UMF
IULIU HAȚIEGANU
UNIVERSITY OF
MEDICINE AND PHARMACY
CLUJ-NAPOCA
ROMANIA

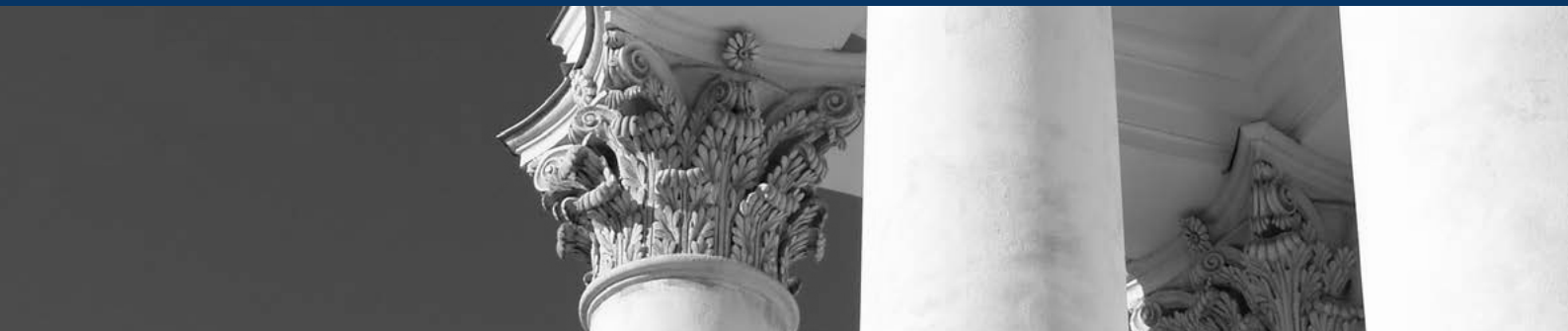
"IULIU HATIEGANU" UNIVERSITY
OF MEDICINE AND PHARMACY

DOCTORAL SCHOOL NEUROSCIENCE

PROGRAM

2020-2021 | SECTION 6

11 MAY, 2021
VIRTUAL MEETING



PhD NEUROSCIENCE PROGRAM COORDINATOR

Dafin F. Mureşanu

President of the European Federation of NeuroRehabilitation Societies (EFNR)

Chairman of EAN Communication and Liaison Committee

Co-Chair EAN Scientific Panel Neurotraumatology

Past President of the Romanian Society of Neurology

Professor of Neurology, Chairman Department of Neurosciences "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania

INTERNATIONAL GUEST LECTURER

Wolf Dieter Heiss

Emeritus Director of the Max Planck Institute for Neurological Research, Cologne, Germany

Doctor Honoris Causa "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania

PhD NEUROSCIENCE PROGRAM FACULTY 2020-2021

Claudio Bassetti / Switzerland

Ettore Beghi / Italy

Natan Bornstein / Israel

Michael Brainin / Austria

Anca Dana Buzoianu / Romania

Michael Chopp / USA

László Csiba / Hungary

Marc Fisher / USA

Urs Fischer / Switzerland

Ioan Ștefan Florian / Romania

Antonio Federico / Italy

Francesca Federico / Italy

Max Hilz / Germany

Wolf Dieter Heiss / Germany

Tudor Jovin / USA

Maurizio Leone / Italy

Dafin F. Mureșanu / Romania

Milija Mijajlovic / Serbia

Lăcrămioara Perju-Dumbravă / Romania

Maura Pugliatti / Italy

Johannes Vester / Germany

ORGANIZER

UMF
IULIU HAȚIEGANU
UNIVERSITY OF
MEDICINE AND PHARMACY
CLUJ-NAPOCA
ROMANIA

University of Medicine and Pharmacy
"Iuliu Hatieganu", Cluj Napoca, Romania
www.umfcluj.ro

ACADEMIC PARTNERS

DONAU UNIVERSITÄT KREMS

www.donau-uni.ac.at

Fundatia pentru Studiul Nanoneurostiintelor si Neuroregenerarii
fsnn
Foundation for the Study of Nanoneurosciences and Neuroregeneration

