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UNIVERSITY OF
MEDICINE AND PHARMACY
CLUJ-NAPOCA
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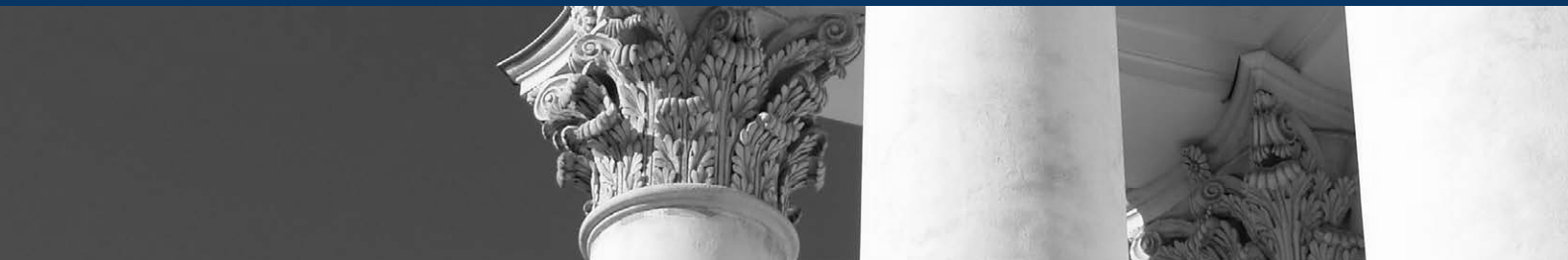
"IULIU HATIEGANU" UNIVERSITY
OF MEDICINE AND PHARMACY

DOCTORAL SCHOOL NEUROSCIENCE

PROGRAM

2018-2019 | SECTION 6

14 MAY, 2019
"MULTIMEDIA" AUDITORIUM, "IULIU HATIEGANU" UMF CLUJ-NAPOCA
8 VICTOR BABES STREET | CLUJ-NAPOCA | ROMANIA



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INTERNATIONAL GUEST LECTURER

Michael Chopp

Henry Ford Hospital, Department of Neurology, Detroit, MI, USA

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COURSE PROGRAM

COURSE PROGRAM

MAY 14TH, 2019

"MULTIMEDIA" AUDITORIUM, "IULIU HATIEGANU" UMF CLUJ-NAPOCA

8 VICTOR BABES STREET | CLUJ-NAPOCA | ROMANIA

09:50 – 10:00	Welcome Address
10:00 – 10:45	Michael Chopp/ USA Inducing recovery and brain plasticity post stroke/TBI
10:45 – 11:30	Michael Chopp/ USA Use of exosomes to treat subacute stroke and TBI
11:30 – 12:15	Michael Chopp/ USA Cerebrolysin for the treatments of stroke and TBI-and underlying mechanisms of action

INTERNATIONAL GUEST LECTURER

MICHAEL CHOPP
USA

Dr. Michael Chopp, is Vice Chairman for Research of the Department of Neurology, Scientific Director of the Henry Ford Neuroscience Institute, and is the Zoltan J. Kovacs Chair in Neuroscience Research. He is also Distinguished Professor of Physics at Oakland University.

Dr. Chopp's research has primarily focused on: 1) cellular and molecular biology of ischemic cell injury, 2) the pathophysiology of stroke, traumatic brain injury, peripheral neuropathy, multiple sclerosis, and glioma, 3) combination thrombolytic and neuro and vascular protective therapies for stroke, 4) mechanisms of neuroprotection, 5) cell-based and pharmacological neurorestorative therapies for stroke, traumatic brain restorative therapies for stroke, traumatic brain injury and neurodegenerative disease, 6) molecular and cellular mechanisms underlying neurogenesis and angiogenesis and the induction of brain plasticity leading to functional and behavioral recovery after neural injury, 7) treatment of glioma and breast cancer, 8) magnetic resonance imaging, 9) exosomes/ microRNA for treatment of neurological injury, neurodegenerative disease, and cancers. Dr. Chopp has 715 peer reviewed publications (h-index 111), ~ 50 book chapters and has given 478 plenary lectures and invited presentations. He has chaired National Institutes of Health (NIH) study sections and has often served as a consultant to government agencies, the U.S. National Institutes of Health, and the pharmaceutical industry.

