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# 14TH CONGRESS OF THE SOCIETY FOR THE STUDY OF NEUROPROTECTION AND NEUROPLASTICITY

OCTOBER 4TH, 2018
ELBA ESTEPONA GRAN HOTEL
COSTA DEL SOL | SPAIN

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The official language is English. Simultaneous translation will not be provided.

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The organizers cannot assume liability for any changes in the program due to external or unforeseen circumstances.

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Participants are kindly requested to wear their name badge at all times. The badge enables admission to the scientific sessions and dinners.

## FINAL PROGRAM & ABSTRACT BOOK

The participants documents include the program and abstract book which will be handed out at the registration counter.

## COFFEE BREAKS

Coffee, tea and water are served during morning coffee breaks and are free of charge to all registered participants.

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Participants are kindly requested to keep their mobile phones turned off while attending the scientific sessions in the meeting rooms.

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# SCIENTIFIC PROGRAM

14TH CONGRESS OF THE

# SOCIETY FOR THE STUDY OF NEUROPROTECTION AND NEUROPLASTICITY

OCTOBER 4TH, 2018 | ELBA ESTEPONA GRAN HOTEL | COSTA DEL SOL | SPAIN

## *THURSDAY, OCTOBER 4TH, 2018*

| | |
|---|---|
| 08:45 – 09:00 | ***WELCOME ADDRESS*** |

***SESSION 1***
***CHAIRPERSONS:*** Dafin F. Mureșanu (Romania), Natan M. Bornstein (Israel)

| | |
|---|---|
| 09:00 – 09:20 | Dafin F. Mureșanu (Romania)<br>The science of neurorehabilitation – from infancy to school age |
| 09:20 – 09:40 | Natan Bornstein (Israel)<br>A meta-analysis of nine randomized clinical trials: safety and efficacy of neurotrophic factors in early post-stroke recovery |
| 09:40 – 10:00 | Michael Brainin (Austria)<br>The global stroke epidemic: prevention is the main issue |
| 10:00 – 10:20 | Volker Hömberg (Germany)<br>Does the concept of proportional recovery impede impairment oriented neurorehab in the postacute phase after stroke? |
| 10:20 – 10:25 | Discussions |
| 10:25 – 10:45 | ***COFFEE BREAK*** |

## *SESSION 2*

***CHAIRPERSONS:*** Michael Brainin (Austria), Antonio Federico (Italy)

| | |
|---|---|
| 10:45 – 11:05 | Michael Chopp (USA)<br>Mechanisms underlying the use ofneurotrophic factors in combination with tPA and thrombectomy after stroke |
| 11:05 – 11:25 | Ovidiu Băjenaru (Romania)<br>Brain resting-state neuronal networks modifications in Parkinson's disease - an fMRI study |
| 11:25 – 11:45 | Antonio Federico (Italy)<br>Update of inherited small vessel diseases |
| 11:45 – 12:05 | Johannes Vester (Germany)<br>The concept of high quality, non-interventional comparative effectiveness in neurorehabilitation - new pathways within the framework of evidence-based medicine |
| 12:05 – 12:10 | Discussion |
| 12:10 – 13:40 | ***LUNCH*** |

## *SESSION 3*

***CHAIRPERSONS:*** Volker Hömberg (Germany), Ovidiu Băjenaru (Romania)

| | |
|---|---|
| 13:40 – 14:00 | Hari Shanker Sharma (Sweden)<br>Superior neuroprotection by co-administration of TiO2 nanowired neurotrophic factors together with antibodies to neuronal nitric oxide synthase and mesenchymal stem cells following exacerbation of Alzheimer's disease brain pathology after concussive head injury |

| | |
|---|---|
| 14:00 – 14:20 | Wolf-Dieter Heiss (Germany)<br>Methods to improve the therapeutic window for rTPA-Thrombolysis |
| 14:20 – 14:40 | Anton Alvarez (Spain)<br>VEGF as a new drug target in Alzheimer's disease |
| 14:40 – 15:00 | Veronika Golovacheva (Russia)<br>Neuroplasticity in chronic headache: its "dark" and "light" sides |
| 15:00 – 15:05 | Discussions |
| 15:05 – 15:25 | ***COFFEE BREAK*** |

***SESSION 4***
***CHAIRPERSONS:*** Hari Shanker Sharma (Sweden), Michael Chopp (USA)

| | |
|---|---|
| 15:25 – 15:45 | Lynne Lourdes Lucena (Philipinnes)<br>Efficacy of neurotrophic factors in severe traumatic brain injury: a multi-center, retrospective cohort study |
| 15:45 – 16:05 | Agata Tomczak (Poland)<br>Good recovery from severe traumatic brain injury (TBI) - two cases study |
| 16:05 – 16:25 | Rhoderick M. Casis (Philipinnes)<br>Neurotrophic drug as an add on treatment in a patient with severe traumatic brain injury |
| 16:25 – 16:30 | ***CLOSING REMARKS*** |

# ABSTRACTS

## VEGF AS A NEW DRUG TARGET IN ALZHEIMER'S DISEASE

**ANTÓN ÁLVAREZ[1,2]**

***IRENE ALVAREZ[1], ANTÍA MARTINEZ[1], MANUEL ALEIXANDRE[3], CARLOS LINARES[4], JESUS FIGUEROA[1,5], DAFIN MUREȘANU[6]***

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Vascular endothelial growth factor (VEGF) is a hypoxia-inducible angiogenic growth factor regulating vascular, endothelial/blood brain barrier, and neural functions that have been involved in the pathophysiology of Alzheimer's disease (AD). Alterations in the brain, cerebrospinal fluid (CSF) and plasma/serum levels of VEGF have been reported in AD patients. VEGF expression was found to be enhanced in vascular and parenchymal compartments of AD brains compared to non demented subjects; to co-localize with amyloid plaques and with clusters of glial cells; and to correlate with amyloid and tau pathology. Increased levels of VEGF in the CSF of AD and vascular dementia patients have been reported too, although other authors observed no variations or reduced CSF VEGF values in mild dementia stages. Investigations on plasma/serum VEGF yielded controversial results showing increased, unchanged or even decreased VEGF levels in AD compared to controls. Apart from discrepancies of results, all these studies included small samples of AD cases, and none of them evaluated variations in circulating VEGF according to stages of clinical severity of the disease.

VEGF demonstrated relevant neuroprotective, neurotrophic and cognitive effects in experimental conditions. The accumulation of VEGF within amyloid plaques and the inverse correlation of VEGF-positive microvessels with tau and amyloid deposits found in AD brains suggest that an enhanced VEGF activity could reflect a protective brain response counteracting AD pathology, whereas a reduced VEGF signaling might contribute to enhance it. In fact, elevated CSF levels of VEGF were recently reported to be associated with more optimal brain aging outcomes (less decline in hippocampal volume, episodic memory, and executive function), particularly in individuals showing early AD biomarkers. However, the relationships of serum VEGF concentrations with measures of cognitive performance were not properly assessed in previous studies.

We first investigated the influence of AD clinical severity (mild, moderate and moderately-severe stages) and ApoE4 status (ApoE4 carriers and non-carriers)

on the serum levels of VEGF and its relationship with cognition. Baseline serum VEGF levels, cognitive and functional performance were evaluated in AD (n=245), amnestic mild cognitive impairment (MCI) (n=48) and control subjects (n=62). VEGF levels were measured in serum samples by using specific ELISA kits for VEGF165. Our results indicated that VEGF levels were higher in AD patients than in MCI cases and controls ($p<0.05$), and showed a progressive increase with clinical severity in the whole study population ($p<0.01$). Among AD patients, severity-related VEGF elevations were significant in ApoE4 carriers ($p<0.05$), but not in non-carriers. Increased VEGF levels were associated with disease severity, and showed mild correlations with cognitive impairment that were only consistent for the ADAS-cog+ items remembering test instructions (memory) and maze task (executive functions) in the group of AD patients ($p<0.05$). However, higher VEGF values were related to better memory and language performance in ApoE4 carriers with moderately-severe AD. According to these results showing severity- and ApoE4-related differences in serum VEGF and positive VEGF-cognitive correlates in moderately-severe ApoE4 cases, it is suggested that increases in VEGF levels might represent an endogenous response driven by pathological factors and could entail cognitive benefits in AD patients, particularly in ApoE4 carriers.

We also investigated changes in circulating VEGF and the interactions between VEGF and clinical responses after drug treatment in AD patients participating in a 28-week RCT. Serum VEGF levels, cognitive and functional performance were evaluated at baseline, week-16 (end of Cerebrolysin treatment) and week-28 (endpoint) in AD patients treated with Cerebrolysin (n=52), donepezil (n=52) or a combination of both drugs (n=53).

