Era-Net Neuron – Cutting (technological) edges

Figure legend: *Researchers and ERA-NET NEURON members at the symposium in EIn Bokek, Israel, January 2013*

An umbrella of activities integrates the key elements of the ERA-NET NEURON, Joint Transnational Calls for proposals (JTCs), thematic workshops with renowned researchers and the Excellent Paper in Neuroscience Award (EPNA). Since 2007 ERA-NET NEURON creates a strategically operating group of research funding organizations in Europe and beyond to implement research funding programmes in the area of brain diseases. ERA-NETs are projects funded by the European Commission in various research fields. Their goal is to create a European Research Area in which research is conducted and funded across countries, allowing research groups to jointly work on specific problems, exchange ideas, and benefit from cross border expertise. Twenty-one funding organizations from 16 European countries, Israel as EU-associated country, and Canada participate in ERA-NET NEURON.

In normal life, the necessity to cut edges may for instance occur when you head off to mow the grass properly or trim the hedges (in your garden). In scientific terms cutting edge research refers to creative idea and/or hypothesis driven high-risk developments, undertaken in the hope to overcome existing hurdles or limitations. In neuroscience during the last three decades particularly the technological developments like patch-clamp, (functional) Magnetic Resonance Imaging (MRI) or Positronic Emission Tomography (PET), the latter two as imaging procedures, paved the way for the most incredible research approaches and findings. Such high risk research benefits from two preconditions that may even pose success factors: interdisciplinary teams, and expertise, and (sufficient) funding. This paradigm was evidenced as functional at an ERA-NET NEURON symposium in January 2013. The symposium gathered a number of researchers funded by the ERA-NET

and provided an excellent view on the technological progresses in the field of disease-related neurosciences. As Heinz Beck, coordinator of a consortium analyzing epileptic networks summarized "All researchers would be keen to collaborate again, should the opportunity arise, because the ERA-NET NEURON funding gave the freedom to do good science".

The challenges for understanding how the brain (dys)functions at multiple levels of integration are numerous. Technical developments may open promising new avenues for a better understanding of the functional mechanisms in the brain. Therefore in 2009, the ERA-NET NEURON launched a Joint Transnational Call for proposals on novel methods and technologies in neuroscience. The scope of this call was method development – ranging from optical, genetic and/or electrophysiological to modeling approaches, or combinations thereof - beyond specifically defined diseases. For projects along the "Development and advancement in methods and technologies towards the understanding of brain diseases" only interdisciplinarity – and of course excellence - in groups from different countries were the requirements to be met. The research question, technique(s) and methodologies were to be freely chosen according to the necessities of the addressed problem. The unbureaucratic funding procedures promoted early-on creative project work and the possibility for international networking in small consortia" appraised Rafael Fernández-Chacón, coordinator of a consortium investigating nerve terminals (synapses) with nanotechnologies. After three years funding all consortia held a final symposium where in inspiring contributions the speakers presented exquisite results, outcomes and potential new research questions (please visit also www.neuron-eranet.eu).

Sensory functions

Deficits in sensory function occur normally during ageing but are common following injury or in neurodegenerative diseases. In addressing this field, a new testing protocol was developed by the international consortium of Carles Escera. It is based on a key principle in cognitive **auditory** function: the ability of the auditory system to extract the necessary information in the acoustic environment. Such specific functions – called Mismatch Negativity (MMN, the detection of novelty) – decline in neuropsychiatric and neurological diseases and in aging.

Using Transcranial Magnetic Stimulation (TMS), a non-invasive technique which delivers (non-hazardous) magnetic pulses to a specific region of the brain, the international team around Antoni Valero-Cabré addressed **visual** abilities. Researchers hope their study could set up a new strategy for the restoration of certain types of visual problems induced by brain damage in stroke or retinal neurodegenerative disorders. "We do not want to replace current therapies but to supplement such interventions and strengthen their outcomes," explains Valero-Cabré.

Olfactory deficits are very common in neurodegenerative diseases like Parkinson's disease and Alzheimer's disease. These deficits may be in part due to alterations in the maturation of adult-born new nerve cells (neurons) which incorporate into the cellular network of the olfactory bulb. Jochen Herms and his intentional team confirmed by cutting-edge imaging techniques that the turnover of adult-born neurons is indeed reduced in the Parkinson's disease model due to a decreased survival of the newborn cells.

Communication and electrical signaling

Brain function relies on regulated communication between neurons at contact points called synapses, where nerve terminals release chemical transmitters. These nerve terminals are degenerated in some neurological diseases with severe consequences. "Normally, nerve cells exchange electrical signals at high speed, a signal exchange disturbed in neurological diseases. When in epilepsy too many nerve cells are active at the same time, in Alzheimer's disease in contrast nerve cells fail to properly communicate: some fall silent, while others show abnormal levels of activity" explained Arthur Konnerth. His team combined fast two-photon microscopy with *in vivo* electrophysiology to analyze the neuronal network dysfunction in animal disease models.