FUNDATIA JURNALULUI
Journal of Medicine and Life

TEL AVIV UNIVERSITY

www.tau.ac.il

RoNEURO
Institute for Neurological
Research and Diagnostic

www.roneuro.ro

ACADEMIA ROMANA

www.acad.ro

Academia de Științe Medicale
Romania

Academia de
Științe Medicale
din România

www.adsm.ro

COURSE PROGRAM

COURSE PROGRAM

11 MAY, 2021

VIRTUAL MEETING

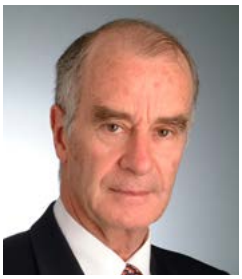
12:00 – 12:30	Dafin F. Mureșanu / Romania CAPTAIN Trials (I and II) – a new horizon in TBI treatment
12:30 – 13:00	Wolf Dieter Heiss / Germany Imaging for prediction of recovery and outcome after stroke
13:00 – 13:30	Wolf Dieter Heiss / Germany Post Stroke Pain – PSP
13:30 – 14:00	Wolf Dieter Heiss / Germany Imaging in Acute Ischemic

INTERNATIONAL GUEST LECTURERS

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 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 500 scientific participations as "invited speaker" in national and international scientific events, a significant portfolio of scientific articles (231 papers indexed on Web of Science-ISI, H-index: 23) 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.



WOLF DIETER HEISS
GERMANY

Wolf-Dieter Heiss graduated in medicine from the University of Vienna, Austria, in 1965. He achieved his training in neurology, neurophysiology, psychiatry and nuclear medicine at the University hospital in Vienna and spent research fellowships at the MIT, Cambridge, USA, the Physiological Institute in Stockholm, Sweden, the Department of Physiology of SUNY, Buffalo, NY and the Department of Neurology of the University of Minnessota, Minneapolis, USA. 1976 he was appointed associate professor at the Department of Neurology of the University of Vienna. In 1978 he became director of the Center for Cerebrovascular Research of the Max Planck Institute for Brain Research and of the Department of Neurology of the City Hospital Cologne-Merheim, Germany. 1981 he was appointed as director at the Max Planck Institute for Neurological Research. 1985 – 2005 he was professor of neurology and chairman of the Department of Neurology of the University of Cologne and director of the Department of General Neurology at the MPI in Cologne. He was president of the International Stroke Society 1992-96, was on the board of directors of the Society for Cerebral Blood Flow and Metabolism, deputy editor of the Journal of Cerebral Blood Flow and Metabolism and at present is associate editor of the Journal of Nuclear Medicine and section editor of Stroke. He was chairman of the program committee of the European Federation of Neurological Societies (EFNS) 1998 - 2001 and was president of the EFNS 2001 – 2005. Since 2005 he is Visiting Professor at the Danube Univerity in Krems, Austria, since 2009 Adjunct Professor at the McGill University in Montreal, Canada, and since 2013 Associate Professor, Dept of Neurosciences, Univ. Iuliu Hatieganu, Cluj, Romania. In December 2014 he received Dr. honoris causa of Univ. Iuliu Hategianu, Cluj, Romania.

ABSTRACTS

RESULTS OF THE CAPTAIN II TRIAL - A NEW HORIZON IN TBI TREATMENT

DAFIN F. MUREȘANU
JOHANNES VESTER, KLAUS VON WILD, VOLKER HOMBERG
Chairman Department of Neurosciences University of Medicine and Pharmacy 'Iuliu Hatieganu', Cluj-Napoca, Romania

Background and aims
Traumatic brain injury (TBI) is a leading cause of injury-related disability and death worldwide. In 2016, an estimated 27 million new cases of TBI we added to the global burden. The CAPTAIN-RO trial enriches compelling evidence that currently exists for neurotrophic factors, an approved agent for neuroprotection and neurorecovery after TBI in many countries, using a novel approach: multidimensional analysis.