Overall, there were no significant treatment effects on VEGF levels. However, in moderately-severe AD patients: 1) The combination therapy reduced elevated VEGF levels significantly ($p<0.05$) at week-16 and week-28 as compared to donepezil alone; 2) higher baseline VEGF levels were associated to better functional ($p<0.05$) and cognitive ($p<0.01$) improvements at week-16 and week-28, respectively; and 3) reductions in VEGF at endpoint (week-28) correlated with a significant ($p<0.05$) improvement in praxis and executive functions. In addition, and independently of the treatment option, VEGF reductions at study endpoint were associated with improvements in cognition, praxis and executive functions in the whole study population ($p<0.05$) and in the subgroup of APOE4 cases ($p<0.05$), and with a functional improvement ($p<0.05$) in APOE4 cases only. In summary, elevated VEGF levels were found to be associated with improved cognition-functioning in moderately-severe AD; while drug-induced decreases in VEGF were accompanied by cognitive-functional improvements, particularly in APOE4 cases, and by better praxis and executive functions in advanced cases receiving Cerebrolysin plus donepezil. These findings are indicating the influence of VEGF on

cognitive-functional performance and response to therapy in AD; and suggest that VEGF increases might represent a neuroprotective response in AD, especially in advanced cases and in APOE4 carriers.

## *BRAIN RESTING-STATE NEURONAL NETWORKS MODIFICATIONS IN PARKINSON'S DISEASE - AN FMRI STUDY*

***OVIDIU BĂJENARU***

***ROCEANU A., ONU M., BADEA L.***

University of Medicine and Pharmacy "Carol Davila" Bucharest, Romania

The recently developed fMRI studies, allowed the possibility to better identify the resting state neuronal networks activity in the human brain in normal and pathologic conditions. This method is particulary useful in studying and understanding the the dynamics of the functional pathophysiology in neurodegenerative diseases and neurocognitive disorders. We have analyzed resting-state functional magnetic resonance imaging (rs-fMRI) data in 27 PD patients and 16 healthy subjects. Differences for intra- and inter-network connectivity between healthy subjects and patients were investigated. Intra-network connectivity changes, eight components showed a significant connectivity increase in patients ($p<0.05$); these were correlated with clinicalscores and were largest for (sensori)motor networks. For inter-network connectivity changes, we found higher connectivity between the sensorimotor network and the spatial attention network ($p=0.0098$) and lower connectivity between anterior and posterior default mode networks (DMN) ($p=0.024$), anterior DMN and visual recognition networks ($p=0.026$), as well as between visual attention and main dorsal attention networks ($p=0.03$), for patients as compared to healthy subjects. The area under the Receiver Operating Characteristics (ROC) curve for the best predictor (partial correlation between sensorimotor and spatial attention networks) was 0.772. These functional alterations were not associated with any gray or white matter structural changes.

Conclusion. Our results show higher connectivity between sensorimotor and spatial attention areas in patients, which in our view probably represents a biologic functional compensatory mechanism as a consequence to the chronic neurodegenerative process.

## *A META-ANALYSIS OF NINE RANDOMIZED CLINICAL TRIALS: SAFETY AND EFFICACY OF NEUROTROPHIC FACTORS IN EARLY POST-STROKE RECOVERY*

***NATAN BORNSTEIN***
Director of the Brain Division, Shaare-Zedek Medical Center, Jerusalem, Israel

This meta-analysis combines the results of nine ischemic stroke trials, assessing efficacy of Cerebrolysin on global neurological improvement during early post-stroke period. Cerebrolysin is a parenterally administered neuropeptide preparation approved for treatment of stroke. All included studies had a prospective, randomized, double-blind, placebo-controlled design.

The patients were treated with 30–50 ml Cerebrolysin once daily for 10–21 days, with treatment initiation within 72 h after onset of ischemic stroke. For five studies, original analysis data were available for meta-analysis (individual patient data analysis); for four studies, aggregate data were used. The combination by meta-analytic procedures was pre-planned and the methods of synthesis were predefined under blinded conditions. Search deadline for the present meta-analysis was December 31, 2016.

The nonparametric Mann-Whitney (MW) effect size for National Institutes of Health Stroke Scale (NIHSS) on day 30 (or 21), combining the results of nine randomized, controlled trials by means of the robust Wei-Lachin pooling procedure (maximin-efficient robust test), indicated superiority of Cerebrolysin as compared with placebo (MW 0.60, $P < 0.0001$, $N = 1879$). The combined number needed to treat for clinically relevant changes in early NIHSS was 7.7 (95% CI 5.2 to 15.0). The additional full-scale ordinal analysis of modified Rankin Scale at day 90 in moderate to severe patients resulted in MW 0.61 with statistical significance in favor of Cerebrolysin (95%CI 0.52 to 0.69, $P = 0.0118$, $N = 314$).

Safety aspects were comparable to placebo. Our meta-analysis confirms previous evidence that Cerebrolysin has a beneficial effect on early global neurological deficits in patients with acute ischemic stroke.

## *THE GLOBAL STROKE EPIDEMIC: PREVENTION IS THE MAIN ISSUE*

***MICHAEL BRAININ***
Professor in Clinical Neurology, Danube University Krems, Austria
President Elect, World Stroke Organisation

Today, there is an increase in stroke mortality which is most dramatic in low and middle income countries. If we include prevalence rates and the overall burden of the disease, dementia and stroke combined are by far the most burdening diseases globally. Moreover, in countries with aging populations the increase is also seen due to demographic changes.

More recently, several studies have shown that a decrease of incidence rates is possible by improving modifiable risk factors, mostly of life style. For example, The Global Burden of Disease Study and the Interstroke Study both report that the burden of stroke is strongly influenced by modifiable risk factors and up to 90% of stroke occurrence can be explained by these risk factors. Conversely, a major reduction of incidence might be expected if behavioral and metabolic risk factors are managed appropriately. Recently, environmental factors (indoor and outdoor air pollution and lead exposure) have been recognized as major risks. Air pollution alone explains 30% of the stroke risk burden globally.

Prevention on a population scale can only be effective if large programs are established that target not only high-risk persons but aim also at medium risk and low risk persons. The WHO led initiative of reducing the NCDs (non-communicating diseases such as heart disease, cancer, diabetes, stroke and cardiopulmonary disease) can only become effective if the prevention issues are carried across diseases and are not only focused on one specific illness. This NCD Alliance has published a WHO Global Action Plan 2013-2020 which aims at reducing the NCD burden by 30% in 2030 (30 by 30). Regional assessments of the effectiveness of such initiatives show that in some world regions this may be reached but in others the targets will be missed if additional efforts are not made.

## *NEUROTROPHIC DRUG AS AN ADD ON TREATMENT IN A PATIENT WITH SEVERE TRAUMATIC BRAIN INJURY*

***RHODERICK CASIS***
St. Luke's Medical Center Quezon City and Global City, Philippines

Traumatic brain injury (TBI) is a problem seen by primary physicians and specialists all-over the world. Treatment of TBI can present as a dilemma to treat especially with the heterogenous aspect of the disease coming from both primary and secondary brain injury. The treatment options range from surgery, medications, intensive care, nutrition and rehabilitation. This is a case about a particular patient who was GCS 3/15 with anisocoria at the emergency department. With aggressive resuscitation, her GCS improved to 4/15. Because of the improvement, her condition was discussed with the relatives regarding treatment and expectations and prognosis. They agreed to the treatment options suggested which is immediate surgery, decompressive hemicraniectomy with evacuation of subdural hematoma and intracerebral contusion hematoma. The primary treatment, surgery, was done and all available additional treatment present in the hospital was given to the patient. The option of giving a neurotrophic drug, Cerebrolysin, was discussed with the relative. It was given to the patient 1 day after surgery and was continued for 14 days. No other neuroprotective drug was given before or after the operation. Together with surgery and Cerebrolysin, extensive rehabilitation and occupational therapy was also done. The patient underwent early repair of her hemicraniectomy, 1 ½ months after the first surgery. She was discharged GCS 15/15. She was asked to continue with rehabilitation and occupational therapy. She was able to go back to her work without any problem or residual deficit. With the patient's remarkable recovery, the combination of treatment options may be the answer in the treatment and recovery of patients with severe traumatic brain injury.