Highly advanced electrophysiological recording and electrical stimulation techniques in combination with voltage-dependent dye imaging were also applied by Heinz Beck and his team to investigate the functional changes in the neuronal (micro)circuitry underlying epilepsy. This is important because the cardinal symptom of epilepsy - seizures – consists of synchronized electrical discharges. So far, the complexity of neuronal networks has hampered the investigation of the cellular basis of seizures using conventional electrophysiological approaches.

A pioneering *in vitro* system able to identify the electrical signaling dysfunctions induced by genetic Parkinson's disease mutations was presented by Vania Broccoli. So called induced pluripotent stem cell (iPS) lines were generated as a system to model the (disturbed) electrical activity. The international consortium successfully converted skin cells into such cells that were functionally equivalent to specific neurons *in vitro*, and moreover exactly those that are affected in Parkinson's disease. The disturbed synaptic communication was also the target of the studies by Daniel Choquet and his team. They developed dynamic super-resolution imaging of certain receptor (sensor) proteins on living cells at ultra-high density. The mobility of these receptors is crucial for fast synaptic transmission and disturbed in neurodegenerative diseases. The team discovered that the brain extracellular matrix affects the lateral mobility of these proteins and showed that the receptors inside the synaptic nerve terminals are dynamically organized in nanodomains.

Live cell imaging on the level of single proteins was also applied by the multidisciplinary team of Carsten Korth to characterize in detail a certain protein complex that is relevant in mental illnesses like schizophrenia. Molecular interactors, their function in nerve cells and in the development of the nervous system were identified. "Such results will provide insights that may translate into much-needed progress in clinical psychiatry: for example, detection methods to

establish biological phenotype and testing or novel pharmacological targets" anticipated Korth.

A "nanotechnology" approach was central to the work of Rafael Fernández-Chacón. The team engineered light responsive microcapsules loaded with either substitutes for damaged proteins or facilitators for protein repair in nerve cells. The controlled remote release of repair cargo was confirmed by Structured Illumination Microscope (SIM), a cutting-edge technology combining 3-D super-resolution with high acquisition speed.

Transport

"The blood brain barrier (BBB) is a delicate guardian of the central nervous system against the transport of medical drugs" explained Claus Pietrzik. The mechanism for maintaining this barrier function lies in the capillary network supplying blood to the brain. To facilitate the transport across the BBB and allow targeted drug delivery to the brain tissue, Pietrzik and his team designed a drug-vehicle nanoparticle system. A proof of concept *in vivo* study confirmed the increase of a specific AD medication transport to the brain. The hope is that such correct transport into the brain tissue will increase the safety and efficacy of pharmacotherapy in the brains of patients.

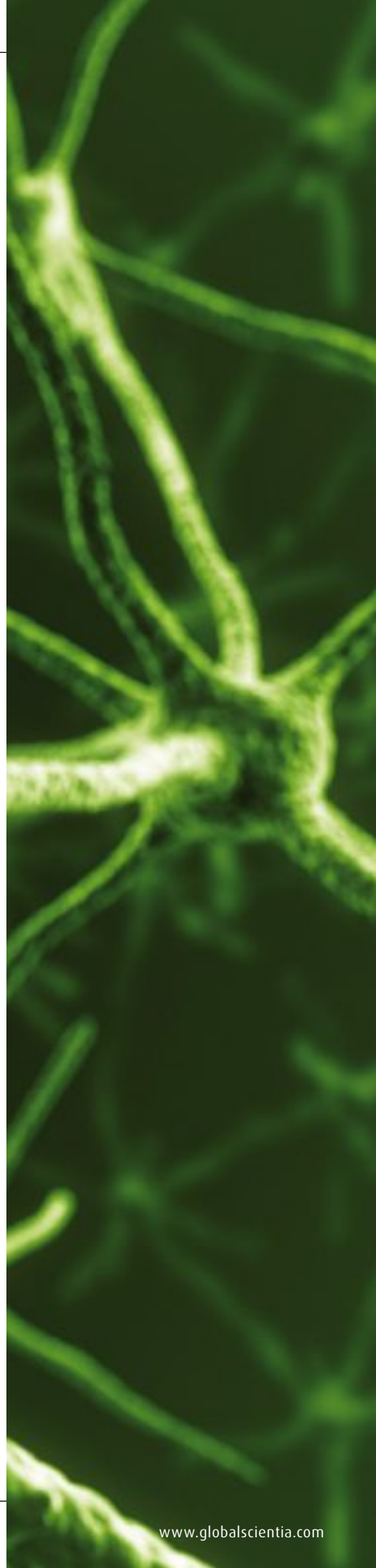
Dr. Marlies Dorlöchter.

