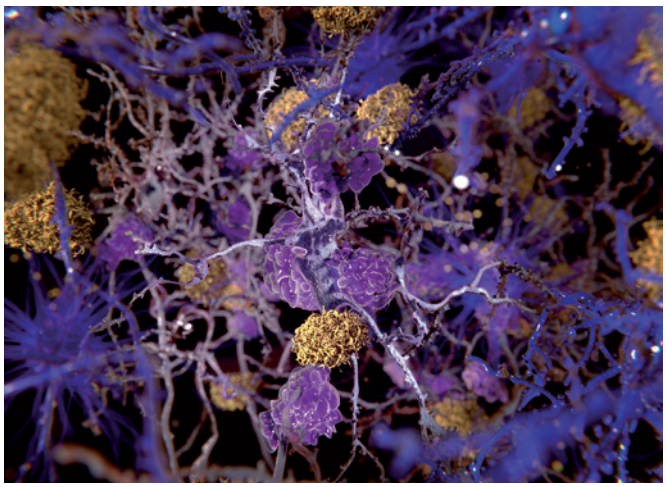
ISSUE JULY 2018

NEUREX NEWSLETTER N° 32



CONTENT

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EDITO

The death on the 14th of March of Stephen Hawking, a brilliant physicist and mathematician, shaked the scientific community and beyond. Having contracted Amyotrophic Lateral Sclerosis (ALS) in 1963, S. Hawking lived for another 55 years... challenging the cruel statistics of this uncurable motor neuron disease. As for most neurodegenerative diseases, the pathophysiological mechanisms of ALS remain a complex issue. Interestingly, in 2015, the expression of some endogenous retroviruses-K genes has been identified as a potential additional risk factor for ALS. A recent finding – published in the June issue of Neuron – just pointed out the putative involvement of human viruses in another neurodegenerative disease: the multiscale analysis of Alzheimer's cohorts has revealed a regulation of Alzheimer's Disease risk and APP processing genes by several common viruses, in particular herpes viruses. Could viral infections – contracted million years ago in the case of endogenous retroviruses or during a lifetime for Herpes viruses – play a key role in neurological and psychiatric diseases? These findings further show that the frontiers raised between the disciplines become somewhat artificial and that interdisciplinary training will probably be a cornerstone of 21st century's research. Cross-disciplinary insights are already a rule in stem cells research, a field which naturally covers several disciplines and bears important hopes for regeneration and repair in neurological diseases. A meeting held in Basel at the end of August (see p. 7) will highlight the most recent findings, thanks to a fruitful collaboration between the Basel Stem Cells Network and Neurex: come and join us!

Another – often forgotten – advantage of networking lies in pushing forward scientific and medical fields in which the paucity of data is unfortunately a normal situation: this is the case of rare diseases research. A meeting on Niemann Pick Type C disease – a potentially fatal disorder which may affect children from birth – will bring together international experts, including several Neurex scientists, in Basel in September. This event echoes the actions undertaken by EU and individual countries – such as the recently-released third French National Plan on Rare Diseases (PNMR3) – to support this important public health issue. Let's bet that the participation of the Neurex members in this event will confirm the engagement of our network for forgotten causes.

P.P.

PORTRAIT

Prof. Dr.
Johann Bollmann

A NEW PROFESSOR AT THE INSTITUTE OF BIOLOGIE I FREIBURG:

PROF. DR. JOHANN BOLLMANN

We are pleased to welcome in Neurex Johann Bollmann, who moved to Freiburg in October 2017. Johann Bollmann is a professor at the Institute of Biology I at the University of Freiburg. He has been awarded a Heisenberg-professorship from the German Research Foundation (DFG) since May 2018. Previously, he was a group leader at the Max-Planck-Institute for Medical Research in Heidelberg (MPImF, 2009-2017). Earlier, he studied physics and physiology in Göttingen, Berkeley and Heidelberg, received a doctorate with research on synaptic physiology from the University of Heidelberg/MPImF (2001), and performed postdoctoral research on visual processing at Harvard University (2004-2008). Zoom on his research topics below.

INTERNATIONAL RESEARCH CENTER

Humans and animals rely on their visual organs to perceive and assess what is happening in their immediate surroundings. The visual system enables an animal to detect and classify objects rapidly and to decide which objects in their complex environment require an immediate response. Frequently, a rapid perceptual decision does not depend on conscious deliberation, but is the result of sensory pattern recognition and classification processes performed by dedicated brain circuitry. Research in the Bollmann lab explores the neural circuits involved in visual processing and behavioral choice in the zebrafish model system.

The decision how to best respond to an object in the environment depends on critical features such as its size, its form or whether or not it is moving. In the animal kingdom, this decision often concerns whether or not to move towards a prey-like object ('prey capture') or to move away from a predator ('escape'). These features are encoded in patterns of neural activity, a process that begins in the retina. However, where in the brain and how the distribution of neural activity eventually assumes critical states that represent the commitment of an animal to perform one out of several possible actions is not clear. The basic mechanisms of object classification and behavioral choice can be studied using zebrafish larvae as a model system. The visual system of zebrafish resembles that of other vertebrates. Moreover, the zebrafish genome has been decoded and their larvae are small and have a translucent skin, which makes them suitable for studying the structure, function and development of neural circuits using fluorescent light microscopy, electrophysiology and neurogenetic tools. By developing and improving these techniques, the Bollmann lab has shed light on visual circuit function and motor behavior in this vertebrate model.