## *MECHANISMS UNDERLYING THE USE OF NEUROTROPHIC FACTORS IN COMBINATION WITH TPA AND THROMBECTOMY AFTER STROKE*

***MICHAEL CHOPP***

***ZHENG GANG ZHANG, CHAO LI, HUA TENG***

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

To date, the only approved treatments for acute ischemic stroke are thrombolysis using tissue plasminogen activator (tPA) administered within 4.5 hours after stroke onset and thrombectomy which involves mechanical withdrawal of the occluding clot within 24 hours of ictus of a large vessel. While both therapeutic interventions increase the likelihood of improving neurological outcome, they both remain far from optimum. tPA treatment of eligible patients results in only approximately one third of patients experiencing early brain reperfusion. Recanalization of the occluded large cerebral artery by the thrombectomy only leads to ~70% of patients achieving improved and most often not full tissue reperfusion. The majority of patients obtaining tPA or thrombectomy retain neurological dysfunction. Moreover, due to unfavorably large ischemic cores, many patients with large arterial occlusion are not eligible to receive tPA or endovascular therapy. In the present studies using a clinically relevant in vitro model of the BBB consisting of human cerebral endothelial cells, we provide a mechanistic basis for how tPA and thrombectomy exacerbate blood brain barrier (BBB) disruption which may lead to brain hemorrhage. Secondary thrombosis and vascular damage are prevalent in the ischemic brain after tPA and thrombectomy treatments, and we provide molecular bases that underlie secondary microvascular thrombosis post stroke. Importantly, we demonstrate that Cerebrolysin significantly promotes microvascular integrity and reduces adverse vascular effects attributed to tPA, as well as reduces vascular damage and inflammatory responses to both tPA and thrombectomy. Thus, our data suggest that Cerebrolysin when used in combination with rtPA and thrombectomy may enhance the safety and efficacy of acute tPA and thrombectomy treatment of ischemic stroke.

## *UPDATE OF INHERITED SMALL VESSEL DISEASES*

***ANTONIO FEDERICO***
Department of Medicine, Surgery and Neurosciences, Medical School, University of Siena, Siena, Italy
Past Chairman of the Scientific Committee and Past Member of the Board of the European Academy of Neurology
Chairmen of EAN Task Force for Rare Neurologic Diseases

Cerebral microangiopathies are responsible of a great number of strokes. In the recent years advances in molecular genetics identified several monogenic conditions involving cerebral small vessels and predisposing to ischemic and/or hemorrhagic stroke and diffuse white matter disease leading to vascular dementia. Clinical features and diagnostic clues of these conditions, [cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL), COL4A1-related cerebral small vessel diseases, autosomal dominant retinal vasculopathy with cerebral leukodystrophy (AD-RVLC), and Fabry's disease] are here reviewed. Albeit with variable phenotypes and with different defective genes, all these disorders produce arteriopathy and microvascular disintegration with changes in brain functions. Specific diagnostic tools are recommended, genetic analysis being the gold standard for the diagnosis. We will also discuss on some pathogenetic mechanism responsible for brain abnormalities evident in an early stage of the diseases. Finally, the recent approval by FDA of Cerebrolysin as a useful drug for CADASIL open new therapeutic hopes for the future.

## NEUROPLASTICITY IN CHRONIC HEADACHE: ITS "DARK" AND "LIGHT" SIDES

**VERONIKA GOLOVACHEVA**[1]

**VLADIMIR PARFENOV**

1. Assistant professor, Neurology and neurosurgery Department, I.M. Sechenov The First Moscow State Medical University
2. Professor, the chief of the Department, Neurology and neurosurgery Department I.M. Sechenov The First Moscow State Medical University

Neuroplasticity can present in adult and has two sides – "dark" and "light". On the one side, neuroplastic changes can produce central and peripheral sensitization and lead to chronization of headache (medication-overused headache, migraine, tension-type headache). On the other side, neuroplasticity can be very useful process and used in treatment of chronic daily headache and medication-overused headache. It's known antidepressants, cerebrolysin, cognitive behavioral therapy can lead to beneficial neuroplastic changes in the brain.

We studied new approach in treatment of resistance patients with chronic daily headache and medication-overused headache. The approach was based at combined therapy and included education sessions, withdrawal therapy, antidepressant therapy (amitrityline, duloxetine or paroxetine), cerebrolysin, cognitive behavioral therapy. Twenty patients were enrolled. At 12-month follow-up 70% (N=14) of participants had clinical efficacy of treatment. Nobody had relapse during 12-month follow-up. So combined therapy with neuroplastic effect can be useful for patient with chronic daily headache and medication-overused headache. Future randomized placebo-controlled and comparative studies should be conducted.

## METHODS TO IMPROVE THE THERAPEUTIC WINDOW FOR rTPA-THROMBOLYSIS

**WOLF-DIETER HEISS**

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

The concept of the ischemic penumbra was formulated on the basis of animal experiments showing functional impairment and electrophysiologic disturbances with decreasing flow to the brain below defined values (the threshold for function) and irreversible tissue damage with blood supply further decreased (the threshold

for infarction). The perfusion range between these thresholds was termed the "penumbra," and restitution of flow above the functional threshold was able to reverse the deficits without permanent damage. In further experiments, the dependency of the development of irreversible lesions on the interaction of the severity and the duration of critically reduced blood flow was established, proving that the lower the flow, the shorter the time for efficient reperfusion. As a consequence, infarction develops from the core of ischemia to the areas of less severe hypoperfusion. The translation of this experimental concept as the basis for the efficient treatment of stroke requires noninvasive methods with which regional flow and energy metabolism can be repeatedly investigated to demonstrate penumbra tissue, which can benefit from therapeutic interventions. PET allows the quantification of regional cerebral blood flow, the regional oxygen extraction fraction, and the regional metabolic rate for oxygen. With these variables, clear definitions of irreversible tissue damage and of critically hypoperfused but potentially salvageable tissue (i.e., the penumbra) in stroke patients can be achieved. However, PET is a research tool, and its complex logistics limit clinical routine applications. Perfusion-weighted or diffusion-weighted MRI is a widely applicable clinical tool, and the "mismatch" between perfusion-weighted and diffusion-weighted abnormalities serves as an indicator of the penumbra. Also CTAngiography and CTPerfusion Imaging can be used to detect areas suspicious of penumbra. The findings with both methods should be validated by PET measurements.

Several studies included the selection of patients for intravenous thrombolysis on the basis of a PWI–DWI mismatch or CTPerfusion studies. A metaanalysis of several mismatch-based thrombolysis studies of delayed treatment from the DIAS, DIAS-2, DEDAS, EPITHET, and DEFUSE trials revealed increased recanalization. However, this analysis did not confirm an improvement in clinical outcome with delayed thrombolysis (Mishra et al 2010).Randomized controlled trials that did enroll patients based on the presence of a target mismatch on multimodal imaging demonstrated a higher benefit of revascularisation treatment by comparison with those who did not (Amiri et al 2016).The results of the randomized trial (Jovin TG et al, Int J Stroke 2017demonstrated for the first time that revascularization treatment for BI complicating an ICA or a proximal MCA M1 was still beneficial from 6 to 24hours after onset among patient who did have per their clinical exam and the multimodal brain imaging a persistent penumbra. With this as a background we will discuss the yield of imaging for the selection of patients for a revascularization therapy.

Mishra NK, Albers GW, Davis SM, et al. Mismatch-based delayed thrombolysis: a meta-analysis. Stroke. 2010;41:e25–e33.

Amiri H, Bluhmki E, Bendszus M, et al. European Cooperative Acute Stroke Study-4: extending the time for thrombolysis in emergency neurological deficits—ECASS-4: ExTEND. Int J Stroke. 2016;11:260–267.

Jovin TG et al, Int J Stroke 2017), Diffusion-weighted Imaging or Computerized Tomography Perfusion Assessment with Clinical Mismatch in the Triage of Wake-up and Late Presenting Strokes Undergoing Neurointervention with Trevo (DAWN)

## *DOES THE CONCEPT OF PROPORTIONAL RECOVERY IMPEDE IMPAIRMENT ORIENTED NEUROREHAB IN THE POSTACUTE PHASE AFTER STROKE?*


***VOLKER HÖMBERG***

Head of Neurology SRH_GBW Bad Wimpfen and Neurology Coordinator for the SRH group of hospitals and clinics, Germany
Secretary General WFNR, Vice President EFNR


Within the last 10 years the number of survivors after stroke and traumatic brain injury (TBI) has dramatically increased due to advances in acute medical care. Nevertheless the question remains if we have really made progress to influence impairment by restorative strategies rather than just improving function and consecutively participation by compensatory strategies .

Are we really able to influence impairment i.e. can we reduce the amount of paresis (e.g. after stroke)? „The enigma of proportional recovery „

First published in 2008 (Prabhakaran et al 2008) an intersting phenomenon was described: The spontaneous impairment recovery after stroke at day 90 after the ictus ( with or without treatment) for upper extremity was usually 70% oft he maximum possible difference between initial score and the maximum possible. There were outliers from this rule attributable to severe pathology in the primary descending motor tracts especially the corticospinal tract. In the meantime this"proportional recovery rule was also demonstratesd to apply for impairments in non-motor domains as neglect and language abilities (Lazar et al 2010, Marchi et al 2017). If this 70% proportional spontaneous recovery is a universal rule and cannot be influenced , this of course would mean that impairment oriented rehab is not possible. The challenge is to change the slope ( i.e.from 70% to 80%or more) or to make outliers inliers.

