml). PS thus showed the greatest potential of the samples tested, exhibiting noteworthy inhibition of crucial enzymes implicated in the ageing pathway as well as the ability to diminish the activation of the pathway. Another shining example of anti-ageing skin care by South African plants is *Myrsine africana* (INCI: Alcohol (and) Water (and) *Myrsine africana* Leaf Extract (MA). The semi-pure fraction of the plant inhibited elastase with an IC50 value of 28.04 µg/ml. Semi-pure fractions was evaluated for their anti-ageing efficacy in clinical studies, confirming their activity and a potential licensee is being explored. The results obtained from this study illustrate the value of terrestrial as well as wetland plants of South Africa used by indigenous knowledge systems and will hopefully encourage the recognition and conservation of indigenous knowledge as guarded by their knowledge holders across South Africa. A number of other medicinal samples with significant activity for skin-hyperpigmentation, acne, oral care, an adjuvant for tuberculosis- patients have been identified. The samples were subjected to clinical studies and have been recommended for their use for melasma, skin-toning purposes and for acne. The research results have attracted a number of national and international Cosmeceutical companies who are willing to commercialize extracts and purified compounds which might eventually lead to entrepreneurship.

Speaker Biography

Namrita Lall has completed her PhD from the University of Pretoria and was a visiting Scientist at the University of Illinois, Chicago and Kings College London. She has published more than 120 papers in reputed journals. She is also the Co-inventor of 16 national and international patents. This medicinal plant scientist at the University of Pretoria is ranked in the top 1% of the global Essential Science Indicators list of influential academics who write about pharmacology and toxicology. In 2014, she received the Order of Mapungubwe - South Africa's highest honor - from President Jacob Zuma, in recognition of her research.

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Segundo Mesa Castillo

Psychiatric Hospital of Havana, Cuba

Direct evidence of viral infection and mitochondrial alterations in the brain of fetuses at high risk for schizophrenia

Introduction: There are increasing evidences that favor the prenatal beginning of schizophrenia. These evidences point toward intra-uterine environmental factors that act specifically during the second pregnancy trimester producing a direct damage of the brain of the fetus. The current available technology doesn't allow observing what is happening at cellular level since the human brain is not exposed to a direct analysis in that stage of the life in subjects at high risk of developing schizophrenia.

Methods: In 1977, we began a direct electron microscopic research of the brain of fetuses at high risk from schizophrenic mothers to find differences at cellular level in relation to controls.

Results: In these studies, we have observed within the nuclei of neurons the presence of complete and incomplete viral particles that reacted in positive form with antibodies to herpes simplex hominis type I [HSV1] virus and mitochondria alterations.

Conclusion: The importance of these findings can have practical applications in the prevention of the illness keeping in mind its direct relation to the etiology and physiopathology of schizophrenia. A study of amniotic fluid cells in women at risk of having a schizophrenic offspring is considered. Of being observed the same alterations that those observed previously in the cells of the brain of the studied fetuses, it would intend to these women in risk of having a schizophrenia descendant, previous information of the results, the voluntary medical interruption of the pregnancy or an early anti HSV1 viral treatment as preventive measure of the later development of the illness.

Speaker Biography

Segundo Mesa Castillo worked for 10 years as Specialist in Neurology in the Institute of Neurology of Havana, Cuba. He has worked in Electron Microscopic Studies on Schizophrenia for 32 years. He was awarded with the International Price of the Stanley Foundation Award Program and for the Professional Committee to work as a Fellowship position in the Laboratory of the Central Nervous System Studies, National Institute of Neurological Diseases and Stroke under Joseph Gibbs for a period of 6 months, National Institute of Health, Bethesda, Maryland, Washington DC, USA, June 5, 1990. At present, he is a Member of the Scientific Board of the Psychiatric Hospital of Havana and gives lectures to residents in Psychiatry.

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Yong Li

University of Texas, USA

Adult stem cells and motivation in the injury tissues

Tissue injuries result in changing the host niche and niche factors that govern resident stem cell behaviors as well as disturbs donor stem cell regeneration. In the last few decades, the stem cell studies have become a well-established research area and their applications have moved to the clinic. However, several of the unconvinced issues, such as the injured tissue derived stem cells, how the injured environment involves the cellular reprogramming and differentiation abilities, have not been well investigated. In the recent literature, several publications have reported the significant contributions of injury tissues derived stem cells that explore multipotency and improved differentiation abilities. Those injury-motivated stem cells have been isolated from the injured musculoskeletal tissues, including the traumatic injured skeletal muscles and fractured bones. In this presentation, we will display our recent study on the injury muscle derived stem cells (iMuSCs), which include their potency stem cell behaviors and applications in tissue repair. We aim to create a multidisciplinary forum for discussion on those studies in traumatic injury tissues derived stem cells. We will also focus on talking the injury-environmental change altering stem cell behaviors, as well as their potential biological role. Consequently, understanding the alteration of donor stem cells after implantation will stimulate their applications in the wound healings of various tissues.

Speaker Biography

Yong Li is an Associate Professor within the Center Stem Cell for Regenerative Medicine and Center for Tissue Engineering and Aging Research at the Brown Foundation Institute of Molecular Medicine (IMM), UT Health. He also is appointed as an Associate Professor in the Department of Pediatric and Orthopedic Surgery and Internal Medicine, UT Health. He has accomplished his MD and PhD training in China and was a General Surgeon before he went to London of the United Kingdom in 1997. His first research career as a Post-doctor fellow trained in Imperial College School of Medicine in the UK (1997-1999) and later as a Postdoctoral Research Associate in Children's Hospital of Pittsburgh of UPMC. His academic career includes more than 100 peer-reviewed publications; over seven millions' grant funding from NIH and DOD; over 50 training fellows and students; more than 28 national or international awards; over 30 times grant reviewer or panelist; service 10 journals' editor boards; more than 50 times' lecture in the conferences or seminars and 160 times of posters presentation in conferences.