In concluding remarks Marlies Dorlöchter, the coordinator of the ERA-NET NEURON, emphasized that the funding investments enabled a significant number of outstanding results. "The many methodological and technological developments impact on the understanding of brain functions in normal and disease conditions. Not only do the projects provide fascinating insights into our brains – they help build the basis for new diagnostic tools and therapeutic interventions. The technological devices, techniques and achievements employ the most current and high-level developments; in other words, technology at the frontiers of knowledge – cutting edge research!"

Gifts that keep giving

Since 2009 the ERA-NET NEURON launches the "EXCELLENT PAPER IN NEUROSCIENCE AWARD" (EPNA). On an annual call basis the most remarkable and outstanding scientific publications by young researchers in the field of disease-related neuroscience are awarded. The award is designed as encouragement for young researchers at the early stage of their career and honors the first authorship of a researcher under 35 years of age in a high impact journal within the first five years after dissertation. Laureates are invited for a specific symposium at an international conference to present the work. This offers a perfect opportunity to present the work to an international audience and thus offers high visibility. As Dr. Marlies Dorlöchter, the coordinator of NEURON, pointed out: "This young scientist supportive measure adds very well to the research funding activities of our network because it emphasizes the importance of research into brain function and its diseases and will contribute to integrate the neuroscience research community". Over 200 attendees witnessed the award ceremony at the renowned FENS Forum 2012 in Barcelona, enabled by a special cooperation with the Network of European Neuroscience Schools (NENS) within the Federation of European Neuroscience Societies (FENS).

Within the last four years six female and two male researchers received the highly ambitious reward of their scientific efforts. The attractiveness of neuroscience research within the young generation neuroscientists appears to develop specific emphasis on young female researchers. "The award is indeed a relatively recent honor on the science market..." reckoned Dr. Anat London (Israel), one of this year awardees "...and indeed straight forward to apply to." A friend had alerted her of this opportunity and she submitted the application online 10 minutes before the deadline. Others, like Dr. Fanie Barnabé-Heider (Sweden) were encouraged by their research



director to submit the application, indicative for a growing fan community also within established researchers. In turn such motivations will pay off. The award encourages the young researchers to further proceed their scientific career and – potentially – apply with own larger projects to ERA-NET NEURON's Joint Transnational Calls.

the NEURON work. Targeted to the interested public, topics of the scientific workshops and the research projects funded by NEURON are addressed. The 2013 announcement for the **EPNA** call is expected for June this year and the application deadline will be September.

~100 billion neurons situated in the grey matter - the brain's computational area. The white matter is essential to provide fast communication between neurons, crucial for us to be able to think, move, sense our environment and see. In disease white matter damage leads to mental and/or physical disability. Different to the

Figure legend: *From left to right: Dr. Erkki Raulo, AKA, Finland and initiator of the award programme, Inbal Benhar, Israel, ERA-NET NEURON coordinator Dr. Marlies Dorlöchter, PT-DLR on behalf of the German Federal Ministry of Education and Research (BMBF), Germany, Anat London and Elena Itskovich, Israel. The three young authors from the Weizmann Institute of Science, Israel contributed equally to the awarded publication.*

Mix & Match

One of the objectives of the ERA-NET NEURON is providing information about brain research in general an the network's progress in particular to a broader audience. In late January, NEURON (www.neuron-eranet.eu) expanded its routes of public information for the social media, namely **Facebook**. The new presence addresses the public at large to deliver directly actionable information. That fits in well to NEURON's information policy already fostered by the release of yet five **educational video clips** on neurological and psychiatric diseases and their treatment options. The **newsletters** summarize relevant events or other parts of

European Month of the Brain – May 2013

Brain disorders are an increasing social and economic burden to Western societies. During the last decades, brain research has made great progress on all fronts but much more is still to be discovered. As part of the European Month of the Brain in May 2013, the ERA-NET NEURON organizes a symposium on **'Neurodevelopment and related disorders'** in Reykjavik, Iceland (www.neuron-eranet.eu). A special lay audience presentation by Dr. Ragnhildur T. Karadottir will focus on the 'The bright side of the brain'. As Dr. Karadottir explained: "The human brain is equally segregated into grey and white matter. The brain's white matter provides a data superhighway that links

grey matter the white matter has the capability of repair. This lecture will focus on the function of the brains' superhighways and how they may be repaired when damaged in disease." The European Commission 'Month of the Brain' initiative is also well matched by ERA-NET NEURON's other activities. Already since 2010 projects funded by NEURON's Joint Transnational Call study basic mechanisms through clinical applications to advance our knowledge and treatment of specifically mental disorders. Due to the high call feedback and many impressive publications a new call on mental disorders was published in early 2013.

Hella Lichtenberg
and **Marlies Dorlöchter**