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UNIVERSITY OF
MEDICINE AND PHARMACY
CLUJ-NAPOCA
ROMANIA

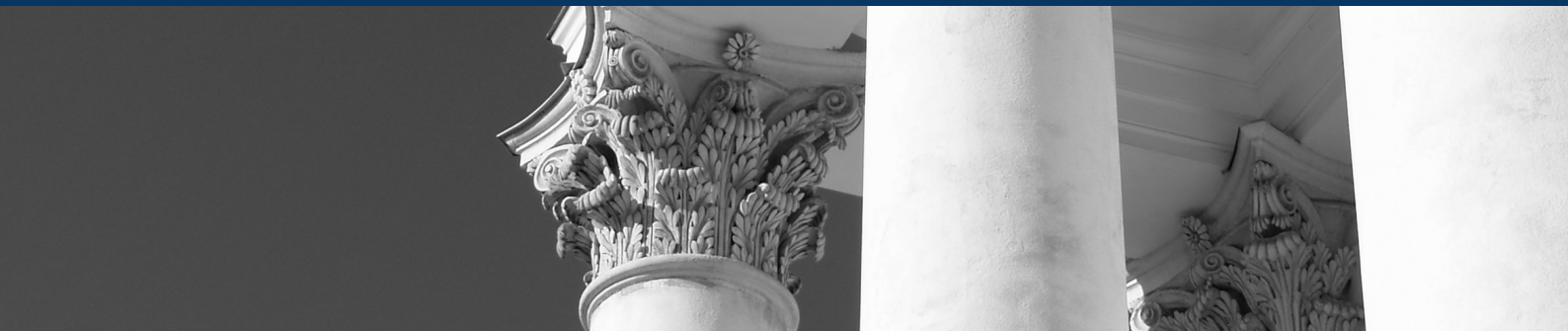
"IULIU HATIEGANU" UNIVERSITY
OF MEDICINE AND PHARMACY

DOCTORAL SCHOOL NEUROSCIENCE

PROGRAM

2021-2022 | M 2.6.1

1 FEBRUARY, 2022
VIRTUAL MEETING



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Dafin F. Mureşanu

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Chairman of EAN Communication and Liaison Committee

Co-Chair EAN Scientific Panel Neurotraumatology

Past President of the Romanian Society of Neurology

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2021-2022

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COURSE PROGRAM

COURSE PROGRAM

1 FEBRUARY, 2022

VIRTUAL MEETING

12:00 – 12:45	Challenges and opportunities in stroke recovery Dafin F. Mureșanu/ Romania
12:45 – 13:15	New vistas in stroke recovery Dafin F. Mureșanu/ Romania
13:15 – 13:50	Microcirculation and stroke Dafin F. Mureșanu/ Romania

INTERNATIONAL GUEST LECTURER

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), Chairman Communication Committee of the European Academy of Neurology (EAN), Past President of the Romanian Society of Neurology, President of the Society for the Study of Neuroprotection and Neuroplasticity (SSNN), Chairman "RoNeuro" Institute for Neurological Research and Diagnostic, Corresponding Member of the Romanian Academy, Member of the Academy of Medical Sciences, Romania and 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 also a specialist in Leadership and Management of Research and Health Care Systems (specialization in "Management and Leadership, Arthur Anderson Institute, Illinois, USA, 1998"; "MBA – Master of Business Administration - Health Care Systems Management, The Danube University - Krems, Austria, 2003"). He has performed valuable scientific research in high interest fields such as: neurobiology of central nervous system (CNS) lesion mechanisms; neurobiology of neuroprotection and neuroregeneration of CNS; the role of the Blood-brain barrier (BBB) in CNS diseases; developing comorbidities in animal models to be used in testing therapeutic paradigms; nanoparticles neurotoxicity upon CNS; the role of nanoparticles in enhancing the transportation of pharmacological therapeutic agents through the BBB; cerebral vascular diseases; neurodegenerative pathology; traumatic brain injury; neurorehabilitation of the central and peripheral nervous system; clarifying and thoroughgoing study on the classic concepts of Neurotrophicity, Neuroprotection, Neuroplasticity and Neurogenesis by bringing up the Endogenous Defense Activity (EDA) concept, as a continuous nonlinear process, that integrates the four aforementioned concepts, in a biological inseparable manner.