How is the behavioral decision between 'attack' and 'escape' encoded in the activity of neural circuits in the intact brain? First, in a quantitative behavioral approach, the group develops virtual stimulus environments to study the role of stimulus parameters on behavioral decisions. In earlier work, they found that the size and speed of moving objects critically determine whether zebrafish make orienting swims towards a visual stimulus or, in the case of larger stimuli, swim in the opposite direction in an effort to escape. Using closed-loop versions of this stimulus environment, they also studied the impact of expected and unexpected visual feedback on the execution of complex motor sequences. Next, to analyze the underlying neural circuits, the group uses functional multiphoton microscopy to measure the distribution of visually driven activity in visual centers and motor circuits in the central nervous system. In this way, the group identifies cell types, neuronal structures and circuit motifs that respond to critical features of a visual stimulus (e.g. size or motion direction) or that are active during specific phases of a behavior [1]. Furthermore, the group has pioneered approaches to combine multiphoton functional imaging with single cell electrophysiology, which allows them to measure how the excitatory and inhibitory synaptic inputs in individual neurons determine their sensitivity to specific stimulus features during visually guided behaviors [2]. These approaches yield important information on the mechanisms that visual systems use to extract visual features, to classify objects and to compute behavioral decisions.

The neuronal circuitry that ultimately converts the behavioral decision into a movement pattern is located in the spinal cord. To obtain information on whether spinal neurons are connected to each other in specific ways, a complementary, electron-microscopical approach was used recently (collaboration with W. Denk, MPI of Neurobiology). In a three-dimensional electron microscopical dataset, the synaptic connectivity between certain types of interneurons and motor neurons in the spinal cord was comprehensively reconstructed [3]. This pioneering study provides an unprecedented, detailed view into how neurons that are active at the same swim speed are specifically connected to each other.

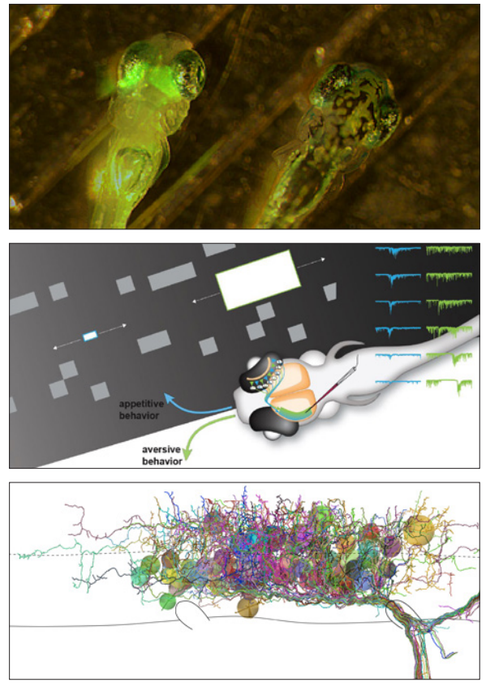
In summary, the long-term goal of research in the Bollmann lab is to build a comprehensive model of information processing in a tractable vertebrate nervous system, which may reveal functional principles important to understanding function in the healthy and diseased brain.

J.B.

Fig. 1: Zebrafish larvae.
Left, Larva with GFP expression in the optic tectum, a major brain area for visual information processing. Right, wild type.

Fig. 2: Behavioral choice in larval zebrafish
Larval zebrafish perform appetitive swims towards small moving objects (blue) and aversive swims away from large moving objects (green). Traces in upper right corner: synaptic input currents in neurons in the visual system in response to small and large objects. For details, see Preuss et al (2014).

Fig. 3: Reconstruction of motor neurons in a spinal cord hemisegment of a zebrafish larva.
For details, see Svara et al. (2018).



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NEWS

NEW DIRECTORS FOR THE NEUROPOLE STRASBOURG

Jean-Christophe Cassel
& Valérie Simonneaux

In December 2017 the new executive board of the Neuropole federation was elected in Strasbourg. Interviewed by Laurent Nexon (Neurex), Valérie Simonneaux and Jean-Christophe Cassel, respectively elected Director and Deputy Director, tell us about their vision for the neuroscientific community of Strasbourg.

INTERVIEW

Laurent Nexon, Neurex: Who are you?
Jean-Christophe Cassel: We are the spokespersons of a neuroscientific structure which represents several hundreds of people, researchers, students, engineers and technicians. A community defined in terms of specificity and agreement on both research and education.

LNN: What do you seek?
Valérie Simonneaux: Before being elected Director, I was a member of the Neuropole board. I have witnessed the emergence of a true community spirit among the neuroscience researchers of Strasbourg, thanks in particular to the substantial work of Christian Kelche (former Deputy Director). We had to take advantage of this unique moment when the neuroscience society was aggregating, to give it an impulse and take it further on.
JCC: This was our absolute priority, to contribute to the perpetuation of a coherent community where people can share knowledge, know-how, and can rely on the support of their peers.

LNN: Can you specifically define this community?
JCC: If I had to define the Neuropole with key-words, I would say research, education and people.

VS: In terms of research, the Neuropole is defined by three main specific themes: pain/nociception, neuronal treatment of time, and neurodevelopment/neuro-degeneration. The link is created by transversal topics, common to the whole neuroscience field in Strasbourg: epigenetics, neurological and psychiatric diseases, and societal problematics (effects of gender, age and environment). We address every neuroscience question with a continuum approach between the levels of the molecule, the cell, the system and the clinic, that is to say from the molecule to the human, with the associated diseases and treatments.

LNN: What are your objectives as directors?
VS: We want to use every opportunity to continue and enhance the structuring of the neurosciences in Strasbourg.
JCC: The graduate school "Euridol" is an example to follow. Euridol started with a little group of people, all interested in the question of pain, at the level of a network, at the cellular and subcellular levels, or as a cultural, subjective, societal and theological concept. All those people gathered around a single thematic to regroup their talents and allow themselves to build a useful project.