Awards include (selected):

2001 Top Ten Research Advances of 2001, "Treatment of Stroke with Bone Marrow Stromal Cells", American Heart Association
2005 Distinguished Scientist Award, Henry Ford Medical Group, Board of Governors
2012 Lecture of Excellence and World Stroke Organization (WSO) Award, Remodeling and rewiring the intact CNS as a treatment for Stroke, 8th World Stroke Congress, Brasilia, Brazil, October
2014 Abraham White Distinguished Science Award. "For discovery of the role of thymosin beta 4 in the treatment of brain injuries and neurodegenerative diseases; 4th International Symposium on Thymosins in Health and Disease, Washington, DC, October
2015 Thomas Willis Lecture Award, International Stroke Conference, Nashville, TN, February
2015 Doctor Honoris Cause, Universitas Medicinae Et Pharmaceuticae Artium Napocensis "Iuliu Haieganu",
5th European Teaching Course of NeuroRehabilitation, Cluj-Napoca, Romania
2016 Lecture of Excellence and Barbro B. Johansson Award, 10th World Stroke Conference, Hyderabad, India, October

DAFIN F. MUREȘANU
ROMANIA

Professor of Neurology, Senior Neurologist, Chairman of the Neurosciences Department, Faculty of Medicine, "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca, President of the European Federation of Neurorehabilitation Societies (EFNR), Co-Chair EAN Scientific Panel Neurorehabilitation, Past President of the Romanian Society of Neurology, President of the Society for the Study of Neuroprotection and Neuroplasticity (SSNN), member of the Academy of Medical Sciences, Romania, secretary of its Cluj Branch. He is member of 17 scientific international societies (being member of the American Neurological Association (ANA) - Fellow of ANA (FANA) since 2012) and 10 national ones, being part of the executive board of most of these societies.

Professor Dafin F. Muresanu is a specialist in Leadership and Management of Research and Health Care Systems (specialization in Management and Leadership, Arthur Anderson Institute, Illinois, USA, 1998 and several international courses and training stages in Neurology, research, management and leadership). Professor Dafin F. Muresanu is coordinator in international educational programs of European Master (i.e. European Master in Stroke Medicine, University of Krems), organizer and co-organizer of many educational projects: European and international schools and courses (International School of Neurology, European Stroke Organisation summer School, Danubian Neurological Society Teaching Courses, Seminars - Department of Neurosciences, European Teaching Courses on Neurorehabilitation) and scientific events: congresses, conferences, symposia (International Congresses of the Society for the Study of Neuroprotection and Neuroplasticity (SSNN), International Association of Neurorestoratology (IANR) & Global College for Neuroprotection and Neuroregeneration (GCNN) Conferences, Vascular Dementia Congresses (VaD), World Congresses on Controversies in Neurology (CONy), Danube Society Neurology Congresses, World Academy for Multidisciplinary Neurotraumatolgy (AMN) Congresses, Congresses of European Society for Clinical Neuropharmacology, European Congresses of Neurorehabilitation). His activity includes involvement in many national and international clinical studies and research projects, over 400 scientific participations as "invited speaker" in national and international scientific events, a significant portfolio of scientific articles (190 papers indexed on Web of Science-ISI, H-index: 20) as well as contributions in monographs and books published by prestigious international publishing houses.

Prof. Dr. Dafin F. Muresanu has been honoured with: „Dimitrie Cantemir" Medal of the Academy of The Republic of Moldova in 2018, Ana Aslan Award 2018 - "Performance in the study of active aging and neuroscience", for the contribution to the development of Romanian medicine, National Order "Faithful Service" awarded by the President of Romania in 2017; "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca, Faculty of Medicine, the "Iuliu Hatieganu Great Award 2016" for the best educational project in the last five years; the Academy of Romanian Scientists, "Carol Davila Award for Medical Sciences / 2011", for the contribution to the Neurosurgery book "Tratat de Neurochirurgie" (vol.2), Editura Medicala, Bucuresti, 2011; the Faculty of Medicine, "Iuliu Hatieganu" University of Medicine and Pharmacy Cluj-Napoca "Octavian Fodor Award" for the best scientific activity of the year 2010 and the 2009 Romanian Academy "Gheorghe Marinescu Award" for advanced contributions in Neuroprotection and Neuroplasticity.