In animal experimentation so called „enriched environments" have been proven to facilitate brain repair. There has however been no translation from this experimental animal world tot he clinical bedside.

So far only three major strategies have been shown to help decrease impairment in the subacute stage e.g. after stroke: The forced use or constraint induced movement therapy approach has been proven to be effectve in the multicenter prospective EXCITE trial (Wolf et al 2008). Also the use of antidepressant agents was shown to be effective in the FLAME trial (Chollet et al 2011). Recently the CARS trial (Muresanu et al 2016) documented for the first time after decades of frustrane attempts to achieve some sort of neuroprotective and/or neurorestorative effects that a mutimodal drug can improve impairment after stroke . This was further corroborated in a consecutive trial (Guekt et al 2017) and further corroborated by a metaanalysis of stroke related trials with cerebrolysin (Bornstein et al 2018).

Possible additional candidates for a true „impairment" oriented treatment approach are neuromodulatory techniques such as peripheral neuromuscular and/ or sensory stimulation ( eg. whole hand subliminal „mesh-glove" stimulation )and more and more also non invasive brain stimulation techniques such as repetitive transcranial magnetic stimulation and transcranial DC stimulation. Also the use of non fatiguable robotic devices to enable a high intensity massed movement treatment appear promising.

As treatment intensity is likely to be the key element for impairment reduction we certainly have to find clever and affordable ways: to increase the daily treatment time of our patients. To day even during inpatient rehabilitation treatment times hardly exceed three hours a day i.e. that we use only a small percentage of waking hours leaving long "idling" time not field by any treatment. In this sense we have to "reinvent" neurorehabilitation within this sensitive post injury period to combat impairment with high frequency treatments combined with neuromodulatory techniques (robot use, peripheral and central stimulation , pharmaceuticals) .

Probably the most important impact in facilitating impairment reduction will however have clever ,economically feasible, approches to increase the net number of therapy or activity hours per day by creating true „ enriched environment" for severely impaired patients . They should enable 6-8 hours of daytime treatment to avoid leaving our patients „inactive and alone" in future.

Neurorehabilitation after the „Proportional Recovery Rule".

But let´s address also the worst case scenario: If the proportional recovery rule cannot be influenced ,there is still ample space if not even more need for neurorehabilitation exploiting our knowledge about compensatory interventions including motor learning. This means optimizing residual motor function at a given a (and unchangeable) impairment level.

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## *EFFICACY OF NEUROTROPHIC FACTORS IN SEVERE TRAUMATIC BRAIN INJURY: A MULTI-CENTER, RETROSPECTIVE COHORT STUDY*

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Background: Severe traumatic brain injury patients with non-operative lesions are known to have a poorer prognosis. Recent modalities are now exploring the utility of cerebroproteinhydrolysate (CBH) in improving patient outcomes among TBI patients. However, limited studies are available showing the efficacy of CBH among severe TBI patients.

Objectives: To determine the effects of CBH as add-on therapy to the standard medical decompression protocol for non-operative severe TBI patients.

Methodology: The study employed a retrospective cohort design. In addition to the current medical decompression protocol for severe TBI, 42 patients received 30 ml/day CBH for 14 days followed by a subsequent dosage of 10 ml/day for another 14 days. Meanwhile, 45 patients with the same GCS range on admission but was not given CBH served as the comparison group. Primary outcomes evaluated were the proportion of patients achieving a GCS ≥9 and GOS ≥4 at Day21. Stata MP version 14 was used for data analysis.

Results: As compared to no CBH group, a significantly higher proportion of patients given CBH patients achieved a GCS ≥9 and GOS ≥4 at Day 21. Improvement in GCS is significantly higher in the CBH group at all follow-up times. Mean length of hospital stay(LOS) is 6 days shorter in CBH group, and a lower proportion of CBH patients have LOS ≥30 days (CBH: 5% vs. No CBH: 51%).

Conclusion: CBH is beneficial for severe TBI patients with non-operative lesions as evident by higher improvement in GCS/GOSand shorter length of hospital stay as compared to standard treatment alone.

## *THE SCIENCE OF NEUROREHABILITATION – FROM INFANCY TO SCHOOL AGE*

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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.

This presentation will focus on the therapeutical effects of multimodal drugs on neurorecovery after stroke and TBI.

## *SUPERIOR NEUROPROTECTION BY CO-ADMINISTRATION OF TIO2 NANOWIRED NEUROTROPHIC FACTORS TOGETHER WITH ANTIBODIES TO NEURONAL NITRIC OXIDE SYNTHASE AND MESENCHYMAL STEM CELLS FOLLOWING EXACERBATION OF ALZHEIMER'S DISEASE BRAIN PATHOLOGY AFTER CONCUSSIVE HEAD INJURY*

***HARI SHANKER SHARMA[1]***

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BACKGROUND

Alzheimer's disease (AD) inflicts over 40 millions people aged 65 and older Worldwide and roughly 5 million Americans are living with the disease that involves huge burden on the society and families as well. In addition, AD is quite frequent in Military personnel because of possible mild traumatic brain injury or concussive head injury that may exacerbate AD induced brain pathology. Thus, exploration of novel therapeutic measures is needed to contain the disease and improve the quality of life of the victims.

Increasing evidences suggest that oxidative stress is one of the key factors in causing AD induced brain pathologies. Brain injury alone induces upregulation of several oxidative stress parameters and thus, a combination of brain injury and AD could lead to devastating brain damage. Few studies in AD also suggest a key role of nitric oxide (NO) in enhancing amyloid beta peptide (AβP) induced neurotoxicity. NO is synthesized by the endogenous enzyme nitric oxide synthase (NOS) that occurs in 3-isoforms, namely neuronal NOS (nNOS), inducible NOS (iNOS) and endothelial NO (eNOS). Thus, blockade of NOS activity appears to be beneficial AD, a feature that requires additional investigation. Moreover, several lines of evidences suggests that mesenchymal stem cells (MSCs) could be possible potential therapeutic agents in AD in formation of new neurons and making novel synaptic connections. Also, MSCs enhance neurotrophic factors within the brain that could help in achieving neuroregeneration and functional improvement in AD. This suggests that AD pathology is complex. Thus, it would be interesting to explore co-administration of key agents that could block NO synthesis, induce regeneration and create new neuronal connections together with exogenous supplement of several neurotrophic factors to treat AD successfully. Thus, in this investigation, we used antibodies to nNOS to reduce toxicity together with MSCs to improve new neuronal connections and supplied exogenous neurotrophic factors using Cerebrolsyin. Cerebrolysin is a balanced composition of several neurotrophic factors and active peptide fragments that could induce neuroplasticity, neuroregeneration and neutralize AβP neurotoxicity. Since nanodelivery of compounds results in higher bioavailability for long time, we used TiO2-nanowred delivery of these agents together to induce superior neuroprotection in AD following concussive head injury (CHI).

METHODS

AD like pathology was produced in rats by administering AβP (1-40) intraventricularly (i.c.v.) in the left lateral ventricle (250 ng/10 µl) once daily for 4 weeks in normal or CHI rats. The CHI was induced in anaesthetized rats by dropping a weight of 114.6 g on the exposed right parietal skull from a 20 cm height thorough a guide tube. This would cause an impact of 0.224 N on the skull surface. Control rats received saline. In separate group of rats either TiO2 nanowired monoclonal antibodies of neuronal nitric oxide synthase (NWnNOS abs, 1:20, 50 µl) together with nanowired

MSCs (NWMSCs 1 million active cells) and nanowired cerebrolysin (NWCBL 50 µl) were administered (i.c.v.) once daily 3 weeks after the 1st AβP administration and continued for 1 week. After 30 days of the 1st AβP infusion, the rats were examined for BBB breakdown, edema, neuronal, glial injuries and AβP deposits in their brain.
Results

CHI results in 2- to 4-fold exacerbation of AD induced brain pathology. Our results showed that co-administration of NWnNOS, NWMSCs and NWCBL was able to significantly reduce AβP deposits in the brain after CHI along with neuronal damage and glial activation. Interestingly, the breakdown of the BBB to Evans blue albumin and radioiodine in cortex, hippocampus, hypothalamus and cerebellum was significantly reduced in drug treated group as compared to control. Combination of these three agents showed superior effects in reducing brain pathology in AD as compared to any combination of 2 agents or all agents alone. These combinations of 3 agents wee also able to reduce AβP deposit in the brain and improved behavioral functions on Rota Rod treadmill and inclined angle platform as well as hidden platform search under water. This suggests that blockade of nNOS together with supplement of exogenous neurotropic factors and MSCs are capable to reduce AD induced brain pathology. Interestingly, when these 3 agents were delivered without using nanotechnology, there neuroprotective effects were much diminished in AD with CHI. However; tehse agents were able to thwart Ad induced brain pathology in normal animals. This suggests that TiO2-nanowired delivery of tehse agents are needed to induce superior neuroprotection in AD brain pathology following CHI. Our results further showed a close correspondence with reduction in AβP deposits in the brain and neuronal damage and glial activation following AD in CHI. Also, breakdown of the BBB and brain edema formation was absent in AD with CHI in nanowired delivery of these 3 agents as compared to either agents alone. Thus, a combination of NWnNOS, NWMSCs and NWCBL is needed to induce superior neuroprotective effects in reducing brain pathology in AD after CHI.