VS: The Neuropole must be a catalyst to rally the people around similar projects, on themes which concern the whole neuroscientific field of Strasbourg. It will provide a recognition at the local, national and international levels.

LNN: How do you see the Neurex network in this context?
VS: The transborder interaction we develop thanks to Neurex is a very specific asset we have in our region. This interaction is two-way: the Neuropole benefits from the Neurex network for its own structuring, and in return Neurex can rely on the Neuropole to serve the neuroscience community of the Upper Rhine valley.
JCC: The Neuropole cannot function in parallel of such a network. We are necessarily in it. Identified as Neuropole, not as Jacques, Paul or Pierre. It is only as a federation that the Neuropole can weigh and contribute to the development of the Neurex network.

L.N.

REPORT

VISIT OF INOVIEM LABORATORIES

On June 25th, a group of members of the Neurex labs visited Inoviem Scientific, a company located on the Pôle d'Innovation in Illkirch (FR). Inoviem is a privately-owned contract research biotech founded in 2011 by Dr. Pierre Eftekhari.

The two main technologies developed in the company were presented to the visitors: NPOT® and PIMS®, both aiming at studying the interaction of a drug and its targets in their natural environment (i.e. crude tissue). To illustrate the use of those technologies the first steps of a case study (target's deconvolution of the molecule Clozapine) were sketched. The organization chart of the company and the background and the profiles of the Inoviem members were also presented. Finally, participants had the possibility to visit the premises (lab rooms, offices) of the company.

We would like to thank all the members of Inoviem Scientific for welcoming us, and particularly Diane Witalis (Project manager) who organized the visit, Pierre Eftekhari (President and founder), Daniel Da Costa (CCO), François Louis (QSE manager) and Judith Eschbach (R&D project manager).

D.B.

MEETING

CONSCIOUSNESS UNDER THE SPOTLIGHT OF SCIENCE

Long regarded as unaffordable, the topic of Consciousness has been opened to empirical approaches over the last few decades. If defining consciousness still remains an unreachable dare for searchers, recent theories and hypotheses seek to outline this enigmatic phenomenon, which insistently challenges us in the deepest part of our humanity.

From minimal self to voluntary conscious mind that could typically concern humankind features, from theory of mind to artificial intelligence, from medicine to quantum physics, from neurosciences to introspective approaches that for millennia aimed at exploring its most accurate mechanisms, Consciousness, either of the self, of others or of the world, lies definitely at the heart of societal burning issues :

- What would be the origin and the significance of Consciousness from both phylogenetic and ontogenetic point of view? Would it be an intrinsic property of the living matter or rather an emergent mechanism?
- What does research on coma and various states of consciousness tell us about the connection between mind and brain? Can we postulate equivalence between mental and cerebral states? Is Consciousness a continual process? May consciousness reach higher levels than wakefulness? How do our unconscious and conscious systems cohabit with each other?
- What are the latest technological and computer improvements in the field of artificial intelligence? Can we already develop autonomous systems able to build up a representation of themselves in their environment, thus addressing the relationship between artificial and human consciousness?
- What are the significant contributions of quantum physics in the field of consciousness study?

A SYMPOSIUM HELD ON THE 30TH AND 31ST OF AUGUST in Strasbourg will bring together international experts drawn deliberately from a variety of different backgrounds but internationally recognized in the field of Consciousness study in order to review actual knowledge. By inviting this meeting of different points of view and fostering the sharing of experience, it will stimulate the discussion and open up interesting research avenues. This symposium will also concern master and doctoral students (Neurosciences, Psychology, Ethology, Medicine, Computer science...) in order to enrich their training and support their opening towards interdisciplinary thinking.

S.S.

MEETING & PORTRAIT

STEM CELL DYNAMICS THROUGHOUT LIFE: FROM DEVELOPMENT TO THE ADULT

Stem cells are essential for embryonic development and adult function in many organs. Recent breakthroughs have provided novel insights into how an organism is formed, how physiological signals are coordinated among different tissues, and what regulates stem cell dynamics and plasticity during development, and under homeostasis and in different physiological and pathological states in the adult. Newly developed technologies are allowing unprecedented insight into in vivo imaging of stem cell behaviour and dissection of stem cell heterogeneity using single cell approaches. They have shed light on stem cell origins, identity and function, redefined our concepts of the niche, uncovered key roles for global physiological signals, and highlighted the complexity of different organs.

The 2018 *«Stem Cell Dynamics Throughout Life: From Development to the Adult»* meeting being organized by the Basel Stem Cell Network and Neurex, held in Basel from August 29-31, 2018, will cover the latest findings on endogenous stem cells in different organs and organisms at different stages, including the brain. Key questions that will be addressed include the principles underlying formation of an organism, how cells communicate and how tissue architecture impacts organ formation. What are the first steps in early human development and how do they compare to other organisms? What is the embryonic origin of adult stem cells and what controls their quiescence and activation? What is the functional significance of stem cell heterogeneity and plasticity, an how do their dynamcis change in different states? How do stem cells age and can this be reversed? Which mechanisms underlie intrinsic stem cell regulation (ribosome diversity, nuclear architecture, organelle control of stem cell behaviour, tissue specific regeneration enhancers), and extrinsic regulation (nutrient control of stem cells, whole organism physiology, metabolism, neuronal activity). This meeting will stimulate discussions and insights arising from different model systems and foster interactions among a diverse group of scientists with synergistic backgrounds.

F.D.