ABSTRACTS

INDUCING RECOVERY AND BRAIN PLASTICITY POST STROKE/TBI

MICHAEL CHOPP
Henry Ford Hospital, Department of Neurology, Detroit, MI, USA
Oakland University, Department of Physics, Rochester, MI, USA

In this presentation, I will describe how the brain, as well as the central nervous system (CNS) in general, responds to a cerebral insult, such as stroke or traumatic brain injury (TBI). I will demonstrate that the CNS post injury initiates a set of highly coupled neurovascular restorative processes designed to promote neurological recovery. Included within these restorative processes are neurogenesis (generation of new brain cells), angiogenesis (generation and growth of cerebral vasculature), axonal and dendritic plasticity, and oligodendrogenesis. These remodeling events are highly coupled. I will also show that cerebral injury induces changes and neural plasticity in the spinal cord, with neurological motor recovery highly correlated to spinal cord plasticity. Although many cerebral parenchymal cells contribute to repair/remodeling, I will focus on the roles of the astrocyte in mediating recovery. We show that activation of astrocytes as indicated by an upregulation of GFAP/Vimentin contribute to neural plasticity and that inhibition of the astrocytic responses to injury or use of GFAP/Vimentin knockout mice demonstrate a pivotal role of astrocytes in mediating neurological recovery. Molecular pathways that contribute to the induction of neurovascular plasticity will also be discussed. As an example, we show that stroke/TBI upregulates expression of the morphogen, sonic hedgehog (SHH). SHH is an important developmental transcription factor that upregulates many restorative molecules, among which is tissue plasminogen activator (tPA), traditionally employed clinically as a thrombolytic agent. We then show that intranasal administration of tPA which increases tPA expression in parenchymal cells induce CNS plasticity and promote recovery. Thus, in this first lecture, I have described how the CNS, by endogenous stimulation of neurovascular plasticity, attempts to remodel itself in an effort to reduce neurological dysfunction.

USE OF EXOSOMES TO TREAT SUBACUTE STROKE AND TBI

MICHAEL CHOPP
Henry Ford Hospital, Department of Neurology, Detroit, MI, USA
Oakland University, Department of Physics, Rochester, MI, USA

In the first lecture I discussed endogenous restorative mechanisms that are activated after stroke and TBI. Here and in the next 2 lectures, I describe ways to amplify these restorative and vascular protective processes, by the exogenous administration of exosomes (lecture 2), and Cerebrolysin (lecture 3). Exosomes are bilipid layer nanoparticles (~30-100nm) containing proteins, RNAs, and lipids. They are generated by essentially all cells and are primary mediators of intercellular communication. We have demonstrated that restorative therapeutic benefit for neural injury induced by administration of cell-based therapy is mediated by the production of exosomes by the administered cell. Thus, we have harvested exosomes from mesenchymal stromal cells (MSCs) and many other "restorative" cells and administered the exosomes in preclinical studies to animals with neural injury. We then demonstrated robust therapeutic effects solely using the harvested exosomes without the cells. Exosomes contain non-coding RNA, among which are microRNAs (miRs). miRs regulate post transcriptional gene expression and each miR can potentially regulate literally hundreds of genes. Thus, the ability to transfer select miRs to recipient cells which dictates gene translation provides a master "network" and a highly effective multimodal therapy. Here I describe some of use of these exosome therapies for the treatment of neural injury from the rodent to the non-human primate and demonstrate thereby a remarkable therapeutic potential for these biological nanoparticles. I then proceed to describe how we can improve on "nature" and engineer exosomes containing specific miRs. This engineering is performed within the context of bioinformatics, informing us of important regulatory miRs which can induce neurovascular plasticity and contribute to recovery. I then finish this lecture by also describing how a brain injury can negatively impact other organs in the body. I discuss how stroke can generate cardiac dysfunction. I then show how exosomes can obviate this neural injury induced cardiac dysfunction. In general recovery from stroke/TBI depends on how the body acts endogenously to promote neurovascular remodeling and how an exogenous molecular switch, i.e., miRs, by regulating intercellular communication as a network therapy can greatly enhance this recovery, both within the affected brain and within an organ that is a secondary target of this injury, e.g., the heart. I also very briefly describe how exosome therapy is employed for treatment of neurodegenerative diseases in the CNS and peripheral nervous system.