CONCLUSION

Taken together, our observations are the first to show that blockade nNOS activity, enhancement of neuronal connection with MSCs and exogenous supplement of neurotrophic factors by cerebrolysin potentiate the neuroprotective effects in AD brain pathology following CHI, not reported earlier.

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## *GOOD RECOVERY FROM SEVERE TRAUMATIC BRAIN INJURY ( TBI ) - TWO CASES STUDY*

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TBI ( traumatic brain injury ) is the most common cause of death or disability in a younger population.

Consequences of traumatic brain injuries can worsen rapidly without treatment, but some of their signs or symptoms may appear days or weeks later
It is estimated that in highly industrialized countries ( e.g US, countries in Western Europe ) about 1,5 million craniocerebral injuries occur annually and mortality is estimated at 15-30 per 100.000.

The effects of TBI are the cause of disability of around 2% of the whole population in these countries.

TBI can have wide-ranging physical and psychological effects, so long-term multidisciplinary treatment (especially rehabilitation) is necessary.
We present two cases of patients with severe craniocerebral injuries, who after treatment (neuro-surgical intervention, rehabilitation, speech and psychological therapy) regained mobility and the ability to function independently.
The first case is a 20-year-old student who suffered a severe head injury during New Year's Evening as the result of a fall. The second case is a 66-year-old manager of a large company, who suffered a head injury in a bike accident. The initial clinical condition, the treatment that has been applied and the effects of the cooperation with an interdisciplinary medical team (consisting of physiotherapists, psychologists and speech therapists) is discussed.

It should be noticed that sociodemographic factors (such as: age, sex, economic status, place of residence, professional activity, family care and support ) have a significant impact on the course of treatment, especially in its post-hospitalisation phase.

Close cooperation between the patient, his family and the medical team is required. Despite similar treatment regimen (both surgical and pharmaco-therapeutical) as well as psychological care and physical rehabilitation applied, different results at the level of social functioning were observed. We regard the underlying psychological and sociodemographic varieties in both patients as a key to this difference outcome.

## *THE CONCEPT OF HIGH QUALITY, NON-INTERVENTIONAL COMPARATIVE EFFECTIVENESS IN NEUROREHABILITATION - NEW PATHWAYS WITHIN THE FRAMEWORK OF EVIDENCE-BASED MEDICINE*

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Evidence-based practice knocks on the door of clinical research in neurorehabilitation. The clinical trial is the mechanism for comparing and testing therapeutic interventions to determine their effect in human subjects and thus their value in rehabilitation practice (Terrin, 2003, Behrman 2013). But how are the chances to improve therapeutic concepts within the demanding framework of evidenced-based medicine?

While there is growing demand for information about comparative effectiveness (CE), there is substantial debate about whether and when observational studies have sufficient quality to support decision making.

Methodological challenges for analysis and the interpretation of results, as well as the lack of accepted principles to assess quality have limited the practical use of observational research.

Non-randomized studies have been relegated to lower tiers in commonly used hierarchies of evidence, largely because of their heterogeneity, the potential for bias in the results, and the challenges involved in their conduct and interpretation. Within the GRADE system (guidance for use of the Grading of Recommendations Assessment, Development, and Evaluation), observational studies start as low quality evidence and even can be rated further down if relevant evidence comes from studies that suffer from a high risk of bias.

Recent calls for using the full range of high-quality comparative effectiveness (CE) research to inform decisions about medical diagnostics and interventions have brought forth a spate of consensus offerings about recognizing quality in observational CE studies and meta-analysis.

An important milestone has been achieved by implementing the GRACE Principles for High-Quality Observational Studies of Comparative Effectiveness. This important guidance provides a hierarchy of evidence for observational research on comparative effectiveness that can be used by decision-makers, as well as key elements of good practice including defining research questions and methods a priori; collecting valid, clinically relevant data; analyzing, interpreting and reporting data, including sensitivity analyses and alternative explanations for findings; and conducting these studies in accordance with accepted good practices.

In this lecture, current perspectives of evidence-based medicine, classic and modern approaches to comparative effecteveness research, future pathways to improve the quality of CE trials, are discussed with examples from different fields of neurorehabiliation.

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Antón Alvarez has 25 years expertise in Basic and Clinical Research on Alzheimer's disease and Neuropsychiatric disorders. He was involved in a number of research projects, including projects funded by Public Institutions, pharmaceutical R&D studies, industrial and R+D+I projects, epidemiological studies and projects funded by the EU. As the result of his research activity Antón Alvarez published more than 100 scientific papers and book chapters.

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- 2001-2013: President of the Romanian Society of Neurology
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- Visiting Professor in Vietnam ( 2013 ) and Kazakhstan ( 2015 ), on behalf of WFN

- Member of the Executive Committee of ENS ( European Society of Neurology ) between 2005-2009, of the Scientific Committee of ECTRIMS ( 2004-2009)
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Professor Brainin was appointed in 2000 full Professor of Clinical Neurology and Director and Chair of the Department of Clinical Neurosciences and Prevention at the Danube University in Krems, Austria. From 1994-2016 he acted as Chair and Director of the Neurological Department of the University Hospital Tulln. In 1997 he set up the first stroke unit in Austria at his institution.

His research focus is on cerebrovascular diseases including acute therapy, recovery and cognition. He has published more than 200 peer-reviewed, Pub med listed articles. His h-index is 40, he has over 8.000 citations.

He has been an invited lecturer and chairperson to more than 1.000 international conferences. He has published and edited several books, among them the Textbook of Stroke Medicine (with WD Heiss, Cambridge Univ Press, 2nd edition 2015'.

From 2012-2014 he was President of the European Stroke Organization (ESO'. In 2015, he was elected President Elect of the World Stroke Organisation (WSO' and is due to take office in 2018. Since 2014 he is elected full Board Member of the European Academy of Neurology. He acted as chairman of the WSO Education Committee (2008-2017' for which he has co-directed teaching programmes in many regions of the world. Since 2008 he is editor-in-chief of the World Stroke Academy. He directs several postgraduate teaching programmes at his university, among them the WSO supported ESO European Master's Programme in Stroke Medicine, currently attended by medical doctors and neurologists from 23 countries.

He serves as Associate Editor for the European Journal of Neurology, also as Senior Consulting Editor for Stroke. He serves on the Editorial Boards of the International Journal of Stroke, the European Stroke Journal, Neuroepidemiology, the Journal of Neurological Sciences, and Frontiers in Neurology.

Professor Brainin is an Honorary Member of the ESO and International Fellow of the American Stroke Association and Fellow of the European Academy of Neurology. He received several awards, such as the Marinescu Award 2015 from the Romanian Society of Neurology and Honorary Doctorates from Hanoi University, Vietnam, and from the University of Cluj, Romania, an honorary professorship from Zhengzhou University, as well as honorary memberships of the French Neurological Society, Hungarian Stroke Society and Indian Stroke Society.

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## MICHAEL CHOPP
### USA

Michael Chopp, PhD, joined the Henry Ford Health System in Detroit in 1983. He was appointed Vice Chairman for Research of the Department of Neurology in 1991, Scientific Director of the Henry Ford Neuroscience Institute in 1999, and is the Zoltan J. Kovacs Chair in Neuroscience Research. Dr. Chopp is also Distinguished Professor of Physics at Oakland University in Rochester, MI.

He received his MS and doctorate degrees in Mathematical and Solid State Physics from New York University. After nearly 10 years of working as a Physicist and as a Professor of Physics, Dr. Chopp made a career change and turned his interest to translational research in neuroscience. 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 neuro-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, 8) exosomes/ microRNA for treatment of neurological injury and disease, and 9) magnetic resonance imaging. Dr. Chopp has received multiple awards and recognitions for his research efforts, including the American Heart Association Thomas Willis Lecture Award, the Abraham White Distinguished Science Award, and the Lecture of Excellence and World Stroke Organization Award. Dr. Chopp has 623 peer reviewed publications and has given 414 plenary lectures and invited presentations. He has served on and chaired National Institutes of Health (NIH) study sections and has served as a consultant to government agencies, the U.S. National Institutes of Health, and the pharmaceutical industry.