Full program & details available
on **www.neurex.org**
and **www.baselstemcells.ch**

MEETING & PORTRAIT

Prof. Fiona Doetsch

PROF. FIONA DOETSCH

BIOZENTRUM, UNIVERSITY OF BASEL

We would like to express our gratefulness to the international speakers who kindly agreed to participate in this event, to Prof Aleksandra Wodnar-Filipowicz, Coordinator of the Basel Stem Cell Center of Competence, as well as to the organizing Committee of the meeting and in particular Prof. Fiona Doetsch (Biozentrum, Basel).
Fiona Doetsch and her research group investigate stem cells in the adult mammalian brain. Fiona Doetsch obtained her B.Sc. at McGill University in Montreal, Canada and her Ph.D. at Rockefeller University in New York City, USA. She then moved to Harvard University, where she was a Junior Fellow of the Society of Fellows and a Fellow at the Radcliffe Institute for Advanced Studies before joining Columbia University as faculty in 2003. In 2014, she moved to the Biozentrum, University of Basel in Switzerland. Among several honours, she has been awarded the David and Lucile Packard Fellowship for Science and Engineering, the Irma T. Hirschl Scholar Award and the Harold and Golden Lamport Award for Excellence in Basic Science Research, and most recently an ERC Advanced Grant. Zoom on her research interests.

STEM CELLS AND THEIR NICHE IN THE ADULT MAMMALIAN BRAIN

Neural stem cells reside in specialized niches in the adult mammalian brain, where they give rise to new neurons, as well as to glia. The discovery of life-long neurogenesis and resident stem cells in the brain has exciting implications as they may be important for brain plasticity and function. Understanding the signals that regulate adult neural stem cells and their normal functions in homeostasis and regeneration are fascinating unknown aspects of the brain.

The ventricular-subventricular zone (V-SVZ), adjacent to the lateral ventricles, is the largest germinal niche in the adult mouse brain. This region generates neurons that migrate to the olfactory bulb, as well as glia. Intriguingly, adult neural stem cells are a subset of glial cells raising the possibility that glia elsewhere in the brain may have latent stem cell potential. Within the V-SVZ itself, adult neural stem cells exhibit heterogeneity at multiple levels, including their morphology, proliferation state and molecular identity.

Depending on their location in the V-SVZ, they generate different subtypes of neurons, or glial cells. How adult neural stem cells sense and integrate diverse signals from the niche to remain quiescent or become activated, and the intrinsic and extrinsic signals that regulate them is a major focus of research in the laboratory of Fiona Doetsch.

Since identifying the in vivo stem cells as a subset of glia, the Doetsch laboratory has focused on understanding the biology of the in vivo stem cells. They have developed purification strategies using fluorescence activated cell sorting to isolate quiescent and activated adult neural stem cells as well as their progeny directly from the brain, which has provided key insight into the properties of stem cell quiescence and activation. They have identified several novel niche compartments, including a specialized vasculature with an altered permeability to blood derived signals, a key role for the choroid plexus as a niche compartment that changes in different states, including aging, by dynamically altering its secretome. Most recently they have found that long-range neuronal projections from the hypothalamus selectively regulate the division of spatially distinct stem cells and the generation of specific olfactory bulb interneuron subtypes. Together these highlight the key role of physiological states, mediated by long-range diffusible signals and neural circuit innervation from distant brain regions, in the regulation of regionally distinct pools of stem cells.

They are currently exploring adult neural stem cell diversity and dynamics, and how local and long-range global input act synergistically to recruit distinct pools of stem cells to generate specific neuron subtypes in response to different physiological cues. This will lead to insight into the functional significance of adult neural stem cell heterogeneity and stem cell dynamics in the adult mammalian brain. Understanding the biology of endogenous stem cells will also inform how they can contribute to cancer, and eventually how stem cells may be harnessed to enhance brain repair.

F.D.

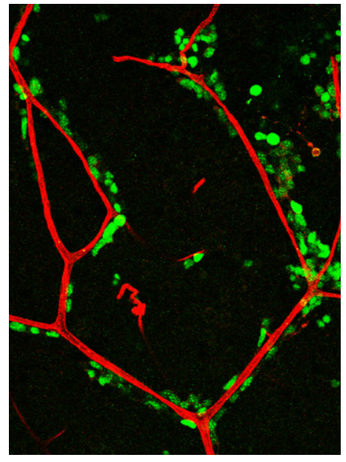

Fig. 1:
Dividing cells (green) are localized close to blood vessels (red) in the adult V-SVZ neural stem cell niche

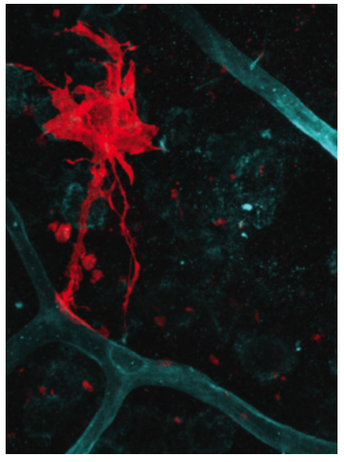

Fig. 2:
Quiescent neural stem cells in the adult brain have a radial morphology (red) and frequently send a long basal process that terminates on blood vessels (blue).

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MEETING & PORTRAIT

Prof. Anne Eckert
University
Psychiatry Clinic,
Basel

TRANSLATIONAL APPROACHES IN CHOLESTEROL & LIPIDS TRANSPORT DYSFUNCTION AND RELATED DISORDERS

While everyone can broadly define Alzheimer's disease or Multiple Sclerosis, much less people are familiar with Niemann Pick Type C disease. Yet, this rare disease is life-limiting and can be fatal within the first few months after birth. What characterizes Niemann Pick type C (NP-C) (& related) disease(s) ? What difficulties are associated to its diagnosis ? How is it related to the dysfunction of cholesterol and lipids transport ? What treatments are currently available ? Which therapy for the future ?