Methods
The study is an interventional, randomized, double-blind, controlled, single-center trial. The full protocol is available for consultation in the ISRCTN registry (no. 17097163). General and neurocognitive outcomes after TBI were measured using full scales, avoiding dichotomization of variables. The multidimensional analysis opens a new direction for clinical and statistical thinking in neurorehabilitation by adding precision to the measurement of complex health states for TBI.

Results
A total of 142 patients aged 19-79 with a diagnosis of TBI and a GCS score between 7-12 at the time of hospital admission were enrolled. Baseline, day 10, 30 and 90 assessments were collected using nine scales that measured cognitive function and emotional status.

Conclusion
CAPTAIN-RO is one of the first trials in TBI history with a truly multidimensional approach based on full outcome scales. We believe this strategy is superior to the single criterion paradigm, commonly used in neuroprotective treatment research. This trial delivers a unique perspective to decades of well-established positive effect trends of neurotrophic factors. These will be extensively discussed and evaluated for implications concerning future TBI research upon completion of data analysis.

Keywords: Randomized Controlled Trial, Traumatic Brain Injury, Multidimensional Analysis

IMAGING FOR PREDICTION OF RECOVERY AND OUTCOME AFTER STROKE

WOLF DIETER HEISS
Max Planck Institute for Neurological Research, Cologne, Germany

Neuroimaging modalities may help to assess functional outcome and to predict the efficacy of rehabilitation in individual patients additionally to functional assessment scales such as NIHSS and others.

CT: The most widely used imaging procedure in acute stroke is CT, especially for differentiation between hemorrhagic and ischemic stroke, for localization of the lesion and for decision making regarding administration of potentially risky stroke therapies as thrombolysis. ASPECTS (the Alberta Stroke Program Early Computed Tomography Score) is a measure to quantify ischemic changes on CT within the territory of the middle cerebral artery (MCA) and can help select patients for acute intravascular treatment.

MRI: With diffusion-weighted imaging (DWI), the size of the lesion can be outlined early and DWI lesion volume significantly increased the power of prediction models. Diffusion tensor imaging (DTI) measures may also be used to predict outcome. The connectivity in networks as assessed by DTI is more important for outcome and recovery than the extent of the primary structural lesion.

Assessment of brain blood supply and cerebral perfusion.

Inclusion of information from CT angiography contributed significantly more to outcome prediction than the ASPECTS score. Evidence of large vessel occlusion is crucial for improving outcome by early endovascular interventions. The final size of an infarct is also influenced by the extent and quality of collateral circulation to the affected brain area. The presence of robust collateral flow is best visualized by conventional angiography, but CT angiography as a non-invasive alternative has better spatial resolution than transcranial Doppler or MR angiography and can depict leptomeningeal collaterals.

The visualization of disturbed interaction in functional networks and of their reorganization in the recovery after focal brain damage is the domain of functional imaging modalities such as PET and fMRI. PET: Mapping of neuronal activity in the brain can be primarily achieved by quantitation of the regional cerebral metabolic rate for glucose (CMRGlc). Quantitative imaging of cerebral blood flow (CBF) is based on the principle of diffusible tracer exchange, using 15O-labeled water. PET detects and, if required, can quantify changes in CBF and CMRGlc accompanying different activation states of brain tissue. The regional values of CBF or CMRGlc represent the brain activity due to a specific state, task or stimulus in comparison with the resting condition, and color-coded maps can be analyzed or correlated to morphological images.

fMRI measures signals that depend on the differential magnetic properties of oxygenated and deoxygenated hemoglobin, termed the blood-oxygen-level-dependent (BOLD) signal, which gives an estimate of changes in oxygen availability. The amount of deoxyhemoglobin in small blood vessels depends on the flow of well-oxygenated arterial blood (CBF), on the outflow of O2 to the tissue (CMRO2) and on the cerebral blood volume (CBV). fMRI images map changes in brain function and can be superimposed on the anatomical image.