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Bekir Cinar

Clark Atlanta University, USA

The STK4/Hippo-YAP axis promotes metastasis by increasing cancer cell stemness

The STK4-encoded MST1 (mammalian STE20-like kinase 1) and its key intermediate LATS1/2 (large tumor suppressor 1 and 2) are core components of the Hippo pathway in mammalian. The transcriptional co-activator YAP1/WWTR1 (thereof YAP) is a prominent nuclear effector of the Hippo pathway, which restricts organ size and tumorigenesis. The MST1 and LATS1/2 signaling cascade phosphorylates and inhibits YAP. Evidence suggests that activation of YAP is linked to poor cancer prognosis. Our studies have indicated that dysregulation of the MST1-YAP1 axis plays critical role in the etiology of metastatic prostate cancer (PC). However, the mechanism of how the MST1-YAP axis contributes to aggressive PC remains elusive. Here, we tested a novel concept that MST1 low cell variants that share cancer stem-like cells (CSCs) and epithelial-to-mesenchymal transition (EMT) phenotypes leads to metastatic PC through increases in interaction of nuclear YAP1 with androgen receptor (AR), a key oncogene for PC. Using our prior knowledge, we developed a novel method to isolate MST1 low and MST1 high cell variants to test this concept. Our functional and molecular analysis demonstrated that unlike MST1 high, MST1 low cells expressed the high levels of CSCs and EMT markers and were resistant to enzalutamide (ENZ), a direct small molecule inhibitor of AR signaling. In addition, MST1 low cells were highly invasive *ex vivo* and *in vivo* compared with MST1 high cells. Moreover, we demonstrated that nuclear YAP1 interacted with AR and that the interaction between YAP and AR occurred independently of androgen hormone signaling and were resistant to ENZ exposure in castration-resistant PC cells in comparison with castration-sensitive PC cells. Furthermore, we demonstrated that silencing of MST1 increased stem cell characteristics as well augmented androgen-independent YAP-AR interactions and PC cell growth *ex vivo*. In addition, MST1 induction had the opposite effects, validating our above observations. In summary, these findings suggest that the STK4/Hippo-YAP signaling axis plays a critical role in the promotion of metastatic disease and targeting of this pathway could reveal a new approach to fight against invasive cancer.

Speaker Biography

Bekir Cinar has completed his Post-doctoral Fellowship, Boston Children's Hospital, Harvard Medical School (HMS), Boston, MA (2002-2006) and PhD from Department of Biochemistry and Molecular Genetics, School of Medicine University of Virginia, Charlottesville, VA (1995-2002), DVM Veterinary Medical School, Ankara University, Ankara, Turkey (1987-1992). Currently, he is working as Associate Professor, Department of Biological Sciences, Clark Atlanta University (CAU), Atlanta, GA (2015 to present). Presently, he is also member of the Center for Cancer Research and Therapeutic Development at CAU and a member of the NCI-designated Winship Comprehensive Cancer Center at Emory University. Prior to joining CAU, he was Assistant Professor of Medicine-Hematology/Oncology and Biomedical Sciences at Cedars-Sinai Medical Center, where he was a member of Samuel Oschin Comprehensive Cancer Institute.

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Feng Tao

Texas A&M University College of Dentistry, USA

Effect of spinal transplantation of embryonic stem cell-derived oligodendrocyte progenitor cells on spinal cord injury pain

Spinal cord injury (SCI) can cause chronic neuropathic pain. Currently, available therapies are inadequate for SCI-induced neuropathic pain. In the present study, we investigated the effect of spinal transplantation of mouse embryonic stem cell-derived oligodendrocyte progenitor cells (OPCs) on SCI pain using a rat contusion SCI model. We observed that chronic neuropathic pain was present on day 7 after SCI and persisted for the entire 56-day observation period. Spinal transplantation of OPCs enhanced remyelination in the injured spinal cord and reduced SCI-induced chronic neuropathic pain. Moreover, we found that SCI decreased the protein level of neuregulin-1 and ErbB4 in the injured spinal cord and that OPC transplantation can rescue the spinal expression of both proteins after SCI. Furthermore, intrathecal injection of neuregulin-1 siRNA, but not the control non-target RNA, reduced OPC transplantation-produced remyelination and counteracted the antinociceptive effect of OPC transplantation. Our results suggest that spinal transplantation of embryonic stem cell-derived OPCs is an appropriate therapy for SCI pain and that neuregulin-1/ErbB signaling is involved in central remyelination under pathological conditions and contributes to OPC transplantation-mediated alleviation of SCI pain.

Speaker Biography

Feng Tao is an Associate Professor in the Department of Biomedical Sciences at Texas A&M University College of Dentistry. He received his RO1 award and Independent Scientist Award from NIH in 2012 and 2014, respectively. He has published more than 40 papers in peer-reviewed professional journals and he is serving as an Editorial Board Member for some professional journals. He also served as an invited reviewer for NIH NRCS Study Section, Johns Hopkins ACCM Seed Grant, NSF-sponsored Pilot Funding at Louisiana State University, Arizona Biomedical Research Commission, Britain Israel Research and Academic Exchange Partnership Regenerative Medicine Initiative, Wings for Life Spinal Cord Research Foundation in Austria, Department of Veterans Affairs Rehabilitation Research and Development Service Spinal Cord Injury and Neuropathic Pain Panel and The French National Research Agency (ANR) in France.

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