THE DIFFICULTIES FACED BY RESEARCH ON RARE DISEASES

These questions unfortunately remind us that research on rare diseases has to deal with difficulties inherent to these disorders. Even though there is no single definition for it, a rare disease can be broadly defined as a disease affecting a small percentage of the population. However, there is little sense to agree upon a cut-off number for this percentage. Thus, at the end of the spectrum, ribose-5-phosphate isomerase deficiency represents an extreme case of rare disease with a single patient that was diagnosed for years, and a second case reported in 2017 (Naik, Shah et al. 2017)! Yet, it has been estimated that there are about 5000 to 7000 rare diseases and that 300 million people are affected worldwide by one of them. Because of their low prevalence, rare disorders suffer from a lack of epidemiological data, and this is why collaborations are of particular importance in this domain.

NIEMANN PICK TYPE C DISEASE

Niemann Pick type C (NP-C) disease is a rare progressive disease which is thought to affect about one in every 100.000 births worldwide. NP-C is caused by a mutation in the NPC1 or NPC2 gene and is inherited in an autosomal recessive manner. Therefore, both parents of children born with NP-C are carriers of the disease but have themselves no symptoms. NP-C can range from a fatal disorder in the first few months of life to a late onset, chronic progressive disorder. Even though most cases are detected during childhood, they may remain undiagnosed well into adulthood and progress to cause life-threatening complications by the second or third decade of life. Many healthcare professionals are not familiar with the disease: because it may affect the storage of fatty molecules in different part of the body, at different ages and in different combinations, symptoms of NP-C vary widely, complicating diagnosis: these symptoms fall into 3 categories: visceral, neurological and psychiatric. They may be as varied as long-lasting jaundice at birth, enlarged liver or spleen, cognitive impairment, psychosis, dystonia, cataplexy and epileptic seizures. NP-C belongs to the family of Lysosomal storage disorders (LSD) characterized by the accumulation of diverse lipid species in lysosomes.

CHOLESTEROL AND LIPID TRANSPORT

In mammalian cells, most exogenous cholesterol comes from receptor-mediated endocytosis of low-density lipoproteins (LDLs). After internalization, LDL cholesteryl esters are hydrolyzed to release free cholesterol, which then translocates to late endosomes (LEs)/lysosomes (LYs) and incorporates into the membranes under the action of NPC1 and NPC2 proteins. However, in NP-C disease, there is a loss of function mutation of the NPC1 gene (95% of the cases) or the NPC2 gene (5% of the cases), resulting in a the accumulation of cholesterol and sphingolipids, particularly in neurons and hepatoyctes. Accumulating evidence suggests that there might be possible pathophysiological pathways common to NP-C disease and other neurodegenerative disorders such as AD or Fronto-Temporal Dementia. Because NP-C is a rare disease, interactions between experts are of tremendous importance in order to accelerate research in that field. Moreover, progress in this domain might shed light on the pathophysiology of other neurodegenerative disorders.

P.P.

Naik, N., et al. (2017). "Rare case of ribose 5 phosphate isomerase deficiency with slowly progressive leukoencephalopathy." Neurology 89(11): 1195-1196.

A meeting entitled : "Translational Approaches in Cholesterol & Lipids Transport Dysfunction and Related Disorders" will address the pathophysiology of NP-C disease and related disorders and the pathways potentially common to other neurodegenerative disorders, highlighting the importance of lipids transfer.
It will take place on the **20TH OF SEPTEMBER 2018** in Basel at Universität Psychiatrie Klinik(1 Hörsaal DR 1.09, Wilhelm Klein-Strasse 27). We would like to express our gratefulness to Prof. Anne Eckert (UPK, Basel) and to all the international scientists who kindly accepted to participate in this event : looking forward to meeting you there!

Prof. Anne Eckert, University Psychiatry Clinic (Basel) is the organizer of the meeting on Cholesterol and Lipids transport dysfunction. Anne Eckert and her research team are specialized in bioenergetics of cells, going from cell cultures, to animal models and to humans. They are interested in particular on the biology of mitochondria and oxidative stress, in particular in aging & Alzheimer's disease, and stress-related disorders. As such they look for biomarkers of mental disorders, like blood markers for stress. They are also interested in the circadian modulation of energy homeostasis. The regulation of lipids metabolism is central to energy homeostasis. With this meeting, Prof. Anne Eckert will address an important issue not only at the cellular level, but using translational approaches. Thanks to Anne Eckert, this event will undoubtly add one more brick to the wall of rare diseases research.

P.P.

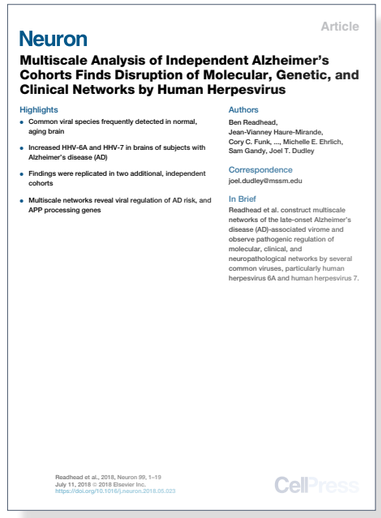
RECENTLY PUBLISHED

ALZHEIMER'S DISEASE : THE VIRAL LINK ?

A recent article published in NEURON[1] reports a link between molecular, clinical & neuropathological features of Alzheimer's disease and viral activity, in particular in relation with human herpesvirus 6A and human herpesvirus 7. If a role for infectious diseases in the aetiology of AD was considered for years, the concept faced significant fading with the growing prevalence of the beta amyloid cascade hypothesis (which favored a causative role for the beta amyloid peptide). However, part of the neuroscience community began to express doubts and disagreements after a while, arguing like Mark Smith[i] and colleagues in 2011 that *«As the hypothesis and its various permutations continue to dominate the literature, the extent to which the scientific community clings to the righteousness of the idea with the passage of time and confrontation of contradictory data is striking. In a different context, such a degree of faith would be the envy of any religion»*[2]. After more than 400 clinical trials which failed to improve the symptoms – despite some obvious success in the destruction of senile plaques, researchers are still actively seeking the pathophysiological mechanisms involved in this devastating neurological disease. In 2012, a Neurex controversy debate entitled «*Alzheimer's Disease: time to abandon the beta amyloid hypothesis?*» took place in which international experts confronted their opposite points of view on the topic.