# ANTONIO FEDERICO
## ITALY

Prof. Antonio Federico, born in Polla (Sa) on the 25.08.48, from 1990 is full professor of Neurology at the University of Siena , Director of the Unit Clinical Neurology and Neurometabolic Disease.

He was Director of the Department of Neurological, Neurosurgical and Behavioural Sciences, University of Siena ( 2002-2008).

He received the degree in Medicine and specialization in Nervous and Mental Diseases, summa cum laude, at the University of Naples in 1972 and 1975 respectively. He received the Lepetit Award for the best degree dissertation in 1972.
His biological training was in the Institute of Biochemistry as student and after in Physiology of the University of Naples, and in the Centre de Neurochimie of CNRS, in Strasbourg, directed by prof. Mandel where he worked in the years 1973-75. He also collaborated with many international research groups, in different countries where he spent in the past years some times: in Montreal (Prof. Andermann, Karpati and Shoudgbridge), in London (dr A. Harding and prof. Morgan-Hughes), in Toronto (dr.Robinson), in Bonn (prof. von Bergmann) , in Paris (dr.Baumann), in Baltimore (proff. Moser and Naidu), in Oxford (prof. Matthews), etc.
His clinical formation was made at the Medical School of the University of Naples, in the Dept, Neurology, and after in Siena, where he moved on 1980 with his mentor, prof. G.C. Guazzi. Associated professor in Neurology in 1982, since 1990 he is full professor of Neurology, Medical School, University of Siena.
In 2013, he received honoris causa degree in Medicine at University Carol Davila, Bucharest, Rumania.

In the years 1990-96 he was Secretary of the Italian Society of Neurology. In the years 2006-08 was President of the Italian Society of Neurology.

He coordinated the Study Group on Clinical Neurogenetics of the Italian Society of Neurology.

He has been referee for projects evaluation in the area of Orphan drugs and Orphan diseases for Biomed Projects from EU, for MURST, CNR and Istituto Superiore di Sanità, and other national and international funding agencies, etc.

He is member of the Second Opinion Group of the American Leucodistrophy Association.

Associated editor of Neurological Sciences in the past 3 years. From 2012, he is Editor-in Chief.

He is author of more than 500 article quoted by Pubmed. He is author of a chapter on Cerebrotendinous Xanthomatosis, Vinken and Bruyn Edts, Handbook of Clincal Neurology, vol 49, Neurodystrophies and Neurolipidoses. On the book McKusick's Mendelian Inheritance in Man,. Ed.1992, Catalog of Autosomal Dominant and Recessive Phenotypes he is cited for 3 different diseases. He was editor of the book Late Onset Neurometabolic diseases (A.Federico, K. Suzuki and N.Baumann Edts), Karger 1991, and many other books from Italian and international Publishing Companies.
Recently he published (2015) Manuale di Neurologia Pratica and Neurologia and Assistenza infermieristica, for students.

His main field of interest is related to neurometabolic, neurodegenerative and rare diseases, investigated from a genetic, metabolic, neuroimaging and clinical point of vue.

Summary of the academic involvements:
- Director of the Section Neurological Sciences, Dept Neurological , Neurosurgical and Behavioural Sciences (2000-2012)
- Director of the Research Center for the Diagnosis, Therapy and Prevention of the Neurohandicap and Rare Neurological Diseases, until the 2010
- Vice-Dine of the Medical School, University of Siena (2003-2006)
- Director of the Postgraduate School of Neurology, University of Siena, from 2006 up to 2014.
- Director of the PhD School in Cognitive and Neurological Sciences, University of Siena (from 2000 up to date)
- Coordinator of the Section of the Univ. Siena of the PhD Program Neurosciences, Univ. Florence.
- Research delegate for the Dept Medicine, Surgery and Neurosciences (2013- )
- Vice-Rector of the University of Siena, from 1st april 2016 to 30 october 2016.

Medical Involvements
- Director of the OU Clinical Neurology and Neurometabolic Diseases, University Hospital of Siena Medical School.
- Director of the Regional Reference Center for Rare Diseases
- Regional Coordinator of the Network for Rare Neurological Diseases, Tuscany Region.
- Member of several Ministry of Health and Regional Committees

National and International Commitments
- President of the Italian Society of Neurology (2009-11)
- Italian delegate to the World Federation of Neurology
- Italian Delegate to the European Union of Medical Specialists ( Section Neurology)
- Italian Delegate and Chairman of the Neuromediterraneum Forum and President
- Consultive Member of the European Brain Council
- Editor – in – Chief of Neurological Sciences, Springer Verlag Editor. He is in the Editorial Board of many national and international journals.
- Member of the American Panel United Leucodystrophies.

- Member of the Scientific Committee of AISM ( Associazione Italiana Sclerosi Multipla)
- Chairman of the Scientific Committee of the European Academy of Neurology
- Chairman of Neuromediterraneum Forum
- Co-Chairman of Research group of WFN Migration Neurology
- Chairman of the European Academy of Neurology Task Force on Rare Neurologic Diseases

Member of the Scientific Societies:
- Società Italiana di Neurologia (Past Secretary, President, Past-President and Member of the Committee)
- Society for the Inborn Errors of Metabolism
- Italian Association of Neuropathology
- SINDEM (Italian Association of Dementias)
- Italian Association for Parkinson's disease
- Italian Association of Neurogeriatrics ( Member of the Scientific Committee)
- Italian Stroke Forum
- European Academy of Neurology (Member of the Board and Chairman of the Scientific Committee)
- Chairman of the EAN Task Force on Rare Neurologic Diseases
- American Academy of Neurology
- World Federation of Neurology (Co-Chair Section of Migration Neurology)
- Neuromediterraneum Forum ( President)

His present positions are:
full professor of Neurology, University of Siena, Medical School
- Director of Unit Clinical Neurology and Neurometabolic Diseases, Siena Hospital.
- Past-Director of the Department of Neurological and Behavioural Sciences of the University of Siena since the 2012, at the fusion of this Department in the Dept Medicine, Surgery and Neurosciences.
- Italian Delegate to the World Federation of Neurology and to European Academy of Neurology Assembly.
- Past- President of the Italian Society of Neurology ( President years 2009-2011)
- From 1995 he is Director of a PhD Programme on Applied Neurological Sciences at University of Siena, from 2004 of the European PhD Programme and European School of Doctorate of Applied Neurological Sciences. Since 2011 he is director of the PhD Programme on Cognitive and Neurological Sciences at University of Siena.
- He is Italian member of the Committee of European Union of Medical Specialists, in the section Neurology.
- Delegate for Research in the Dept. Medicine, Surgery and Neurosciences.
- Coordinator for the Tuscany Region of the Network on Rare Neurological Diseases.
- On 2013, he received Honoris Causa degree from the University Carol Davila, Bucarest
- Chairman of the Neuromediterraneum Forum

- Editor in Chief of Neurological Sciences, Springer-Verlag Editor.
- Co-Editor of many international journals.
- On the 2014 was nominate WHO consultant for Rare Neurological Diseases.
- From june 2014, he is Chairman of the Scientific Committee and Member of the Board of the European Academy of Neurology
- From February 2015 Co-Chairman of the Research Group Migration Neurology of the World Federation of Neurology.
- Chairman of the European Academy of Neurology Task Force on Rare Neurologic Diseases

The main scientific interest is Rare Neurologic Diseases ( genetic, neurodegenerative and neurometabolic diseases ): organization of platforms and methodologies for improving diagnosis. Teaching clinical and genetic strategies for diagnosis of rare neurologic diseases.

## VERONIKA GOLOVACHEVA

### RUSSIA

Veronika Golovacheva works as assistant professor in Neurology and neurosurgery Department I.M. Sechenov The First Moscow State Medical University. She graduated faculty of medicine, residency and residency PhD of Neurology Department in I.M. Sechenov The First Moscow State Medical University. She regularly participates in Russian, International conferences and clinical researches.

Author of 57 journal publications and 1 book "Chronic Pain and its treatment in neurology". Member of Multidisciplinary Medicine Association, Russian Headache Research Society, Russian Pain Research Society. Co-chair Russian Back Pain Committee. Winner of Young Scientist Tournament at the «Pain Management. The Science Behind 2016» (The European League Against Pain, Budapest, Hungary, October 2016).

Fields of interests are chronic nononcological pain, neuroplasticity in therapy of chronic pain, neurorehabilitation of neurosurgery patients, cognitive behavioral therapy in treatment of pain and comorbid disorders (insomnia, anxiety, depression), multidisciplinary programmers in chronic pain treatment, organization of multidisciplinary pain clinic.