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 Neurotraumatology (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 500 scientific participations as "invited speaker" in national and international scientific events, a significant portfolio of scientific articles (260 papers indexed on Web of Science-ISI, H-index: 25) 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

CHALLENGES AND OPPORTUNITIES IN STROKE RECOVERY

DAFIN F. MUREȘANU
Chairman Department of Neurosciences University of Medicine and Pharmacy 'Iuliu Hatieganu', Cluj-Napoca, Romania

Brain damage affects all three levels of structural and functional organization: cellular and molecular level, circuitries level and dynamic network level and launches an endogenous continuous brain defense response which consists in neuroprotection (the immediate response) and neurorecovery (a later response).

Endogenous neuromodulation represents at the cellular and molecular level the optimization of common biological processes that could potentially generate cell death or promote neurodegeneration. At the circuitries and dynamic network levels, it represents the tendency in reinbalancing of functional connectivity in resting-state netwoks.

In the last years, there has been a substantial effort in understanding the brain functioning and how to enhance endogenous neuromodulation and neurorehabilitation in general, by using a large spectrum of neurotechnologies such as imaging techniques (functional magnetic resonance imaging, ligant-based positron emission tomography, diffusion-tensor imaging), quantitative electroencephalogram, magnetoencephalography, eye tracking, optogenetics, transcranial magnetic stimulation, transcranial direct current simulation, deep brain simulation, computational neuroscience and brain-computer interfaces. The combination between these technologies provide valuable information about the structure-function relationship underling resting-state networks, about the dynamic cross-talk between networks and about the abnormalities in the functional connectivity in different pathologies.

Neurorecovery can be enhanced by pharmacological intervention, physical activity, electromagnetic stimulation, psychological support, environmental stimulation or any demonstrated combinations of these factors capable of improving the patient's condition after brain and spinal cord injuries. From the pharmacological perspective, it is clear that the focusing on molecules that are capable of mimic the function of endogenous molecules with multimodal and pleiotropic neuroprotective effects is the best approach in neurorecovery, especially when they are associated with intensive physical training.

Biological agents (e.g., neurotrophic factors and related molecules) with modulating and multimodal effects are better pharmacological agents for brain and spinal cord protection and recovery, because they usually have also pleiotropic neuroprotective effect. That is why they are capable of pharmacologically bridging acute neuroprotective processes with the long-term recovery processes.

There are many animal and human studies trying to elucidate the cellular and molecular mechanisms of plasticity of the nervous system. A better understanding of the mechanisms underlying the neuroplasticity will reflect in a more efficient and comprehensive treatment.

Over the last decades, therapeutic approaches for stroke have significantly evolved and improved as a consequence of the implementation of modern stroke units, improvement of general medical care and more structured and early administered rehabilitation schemes.

Thrombolytic therapy with rt-PA (recombinant tissue plasminogen activator) has been developed and a number of clinical trials have recently confirmed the effectiveness of thrombectomy to be better than rtPA alone.

Except thrombolytic therapy and thrombectomy there is still no widely accepted therapy for acute ischemic stroke. Current data shows that even if advanced procedures can be used, 60% of stroke patients die or remain with a certain level of deficit. As it is widely accepted that immobilization-related complications cause over 50% of stroke patients' deaths, rehabilitation plays an important role in stroke care.

It is getting clearer that multimodal drugs may play an important role in pharmacological support of neurorehabilitation after stroke.

The results of recently published large and well-controlled clinical studies show a positive effect on neurological recovery after acute ischemic stroke.