In 2016, an article entitled "Microbes and Alzheimer's disease" was co-signed by 33 US and European researchers who advocated for *«further research on the role of infectious agents in AD causation, including prospective trials of antimicrobial therapy»*[3]. The team of the first author, Prof Ruth Itzhaki (University of Manchester, Oxford, UK) had suggested that *«Herpes simplex virus type 1 (HSV1), when present in brain of carriers of the type 4 allele of the apolipoprotein E gene (APOE), has been implicated as a major factor in Alzheimer's disease (AD)»*[4]. The researchers put forward that, upon periodic reactivation in many elderly brains (under the effect of stress or immunosuppression, for example), the virus might cause cumulative damage, probably in part through an effect of innate inflammation. Their hypothesis was based –among others- on epidemiological data showing that *«the combination of HSV1 in brain and carriage of an APOE-epsilon 4 allele is a strong risk factor for AD, whereas either of these features alone does not increase the risk of AD»*. Strikingly, Tzeng et al.[5] just reported in February 2018 a decrease in the relative risk of Senile Dementia by a factor of 10 in a longitudinal 10 years follow-up of patients treated aggressively with antiherpetic medications, while the hazard ratio for the development of dementia in the HSV infected-cohort was 2.5 higher than the non-infected cohort.

What could then be the link between infectious pathogens and the formation of senile plaques ? Interestingly, the beta amyloid (Abeta) peptide has been demonstrated in 2010 to possess antimicrobial activity against microorganisms including candida albicans and various bacteria[6]; a recent study reported anti-viral activity of Abeta in cell lines[7], including protective activity against HSV1. An interplay between the beta amyloid precursor peptide (APP) and viral particles has also been suggested to facilitate the transport of viral particles[8]. These observations, together with the failure of the clinical trials, raised the issue of a role of the beta amyloid peptide in innate memory.


Neuron

Article

Multiscale Analysis of Independent Alzheimer's Cohorts Finds Disruption of Molecular, Genetic, and Clinical Networks by Human Herpesvirus

Highlights

- Common viral species frequently detected in normal, aging brain
- Increased HHV-6A and HHV-7 in brains of subjects with Alzheimer's disease (AD)
- Findings were replicated in two additional, independent cohorts
- Multiscale networks reveal viral regulation of AD risk, and APP processing genes

Authors

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In Brief

Readhead et al. construct multiscale networks of the late-onset Alzheimer's disease (AD)-associated virome and observe pathogenic regulation of molecular, clinical, and neuropathological networks by several common viruses, particularly human herpesvirus 6A and human herpesvirus 7.

Readhead et al., 2018, Neuron 99, 1–19
July 11, 2018 © 2018 Elsevier Inc.
https://doi.org/10.1016/j.neuron.2018.05.023

CellPress

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i. 1965-2010

ii. Damage Activated Molecular Pattern

iii. SSPE, or subacute sclerosing panencephalitis, is a fatal brain disease that may reemerge up to a decade after a typical acute Measles Virus infection.

Be it simply a DAMP[ii] released in response to neurodegenerative events or a peptide with a protective role, the beta amyloid peptide might play a role more subtle than the one assessed by the amyloid hypothesis.

In a very recent report[9], Eimer & Coll. suggest that the fibrilization pathways of Abeta mediate antimicrobial activity, thus conferring protection against infectious agents (as they show for the neurotropic herpes simplex virus1 (HSV1) and human herpesvirus 6 (HHV6). In June, a multiscale analysis was just published in Neuron in which the authors "observed regulatory relationships linking viral abundance and modulators of APP metabolism, including induction of APBB2, APPBP2, BIN1, BACE1, CLU, PICALM, and PSEN1 by HHV-6A. This study elucidates networks linking molecular, clinical, and neuropathological features with viral activity and is consistent with viral activity constituting a general feature of AD"[1].

Thus, could AD be a SSPE[iii]-like illness, caused by a slow virus form of herpes simplex as suggested by R. Itzhaki and her team[4] ? Or in other words, could Herpes virus recurrent reactivation constitute a mild type of Herpes Simplex Encephalitis (HSE) leading to memory disorders ? While best known as a common causative factor of muco-cutaneous infections, HSV can also cause HSV encephalitis (HSE), a life-threatening encephalitis. HSE is a rare disease, yet is the most common cause of sporadic fatal encephalitis in Western countries. Over 90 % of HSE cases in adults are due to HSV-1, although cases caused by HSV-2 are documented as well. HSE produces damage in localized regions of the CNS related to the limbic system, and – although its clinical presentation includes many signs and symptoms – is associated with memory, cognitive and affective processes, as well as personality disorders. The most devastating case of amnesia ever recorded secondary to HSE is the one of Clive Wearing, an eminent English musician, who was struck in 1985 by a form of HSE which affected especially the parts of his brain concerned with memory. Clive Wearing is now left with a memory span of 7 to 30 seconds... Since then, he has been unable to store new memories and suffers from retrograde as well as anterograde amnesia.

So, is there a link between viral infections and Alzheimer's disease ? After more than a century of research centered on proteinacious accumulations, additional potential culprits are now under scrutiny. A bigger picture might emerge in a near future from cross-displinary studies spanning the fields of neuroscience, immunology, virology and microbiology. Maybe a future meeting in perspective...