Motor and somatosensory deficits: In most fMRI or PET studies involving active or passive movements, a widespread network of neurons was activated in both hemispheres. During recovery from hemiparesis, a dynamic bihemispheric reorganization of motor networks takes place. Ipsilateral cortical recruitment seems to be a compensatory cortical process related to the lesion of the contralateral primary motor cortex. The unaffected hemisphere actually inhibits the generation of a voluntary movement by the paretic hand. This effect of transcallosal inhibition can be reduced by repetitive transcranial magnetic stimulation (rTMS).

Post-stroke aphasia: Studies of glucose metabolism in aphasia after stroke have shown metabolic disturbances

in the ipsilateral hemisphere caused by the lesion and contralateral hemisphere caused by functional deactivation (diaschisis). Patients with an eventual good recovery predominantly activated structures in the ipsilateral hemisphere. Combination of repetitive transcranial magnetic stimulation (rTMS) with activated imaging: Activation studies in the course of recovery of post-stroke aphasia suggest various mechanisms for the compensation of the lesion within the functional network: restoration of the original activation pattern, activation of areas around the lesion (intrahemispheric compensation) and reduction of transcallosal inhibition causing activation of contralateral homotopic areas. rTMS is a non-invasive procedure to create electric currents in discrete brain areas which, depending on frequency, intensity and duration, can lead to transient increases (with higher frequencies) and decreases (with lower frequencies) in excitability of the affected cortex. The role of activation in the right hemisphere for residual language performance can be investigated by combining rTMS with functional imaging, e.g. PET. Counteraction by rTMS of contra-lateral active areas might open a new therapeutic strategy for post-stroke aphasia.

POST STROKE PAIN

WOLF DIETER HEISS
SIBILLA ZIMMERMANN-MEINZINGEN
Max Planck Institute for Neurological Research, Cologne, Germany

Chronic pain syndromes are common after stroke and affect up to 50% of stroke patients. 70% of these patients experience pain on a daily basis. The reported prevalence of post-stroke pain (PSP) varies, reflecting differences in study design, definitions of pain types, and sampled cohorts. Still, there is a general consensus that PSP is an underreported, underrecognized and undertreated phenomenon. A rough differentiation is between acute Stroke, which is usually time limited and resolves completely and chronic pain, defined as continuous or intermittent for more than 6 weeks. It is usually associated with a chronic pathological process and recurs at intervals of months or years.

Pain is mild in 1/3 of affected subjects and moderate to severe in 2/3 of patients PSP occurs through both neuropathic and nociceptive mechanisms. Efforts to standardize descriptive terms for pain led to a publication by the International Association for the Study of Pain of pain terms and their definitions.

These are commonly used in studies of PSP to define pain subtypes
The commonest types of PSP are: central post-stroke pain (CPSP), Pain secondary to spasticity, Shoulder pain, complex regional pain syndrome (CRPS) and headache. Many patients report more than one pain subtype, with common combinations being CPSP and spasticity, or CPSP and shoulder pain.

By definition, CRPS has features of neuropathic pain, and as such, these syndromes co-occur as well. PSP is usually one sided (Shoulder, including arm, lower limbs, anterior and posterior chest, headaches). The types of pain may vary from paresthesia, spasm, tightness and increased tone.

If not treated properly, pain causes anxiety, sleep disturbances, memory problems, depression, impaired posture and reduced appetite. It interferes with daily activities like going to the bathroom, dressing, and grooming. It reduces the ability to move around, talk to other people and participate in recreational activities. The increased irritability may cause people to refuse care.

Identifying and treating PSP early is important. Treatment is complex and may be even more difficult after the pain is established.

IMAGING IN ACUTE ISCHEMIC STROKE

WOLF DIETER HEISS
Max Planck Institute for Neurological Research, Cologne, Germany

Imaging studies are used to exclude hemorrhage in the acute stroke patient, to assess the degree of brain injury, and to identify the vascular lesion responsible for the ischemic deficit. Some advanced CT and MRI technologies as well as PETare able to distinguish between brain tissue that is irreversibly infarcted and that which is potentially salvageable, thereby allowing better selection of patients likely to benefit from therapy.