CEREBROLYSIN FOR THE TREATMENTS OF STROKE AND TBI-AND UNDERLYING MECHANISMS OF ACTION

MICHAEL CHOPP
Henry Ford Hospital, Department of Neurology, Detroit, MI, USA
Oakland University, Department of Physics, Rochester, MI, USA

In the prior 2 lectures , I spoke about endogenous remodeling of the CNS post neural injury (lecture 1) and the use of exosomes as a means to exogenously enhance neurovascular remodeling and neurological recovery. In this presentation, I will focus on an often overlooked tharpeutic approach for the treatment of neural injury, that of a therapy targeting the microvasculature. In lecture 3, I will present some of our recent work on using Cerebrolysin as a vascular therapy, a therapy designed to protect the microvasculature, to ensure the integrity of the blood brain barrier and to reduce secondary post injury inflammatory effects. I will also discuss and present data promoting the use of Cerebrolysin as an adjunctive therapy for mechanical thrombectomy (MT) and thrombolysis with tPA for the treatment of acute ischemic stroke.

The only approved treatments of acute ischemic stroke is with mechanical thrombectomy (MT), performed within 24 hours of a large vessel arterial stroke and thrombolysis performed within 4.5 hours. These treatments although highly beneficial, are far from perfect. The majority of patients subjected to MT and thrombolysis do not have complete recovery of tissue perfusion and retain functional and neurological deficits post treatment. I will briefly review the vascular changes that occur in the arterial and microvascular levels after MT and tPA thrombolysis. The clot itself while in the artery changes in time and becomes more platelet rich, making it more difficult to lyse with tPA. The arterial site of the clot also undergoes damage with the breakdown of vascular structure and upregulation of prothrombotic molecules. Even if the clot is removed within the appropriate time window, there is the well known no-reflow phenomenon. One can have a patent artery yet low tissue perfusion. Low tissue perfusion caused by secondary thrombosis and inflammatory changes within the microvasculature results in a prothrombotic, procoagulant and proinflammatory state of the microvasculature. This causes the growth of the penumbra and subsequent parenchymal cell dysfunction. Importantly, a major contributor to the proinflammatory state within these vessels is the deposition of fibrin. Fibrin evokes vascular expression of potent proinflammatory molecules.

I then show that Cerebrolysin is fully capable of ameliorating the pro-coagulant-thrombotic and inflammatory state of the microvasculature post stroke. I provide data from an in vitro model of the human blood brain barrier and show that Cerebrolysin can obviate adverse vascular caused by fibrin deposition and treatments with tPA.

I then proceed to describe the underlying therapeutic mechanisms responsible for the beneficial effects of Cerebrolysin. I demonstrate the Cerebrolysin stimulates vascular expression of the highly anti-inflammatory molecule Angiopoietin 1 (Ang1). Ang1 is a vascular protective and restorative molecule. In addition, I re-introduce microRNAs, non-coding RNAs which can concurrently regulate post-transcriptionally hundreds of genes (lecture 2). I note, based on our previous work that Cerebrolysin stimulates vascular and parenchymal upregulation of an important morphogen and transcription factor, Sonic Hedgehog (SHH) (lecture 1). We have shown that SHH upregulates the expression of a very important family of microRNAs, miR-17-92. This miR -17-92 family promotes brain plasticity and neurovascular benefit post stroke and traumatic brain injury. Importantly, it has also been shown to ameliorate anxiety and depression. Thus, Cerebrolysin by stimulating the generation and expression of important proteins and non-coding RNAs plays a vital role in neurovascular recovery. Particularly, Cerebrolysin`s therapeutic impact on the microvasculature compels further investigation of Cerebrolysin in combination with presently approved MT and thrombolysis for acute ischemic stroke.

I hope that this set of lectures provides you with optimism that we are moving towards the development of therapeutictic approaches for he treatment of stroke/TBI and neurodegenerative diseases.


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