P.P.

MEETING
& PORTRAIT

NEUREX-MEDALIS SYMPOSIUM
ON MULTIPLE SCLEROSIS: FROM BENCH TO BEDSIDE

Multiple Sclerosis is an autoimmune disease damaging myelin sheaths in the central nervous system. The severity of the disease varies widely and depends on the amount of nerve damage and which nerves are affected. While treatments can help recovery from attacks, modify the course of the disease and/or manage symptoms, there is no cure for MS.

A SYMPOSIUM HELD ON THE 23RD OF NOVEMBER 2018 will cover the most recent therapeutic approaches in clinical use or being at the clinical study stage (Dr. Buffels, Basel; Dr. Collongues Strasbourg) after a comprehensive presentation of the disease and therapeutic challenges (Prof. Kappos, Basel). Considering the importance of monitoring the course of the disease for better therapeutic schemes, a focus will be done on recent advances in the field of MS imaging and diagnosis (Dr. Stankoff, Paris; Dr. Docagne, Caen). Hence, there is no chance for therapeutic innovation without fundamental research disentangling the molecular mechanisms of such complex disease. This crucial point will be addressed in talks on the contribution of the microglial cells (Dr. Van Loo, Ghent; Dr. Prinz, Freiburg), interleukines (Dr. Mills, Dublin; Dr. Zipp, Mainz) and myelin regeneration (Dr. Nait-Oumesmar, Paris; Dr. Bagnard, Strasbourg).

Altogether, this one day meeting will provide a translational vision of MS research and will offer the opportunity for new collaborative effort towards the development of innovative therapeutics. Indeed, this Neurex symposium is co-organized with the Strasbourg Drug Discovery Center Medalis relying on the four action lines of the latter: Drug Discovery Research dealing with the scientific project, Drug Discovery Platforms providing research infrastructure, Drug Discovery Transfer managing the industrial exploitation and Drug Discovery Education developing and running innovative education programs. This laboratory of excellence (LabEx) has been recognized in 2011 by the French 'Investissements d'Avenir' program and funded for 10 years. This joint symposium with Neurex is part of an alliance to favor education and technology transfer in the Upper-Rhine valley and to further expand European networking with the best drug discovery research. This extraordinary rich industrial, technological and research environment is undoubtedly a source of hope for patients suffering from invalidating diseases such as MS. Our mission is to conduct initiatives fostering innovation into health improvement.

D.B.

MEDALIS

DRUG DEVELOPMENT IN AN ACADEMIC ENVIRONMENT: THE LABORATORY OF EXCELLENCE MEDALIS

Based on strong basic research from CNRS and INSERM research units, Strasbourg Drug Discovery Center Medalis aims to generate a drug discovery pipeline capable of taking molecules for the treatment of cancer and inflammation all the way through the pre-clinical stage. These molecules will be available for licensing to established pharmaceutical or biotechnology companies, or to start-ups arising directly from the Medalis project. Pr. Sylviane Muller is the scientific coordinator of Medalis and heads its Executive Committee, which is co-chaired by Dr Alain Wagner. Ten teams constitute the Medalis partnership. They work in 6 different academic structures located in two different Campus in Strasbourg. In total, Medalis represents 200 people (half have tenure positions and half are PhD students/post-docs). In 5 years, 5 start-ups have been created and 2 more are planned in 2018/19:

• **INOVIEM SCIENTIFIC** - Created in 2011, Inoviem Scientific is a privately owned biotech contract research organization (CRO). It has developed groundbreaking technologies for drug-target interaction analysis under physiological conditions and in human tissue. (www.inoviem.com)

• **HIFIBIO** - Created in 2012, HifiBio has developed ultra-high throughput screening technologies based on microfluidics. One of these technologies, CelliGO™, can be used for the ultra-high-throughput selection of antibodies from single B cells displaying functional modulation of a target cell. (www.hifibio.com)

• **SYNDIVIA** is a biotechnology company that provides best-in-class bioconjugation technologies for the development of antibody-drug conjugates. Syndivia won the France Tech Transfer Invest Award for 2017. (www. Syndivia.com)

• **PEPTIMIMESIS** is a strategic partner in the design, discovery and early development of therapeutic transmembrane peptides. PeptiMimesis will develop its pipeline against key targets in the fields of oncology and immuno-oncology and is open to the initiation of new collaborations with pharma partners on receptors of interest. (www.peptimimesis.com)

• **ADAPTHERAPY®** was founded to improve healthcare for all through the use of personalized and precise information. As an innovative biotechnology company, Adaptherapy® works actively towards the goal of precision medicine, by helping clinicians to select the most suitable therapy for each individual patient with cancer and other complex diseases. (www.adaptherapy.com)

Strasbourg is a central place for drug development, located at the heart of the European Pharmaceutical Industry in the Upper Rhine Valley. The University of Strasbourg has received the initiative of Excellence (IdEx) label in 2011 together with two other French Universities only. A strong Drug Discovery Center will support this strategic position of Strasbourg.

NEWS

NEW !

THE NEUREX GENERAL PUBLIC BROCHURES

Outreach activities are an important part of the actions for a scientific network: that's based on this fact that Neurex launched brochures for the general public in the context of its current NeuroCampus project. The first edition, published in French and in German last January makes an update on "Environmental pollution & brain diseases: the current hypotheses". Its is available for download on www.neurex.org or in paper format on request at contact@neurex.org.

P.P.

PUBLICATION
SHORT REPORT

NATURE COMMUNICATIONS BIOLOGY : SHORT REPORT

ON THE 7TH AND 8TH OF DECEMBER 2017, a Neurex meeting entitled «Of Glia and Microglia» gathered 21 international experts. These speakers addressed developmental and evolutional issues from drosophila to vertebrates.