NEW VISTAS IN STROKE

DAFIN F. MUREȘANU
Chairman Department of Neurosciences University of Medicine and Pharmacy 'Iuliu Hatieganu', Cluj-Napoca, Romania

The results of recently published large and well-controlled clinical studies show a positive effect of Neurotrophic factors on neurological recovery after acute ischemic stroke.

The CARS study assessed the efficacy and safety of neurotrophic factors in combination with a standardized rehabilitation program. The primary study endpoint was the Action Research Arm Test (ARAT) at day 90, assessing upper-limb motor functions. Neurotrophic factors were administered for 21 days, starting within 48-72 hours after ischemic stroke.

The study showed a statistically significant group difference in the upper-limb motor function (ARAT) at day 90 – primary end point. Neurotrophic factors were also superior over placebo in most of the secondary endpoints like the NIHSS, Barthel Index and mRS. Also, at day 90, patients treated with neurotrophic factors showed less depressive symptoms and better quality of life. In addition, the most important measure for early benefit, the NIHSS at day 21, showed statistically significant superiority of neurotrophic factors. Analysis of the safety parameters did not show any clinically statistical significant differences between the treatment groups. The trial indicates that early combination of rehabilitation with a multimodal medication of neuroprotective and recovery properties is a valid therapeutic approach.

Furthermore, CARS 1 and CARS 2 meta-analysis provides evidence that neurotrophic factors has a beneficial effect on motor function recovery in early rehabilitation patients after stroke. All pre-planned primary meta-analytic results were statistically significant.

MICROCIRCULATION AND STROKE

DAFIN F. MUREȘANU
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Revascularization interventions have significantly improved the outcome of patients with acute ischemic stroke. Fibrinolytic agents (rtPA) are highly effective within a narrow therapeutic window but have shown limitations in large proximal arterial occlusions and are associated with serious adverse effects, particularly when administered beyond their intended timeframe. International treatment guidelines recommend thrombolytic therapy as the first line of treatment for acute ischemic stroke, followed by endovascular thrombectomy in eligible patients. This approach dissolves clots by plasminogen activation or mechanically removes them to re-establish blood flow in the brain. Effective cerebral revascularization is considered essential for preventing additional infarction of functionally inactive but viable brain tissue in the ischemic penumbra.

After the success of drugs and endovascular procedures in outcome-based clinical trials for acute ischemic stroke, the race to treat as many patients as possible began in conjunction with the resolved of precision medicine to tailor interventions up to the individual level. To evaluate outcomes of thrombolytic or endovascular therapies, recanalization, and reperfusion, although frequently used interchangeably, are not equivalents. The objective of recanalization is to reopen an occluded vessel, while reperfusion refers to the restoration of blood flow in a formerly occluded vascular territory, particularly at the level of cerebral microcirculation.

A plethora of evidence has recently proven that reperfusion is a much better indicator for post-stroke imaging (infarct volume, infarct growth, salvaged penumbra) and clinical outcomes (NIHSS). Recanalization is neither a prerequisite for reperfusion nor does it always lead to the latter. Full recanalization after rtPA or thrombectomy often fails to induce clinically significant reperfusion, due to a myriad of complex factors related to microvascular circulation, such as distal micro-emboli or extensive endothelial damage.

The potential to improve overall reperfusion requires a multimodal approach aimed at preventing additional vascular damage and enhancing cerebral microcirculation. The key challenge in the current pharmacological environment is safety. Cerebral microcirculation is extremely difficult to regulate, as chemically induced vasodilation that would allow reperfusion, would also significantly increase the risk of serious adverse events in combination with rtPA.

Cerebrolysin, an agent with pleiotropic pharmacodynamic properties, has been proven safe in combination with alteplase (Lang, 2013), registering significantly more patients with favorable response in neurological outcome measures (NIHSS) as compared to placebo in this exploratory study.

The avenues of combination, concomitant and add-on treatment in ischemic stroke are very much worth pursuing not only in the context neurorehabilitation but especially in very early, acute phases of the disease.


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