# 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.

# VOLKER HÖMBERG
## GERMANY

Prof. Hömberg had his medical education at the Universities of Düssel-dorf, Freiburg and Boston Massachusetts. After spending electives in Neurology at Boston City Hospital and the National Hospital for Nerv-ous Diseases Queens Square London he was a research fellow at the C. and O. Vogt Institute for Brain Research in Düsseldorf. In 1981 he started a residency in neurology with Prof. Hans Freund at Heinrich Heine University Düsseldorf. In 1987 he was appointed Director of the Neurological Therapy Centre (NTC) a newly founded Institute at Hein-rich Heine University in Düsseldorf. He was also founding Director of the NTC in Cologne . He was involved in the setup of many in-and outpa-tient rehabilitation hospitals in Germany. In 2001he started the St. Mauritius Therapy Clinic in Meerbusch near Düsseldorf and since 2011 he is Director of the Dept. of Neurology at the Gesundheitszentrum Bad Wimpfen and works as senior neurology group leader for the SRH-Group ,one of the biggest hospital groups in Germany.

He was founder, president and vice president of the German Society for Neurorehabilitation for many years. He serves as Secretary Gen-eral for the World Federation of Neurorehabilitation (WFNR)for more than 12 years and is Vice President oft the European Federation of Neurorehabilitation Societies. (EFNR)

He is regular reviewer and co-editor for many international peer re-viewing journals.

He is regular (co) -programme chairman for neurorehabilitation for major international meetings as the World- and European Neuroreha-bilitation Congresses (WCNR,ECNR), Controversies in Neurology (CONy) and the European Stroke Congress (ESC).

He has published more than 250 articles in international peer reviewed journals and many book chapters. His primary scientific interest are the fields of motor rehabilitation, cognition epistemiology, neurological music therapy and pharmacology in neurorehabilitation.

# *LYNNE LOURDES LUCENA*
## *PHILIPPINES*

Lynne Lourdes N. Lucena , MD, FPCS, FAFNI , PSHS batch 84.
Nellie Kellog Van Schaick Scholar at UPCM Intarmed Class 1991,
Neurosurgery , (serving Bicol Region),
Chair - Philippine Board of Neurological Surgery ,
Secretary of the Board of Directors of the Academy of Filipino Neurosurgeons Inc.

Speaker /Lecturer-Women in Neurosurgery/ World Federation of Neurosurgical Societies 2017 (Istanbul) ,
recipient of scholarship from Turkish Neurosurgical Society and World Federation of Neurosurgical Societies 2017,
recipient of 2016 Greg Wilkins -Barrick Chair Visiting International Surgeon Award given by American Association of Neurological Surgeons and WINS(Women in Neurosurgery) ,
International Basic Neurosurgery Course Scholar 2013( Antalya, Turkey)
President-Philippine College of Surgeons, Bicol Chapter-2005,
Secretary -Board of Governors Philippine College of Surgeons 2006,
President- Rotary Club of Naga 2005, Deputy District Governor 2008
Group Study Exchange Team Leader - South Africa
Member- WFNS-WHO Liaison Committee on Global Neurosurgery
Member- Women in Neurosurgery-ACNS
Co -Author- Task Sharing/Shifting in Neurosurgery
Poet/Author- "Windows to my Soul" . Collection of Poems , 2018

# 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), 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 (189 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.

## *HARI SHANKER SHARMA*
### *SWEDEN*

Hari Shanker Sharma, Director of Research (International Experimental Central Nervous System Injury & Repair, IECNSIR), University Hospital, Uppsala University is Professor of Neurobiology (MRC), Docent in Neuroanatomy (UU) and is currently affiliated with Department of Surgical Sciences, Division of Anesthesiology and Intensive Care Medicine, Uppsala University, Sweden. Hari Sharma was born on January 15, 1955 in an Industrialist town Dalmianagar (Bihar), India. He did his Bachelor of Science with Honors from the prestigious L. S. College Muzaffarpur in 1973 and secured 1st position in his batch. He obtained his Master Degree from Bihar University with special expertise in Cell Biology in 1976 and awarded Gold Medal of Bihar University for securing 1st potion in the 1st Class. Hari Sharma joined the group of Professor Prasanta Kumar Dey, a neurophysiologist by training in the Department of Physiology, Institute of Medical; Sciences, Banaras Hindu University, Varanasi in 1977 to obtain Doctor of Philosophy Degree (D.Phil.) in Neurosciences and was awarded Ph.D. in 1982 on "Blood-Brain Barrier in Stress." Hari Sharma after carrying out a series of Government of India funded Research Projects on the BBB and brain dysfunction (1982–1987), joined the lab of Neuropathology at Uppsala University with Professor Yngve Olsson in 1988 to investigate passage of tracer transport across the BBB caused by stress or traumatic insults to the Brain and Spinal cord at light and electron microscopy. Dr. Sharma awarded the prestigious Alexander von Humboldt Foundation Fellowship of German Government (1989–1991) to work on hyperthermia induced BBB dysfunction at the ultrastructural level in the laboratory of Professor Jorge Cervós-Navarro (a living "Legend in Neuropathology in Europe"). Dr. Sharma joined again Uppsala University and established a network of collaboration on "Experimental CNS Injury Research Group" as a lead investigator with eminent collaborators in various parts of Europe, USA, and Australia (1991–). On his work on hyperthermia Dr. Sharma received the prestigious Neuroanatomy award "Rönnows Research prize" of Uppsala University for "best neuroanatomical research

of the year 1996" followed by the Award of the Degree of Doctor of Medical Sciences of Uppsala University in Neuroanatomy in 1999 and selected for the Best Thesis Award of the Medical faculty, "The Hwassers Prize" of 1999. On his meticulous works on the Blood Brain barrier and Brain edema (2000–2003) Dr. Sharma earned the prestigious title of "Docent in Neuroanatomy" of Medical Faculty, Uppsala University in April 2004. Currently his main research interest is Neuroprotection and Neuroregeneration, in relation to the Blood-brain barrier in stress, trauma, and drugs of abuse in health and disease.

Dr. Sharma on his research on brain pathology and neuroprotection in different models received the prestigious awards from The Laerdal Foundation of Acute Medicine, Stavanger, Norway, in 2005 followed by Distinguished International Scientists Collaboration Award by National Institute on Drug Abuse (NIDA), Baltimore, MD (2006–2008). His recent work on 5-HT3 receptor mediated neuroprotection in morphine withdrawal induced neurotoxicity won the coveted prize of Best Investigator Award 2008 and Best Scientific Presentation by European Federation of the International Association for Study of Pain (ISAP), and Awarded during their VI Annual Meeting in Lisbon, September 9–12, 2008. His recent research is aimed to find out the role of nanoparticles in Neurodegeneration and Neuroprotection using various treatment strategies that is supported by European Aerospace Research and Development (EOARD), London, UK and US Air Force Research Laboratory, Wright Patterson Air Force Base, Dayton, Oh, USA. On his works on Blood–brain barrier in hypertension and diabetes together with Romanian colleagues, University of Medicine and Pharmacy "Iuliu Hatieganu," Cluj-Napoca, Romania awarded Dr. Sharma with Honorary Doctorate of Medical Sciences in 2009. Dr. Sharma's work over 30 years on the blood-brain barrier and brain edema won him the US Neurosurgeon Dr. Anthony Marmarou Award (2011) by the International Brain Edema Society at their 15th Congress in Tokyo, Japan, November 20–24, 2011. His works on Nanoneuroscience and development of nanomedicine to treat the CNS injuries has won accolades at various Government and International Scotties or Organization across the World. Accordingly Dr Sharma was decorated with the most prestigious "Hind Rattan Award 2012" (Jewel of India) on the eve of Republic Day of India 25th January 2012 and Mahatma Gandhi Pravasi Gold Medal on October 12, 2012 in House of Lords, London, UK. Based on his outstanding contribution in Nanoneuropharmacology and nanodrug delivery to treat central nervous system (CNS) diseases including Neurodegenerative diseases such as Alzheimer's and Parkinson's Hari Sharma bestowed with Prestigious Gujarat Govt. International Visionary Award 2012 in a glittering function in Ahmedabad, Gujarat on Nov 23, 2012. His further research on co-morbidity factors e.g., hypertension or diabetes may alter pathophysiology of brain injuries and require higher drug dose or nanodrug delivery of neuroprotective agents to minimize brain dysfunction is recognized by Govt. of India by presenting him one of the coveted "Bharat Jyoti Award 2013" (Glory of India) by His Excellency Governor Balmiki Prasad Singh in Hotel Le Meridien, New Delhi on Jan 12, 2013. Dr Sharma also received the highest Award of the Govt. of India "Navrattan Award 2013" (Nine Jewels of India) on the eve of 64th Republic Day of India (25th January 2013) by His Excellency Governor Bhishma Narain Singh, in Ashok Hotel, New Delhi. Hari Sharma is Founding President of the Global College of Neuroprotection & Neuroregeneration (2004-); Elected President of International Association of Neurorestoratology (IANR) (2014-); and selected Senior Expert of Asia-Pacific CEO Association, Worldwide (APCEO) (2012-) for his contribution to uplift scientific research in many countries Globally that may have better economic and social benefit for

the mankind. Hari Sharma awarded coveted National Award "Sword of Honor" 2015 by Govt. of India on the eve of 66th Republic Day of India 25th January 2015 in New Delhi Eros Hotel International during the 34th Non-resident Indian (NRI) conclave by Speaker of Lok Sabha (Indian Parliament) the Hon'ble Mrs Meira Kumar of Indian national Congress (INC) Party for the continued extraordinary achievement in nanomedicine for public health awareness and possible therapeutic measures.