We are pleased to announce that a short report entitled «Connecting the nervous and the immune systems in evolution»
Was published in the "Comments" section of Nature Communications Biology (June 7th, 2018)*.
Written by Prof. Angela Giangrande (University of Strasbourg) and Prof. Volker Hartenstein (University of Los Angeles, CA), this report addresses «outstanding questions in the seemingly disparate fields of glial development, physiology and evolution, and also provide suggestions for how the field should move forward».
* Hartenstein, V. and A. Giangrande (2018). «Connecting the nervous and the immune systems in evolution.» Communications Biology 1(1): 64.

P.P.

1.200.000 €

1.2 MILLION EUROS

ATTRIBUTED TO PROF. PETER SCHEIFFELE (BIOZENTRUM, BASEL)

TO STUDY AUTISM

Partner in the EU research grant «Autism Innovative Medicine Studies-2-Trials», (EU-AIMS, awarded by the Innovative Medicines Initiative (IMI) and financially supported for a total of 115 million euros), the neurobiologist Prof Peter Scheiffele (Biozentrum, Basel) is interested in the development of animal models of autism and the study of neuronal network dysfunction observed in ASD. The AIMS-2 trials is coordinated by the Institute of Psychiatry, Psychology & Neuroscience (IoPPN) at King's College London. The aim of this EU-funded research project is to decipher the pathophysiological mechanisms of ASD and to develop new therapeutic approaches.

P.P.

NEWS

JUST OUT :
A NEWSLETTER FOR THE NEUROPOLE

All the activities of the Neuropole community are available in the first newsletter :

- Scientific publications
- Portraits of newcomers and newly retired
- Meeting at the European Parliament of Strasbourg
- The Federative Day of neurosciences by Doctoneuro
- Outreach events in middle and high schools
- And more

Available (only in French) at:
https://issuu.com/neuropole/docs/newsletter01_mai18_v7imprim

A NEW WEBSITE FOR THE BIOZENTRUM

A new Biozentrum website was released on the 28TH of June. Go and have a look at: https://www.biozentrum.unibas.ch/home/

COMING EVENTS

AUGUST 2018

29TH – 31ST / NEUREX & BASEL STEM CELLS NETWORK MEETING «STEM CELLS DYNAMICS THROUGHOUT LIFE» BASEL, SWITZERLAND

30TH – 31ST / NEUREX MEETING «CONSCIOUSNESS UNDER THE SPOTLIGHT OF SCIENCE» STRASBOURG, FRANCE

SEPTEMBER 2018

20TH / NEUREX MEETING «TRANSLATIONAL APPROACHES IN CHOLESTEROL & LIPIDS TRANSPORT DYSFUNCTION AND RELATED DISORDERS» BASEL, SWITZERLAND

OCTOBER 2018

3RD – 4TH / NEUREX MEETING «NOVEL ASPECTS IN PAIN INTEGRATION AND MODULATION» STRASBOURG, FRANCE

NOVEMBER 2018

3RD – 7TH / ANNUAL MEETING SOCIETY FOR NEUROSCIENCE, SAN DIEGO, CA, USA

23RD / NEUREX & MEDALIS MEETING «MULTIPLE SCLEROSIS: FROM BENCH TO BEDSIDE» STRASBOURG, FRANCE

27TH / NEUREX WORKSHOP ON CLINICAL TRIALS, BASEL, SWITZERLAND

29TH – 30TH / NEUREX WORKSHOP «NEUROIMMUNOLOGY» STRASBOURG, FRANCE

WINTER 2018 / SPRING 2019

NEUREX MEETING «NEUROECONOMICS» STRASBOURG, FRANCE

NEUREX WORKSHOP & CONTROVERSY «PATHOLOGICAL PROTEIN PROPAGATION» BASEL, SWITZERLAND

This description is not definitive, but lists the events which are ready or in preparation. Please check again on **www.neurex.org** or in the next newsletter for additional events.

INFO & LINKS

NEUROSCIENCE FEDERATIONS & LABORATORIES IN THE UPPER RHINE VALLEY

The neurex network includes the 3 neuroscience federations of Basel (NNB, Neuroscience Network Basel), Freiburg (Neurag) and Strasbourg (Neuropôle) plus additional research units performing research in the NS.

For a detailed description of the institutes making up the neuroscience landscape in Neurex, you may refer to **www.neurex.org** (tab: The research network).

- **NEUROPÔLE** http://neuropole.u-strasbg.fr/
- **NEURAG** http://www.neurag.uni-freiburg.de
- **NNB** http://www.neuronetwork.unibas.ch

NEWSLETTER

- **UNIBASEL** http://www.unibas.ch/Section newsletter
- **A.L.UNI FREIBURG** http://www.studium.uni-freiburg.de/newsletter
- **UNISTRASBOURG** http://www.unistra.fr/index.php?id=1180
- **COMPUTATIONAL NEUROSCIENCE: BERNSTEIN NEWSLETTER** http://www.nncn.de/en/news/BernsteinNewsletter-en/Newsletter-en

Neuro Campus

Program Interreg V Upper Rhine «Transcending borders with every project», Neurex, CNRS, INSERM, Université de Strasbourg, Région Grand Est, Département du Bas-Rhin, Département du Haut-Rhin, Eurométropole Strasbourg, Hôpitaux Universitaires de Strasbourg, Bernstein Center Freiburg, Klinik für Psychiatrie und Psychotherapie Freiburg, Neurozentrum Freiburg, Universität Freiburg, Universität Basel, Universitäre Psychiatrische Kliniken Basel, Kanton Basel-Stadt, Kanton Basel-Landschaft, Confédération suisse.

NEUREX NEWSLETTER N° 32

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Neuro Campus