CT has the advantage of being available 24 hours a day and is the gold standard for hemorrhage.
Hemorrhage on MR images can be quite confusing. On CT 60% of infarcts are seen within 3-6 hrs and virtually all are seen in 24 hours. The overall sensitivity of CT to diagnose stroke is 64% and the specificity is 85%. Hypoattenuation on CT is highly specific for irreversible ischemic brain damage if it is detected within first 6 hours (1). Patients who present with symptoms of stroke and who demonstrate hypodensity on CT within first six hours were proven to have larger infarct volumes, more severe symptoms, less favorable clinical courses and they even have a higher risk of hemorrhage. Obscuration of the lentiform nucleus, also called blurred basal ganglia, and hypodensity and swelling of the insular cortex are also important signs of infarction. A dense MCA sign is a result of thrombus or embolus in the MCA. 15% of MCA infarcts are initially hemorrhagic. Hemorrhage is most easily detected with CT, but it can also be visualized with gradient echo MR-sequences. With CT and MR-diffusion we can get a good impression of the area that is infarcted, but we cannot preclude a large ischemic penumbra (tissue at risk).

MRI: High signal on conventional MR-sequences is comparable to hypodensity on CT.
It is the result of irreversible injury with cell death. So hyperintensity means BAD news: dead brain. On PD/T2WI and FLAIR infarction is seen as high SI. These sequences detect 80% of infarctions before 24 hours. They may be negative up to 2-4 hours post-ictus! DWI is the most sensitive sequence for stroke imaging. DWI is sensitive to restriction of Brownian motion of extracellular water due to imbalance caused by cytotoxic edema. Perfusion with MR is comparable to perfusion CT. The area with abnormal perfusion can be dead tissue or tissue at risk. Combining the diffusion and perfusion images helps us to define the tissue at risk, i.e. the penumbra.

Positron emission tomography (PET) is still the only method allowing quantitative determination of various physiologic variables in the brain and was applied extensively for studies in patients with acute, subacute or chronic stages of ischemic stroke. The quantitative measurement of CBF, CMRO2, OEF and CBV permitted the independent assessment of perfusion and energy metabolism, and demonstrated the uncoupling of these usually closely related variables. These studies provided data on flow and metabolic variables predicting final infarction on late CTs (rCBF less than 12 ml/100g/min, CMRO2 less than 65 µmol/100g/min). Relatively preserved CMRO2 indicated maintained neuronal function in regions with severely reduced CBF; this pattern was coined "misery perfusion" and served as a definition for the penumbra, which is characterized by increased oxygen extraction fraction (up to more than 80 % from the normal 40 – 50 %). Late CT or MRI often showed these regions as morphologically intact. PET thus permits the differentiation of various tissue compartments within an ischemic territory: Irreversible damage by decreased flow and oxygen consumption below critical thresholds; misery perfusion, i.e. penumbra, by decreased flow, but preserved oxygen utilization above a critical threshold, expressed by increased OEF; luxury perfusion by flow increased above the metabolic demand; anaerobic

glycolysis by a change in the ratio between glucose metabolism and oxygen utilization. However, PET has severe disadvantages limiting its routine application in patients with stroke: it is a complex methodology, requires multitracer application, and quantitative analysis necessitates arterial blood sampling. Although PET remains the imaging gold standard for identification of the penumbra in stroke patients, MR studies using diffusion and perfusion-weighted imaging might provide a differentiation between the core and the penumbra: the early diffusion weighted imaging (DWI) lesion might define the ischemic core and adjacent critically hypoperfused tissue might be identified with perfusion-weighted imaging (PWI). However, this surrogate definition of the penumbra has several uncertainties: the mismatch volume in PW / DWI as conventionally calculated does not reliably reflect misery perfusion, i.e. the penumbra as defined by PET.


UNIVERSITAS MEDICINAE ET PHARMACIAE
NAPOCENSIS