Based on his expertise in Nanoneuroscience, Hari Sharma was also invited to organize and chair Nanosymposium in Society for Neuroscience meetings in Chicago (2009), San Diego (2010), Washington DC (2011), New Orleans (2012), San Diego (2013) and Washington DC (2014, Nov 15-19, 2014); Chair Neurobiology Symposium 14th Int. Amino Acid & Peptide, Vienna, Austria; Keynote speaker & Chair Nanotechnology-2015, Frankfurt, Germany. Hari Sharma is also the recipient of Prestigious US TechConnect Global Innovation Award 2013 at the National Innovation Summit & Innovation Showcase, Washington DC May 12-16, 2013 on his work on Nanowired cerebrolysin in Neuropathic Pain, followed by Nanodelivery of Cerebrolysin and Neprilysin for the treatment of Alzheimer's disease, Washington DC, May 14-17, 2017. This investigation is now selected for Defense Innovation in Miami Florida Oct 3-5, 2017 for further funding by Dept of Defense (DOD, US Govt). Hari Sharma Served as one of the Poster Judges in 2014 180th Annual Meeting of American Association of Advancement of Science (AAAS) Held in Chicago, IL, USA Feb 13-17, 2014 followed by 181st Annual Meeting of American Association of Advancement of Science (AAAS) held in San José, CA, USA Feb 12-16, 2015; 182nd AAAS Annual Meeting in Washington DC, USA Feb 11-15, 2016 & 183rd Annual Meeting of AAAS held in Boston, MA, USA Feb 16-20, 2017. Hari Sharma has published over 350 research papers and 85 reviews, 14 monographs, and 80 international book chapters and edited 18 book volumes with Current H-index = 43 (ISI Database) as of today http://apps.webofknowledge.com/CitationReport.do?product=WOS&search_mode=CitationReport&SID=F4HK58CYuRYrlSI6qbC&page=1&cr_pqid=1&viewType=summary&colName=WOS. He served as Guest Editor of Curr. Pharm. Desig. (2005, 2007, 2010–); J Neural. Transmiss. (2006, 2011–) and is the founding Editor-in-Chief of Int. J. Neuroprotec. Neuroregen. (2004–), UK and the European Editor of Central Nervous system-Neurological Disorders Drug Target (2013-). Dr. Sharma is on board of various International Journals including CNS and Neurological Disorders-Drug Targets, USA (2010), Journal of Neurodegeneration and Regeneration, USA (2009–); Austin Journal of Nanomedicine & Nanotechnology (2014-); and is associate editor of Journal of Nanoscience and Nanotechnology (Nanoneuroscience 2006–), USA, Review Editor—Frontiers in Neuroengineering (2007–), Frontiers in Neurorestoratology, and Associate Editor of Frontiers in Aging Neuroscience (2008–), Frontiers of Fractal Physiology (2010–), Switzerland, Journal of Neurorestoratology, Dove Medical press, London, UK (2012–), WebMD Central, Neurology Faculty, Advisory Board Member (2010–), World Journal of Pharmacology (2011–), Journal of Physical Medicine and Rehabilitation, USA (2012–). Dr. Sharma served as volume editor of several progress in Brain research series (Volumes 104, 115, 162 and 180), International review of Neurobiology (Volume 82 and 102) and other Springer Volumes on Spinal cord injury (1988) and Handbook of Neurochemistry (2009) apart from stand alone books (Elsevier, Springer and Academic Press since 1994). His latest edited and contributed Reference Book Drug and Gene Delivery to the Central Nervous System for Neuroprotection. Nanotechnological Advances from Springer Nature Publishing (June

2017; Sharma, Muresanu & Sharma Eds.) became a bestseller book on the subject. His new Volume of International review of Neurobiology (IRN) 137 "Nanomedicine in CNS Injury & Repair" Edited by Hari S Sharma & Aruna Sharma Academic Press, Elsevier, San Diego, CA, USA is just published on November 14, 2017. Dr. Hari Sharma is invited to join several National Academies of repute including New York Academy fo Science, USA (since 1994–); International Academy of Stress, New York (2003–), Swedish Academy of Pharmaceutical Sciences (2010–). Dr. Sharma has served as an expert evaluator and advisor to various Boards, Councils and Institutions for their Research Grants including Wellcome Trust, London, UK (2011–); Catalan Agency for Health Information and Quality, TV3 (2010–), European Commission Projects (2002–), European Nanomed Council (2009–), Ministry of Health Science Foundation; Medical research Council and University Commission of Grants in various countries in Europe, USA, UK, Canada, Hong Kong, Singapore and in Australia. Some of the notable organizations include: Australia and New Zealand Health Council (2000–); University Commission of Grants, Hong Kong (2002–), Singapore Medical Council, Singapore (2003–); UK Charity Organization "Research on Ageing: Help the Aged" (2003–); Euro Nanomed (2010–). Dr. Sharma is designated as ambassador of the City of Uppsala 2007, by Uppsala County administration and Uppsala Tourism for promoting Uppsala, Sweden as International Research Collaboration/Meetings and Conference Destination. Dr. Hari Sharma is married to Aruna Sharma (nee Bajpai) since 23rd April 1979 and has two sons. Dr Sharma is designated as Visiting Professor, University of Basque Country, Bilbao, Spain supported by Basque Govt. Foundation. His political affiliation belongs to Swedish Social Democrat Party (Socialdemokraterna, Sverige) where he is associated with the development of Education and Research matters in Sweden actively.

## *AGATA TOMCZAK*
### *POLAND*

Agata Tomczak. I graduated from Medical University in Gdańsk. I'm specialist in Neurology. Since 2012 I'm the Head of Neurology Department and Stroke Unit in Municipal Hospital ( St Wincenty a Paulo ) in Gdynia.
Member of Polish Neurological Society , member of Polish Parkinson's Disease and Movement Disorders Society.
I'm also interested in medical law. Since 2014 I'm a judge in the Regional Medical Council Court in Gdańsk.

# JOHANNES VESTER
## GERMANY

Born, 1952, he specialized in Veterinary Medicine between 1971 and 1974 at the University in Munich, then changed to the University in Cologne in 1974 and specialized in Human Medicine from 1974 to 1980. In 1976 to 1979, he additionally studied biometric methods for pharmacology and clinical research at the Institute for Data Analysis and Study Planning in Munich.

While studying human medicine, he completed research work on pattern recognition in the visual brain and developed a pharmacodynamic Neuron Simulation Model at the Institute for Medical Documentation and Statistics of the University at Cologne.

From 1985 to 1995, he was member of the Ultrahigh Dexamethasone Head Injury Study Group and the leading biometrician of the German GUDHIS project in Traumatic Brain Injury, involving 10 Departments of Neurosurgery in Germany.

Since 1982 he holds > 100 advanced training courses on biometry for professionals in clinical research as well as teaching courses for universitary institutions and international societies.

Since 1995 he is Senior Consultant for Biometry & Clinical Research. He planned and evaluated about 150 randomized clinical studies worldwide.

Since 2013 Elected Member of the International Scientific Committee of the Society for the Study of Neuroprotection and Neuroplasticity (SSNN).

Since 2013 Elected Member of the World Academy for Multidisciplinary Neurotraumatology (AMN), since 2016 Elected Member of the Presidium of the AMN.

Since 2015 Member of the PhD Neuroscience International Faculty, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania

Since 2017 Invited Associate Professor, Department of Neuroscience, "Iuliu Hatieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania

He is head of the Multidimensional Department at the Institute for Data Analysis and Study Planning, and statistical peer reviewer for leading medical journals such as Stroke (American Heart Association).

He is member of various international Advisory Boards and Steering Committees including participation as biometric expert in regulatory authority panels, in FDA, EMA, and BfArM hearings, and in workshops of the International Biometric Society (IBS)