



# Advances in neurodevelopmental and neurodegenerative disorders

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Neurosciences



3<sup>e</sup> Journées thématiques  
June 7-8, 2018

# PROGRAMME





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# Welcome address

*Welcome to Strasbourg for the 3rd thematic meeting of the French Neuroscience Society, organized in conjunction with the IGBMC.*

*The meeting focuses on the molecular basis of neurodevelopmental and neurodegenerative diseases with a strong emphasis on genetics based breakthroughs and development. The meeting covers the various topics linked to these diseases, including genetics: from gene to function and therapeutic approaches, cellular and molecular mechanisms, as well as animal models for studying neurodevelopmental and neurodegenerative diseases.*

*We have the pleasure to welcome Charles Duyckaerts who will give the Alfred Fessard Lecture during this meeting.*

*The aim of the meeting is to promote discussions and sharing of new findings among basic scientists, clinical researchers, in order to advance our understanding of neurodevelopment and neurodegeneration in areas urgently requiring therapeutic progress.*

*In addition, in partnership with the local student association Doctoneuro, a roundtable «Which career with a PhD?» is organized. Various speakers with a PhD in neurosciences working in industry, associations, national or international agencies or edition, will shortly present their background and then participate in a scientific «speed dating» to share their professional experiences with students.*

*We wish you a fruitful meeting and some enjoyable time in Strasbourg.*

*Local Organizing Committee*





## Local Organizing Committee

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Emmanuel Valjent



# Programme

# Thursday, 7 June

09:00-09:30 *Welcome of participants*

## Session 1 - Genetics of neurological diseases

- 09:30-09:50 **Christelle Golzio** (IGBMC, Strasbourg)  
In vivo modeling of complex genetic disorders
- 09:50-10:10 **David Keays** (IMP Institut of molecular pathology, Vienna)  
Corpus callosum malformations and microtubule associated proteins
- 10:10-10:55 **Plenary conference**  
**Han G. Brunner** (Maastricht University Medical Center, Maastricht)  
Genetics of intellectual disability
- 10:55-11:20 *Coffee Break*
- 11:20-11:40 **Jean-Charles Lambert** (Institut Pasteur, Lille)  
Genetics of Alzheimer's Disease: A field still in motion
- 11:40-12:00 **Jochen Weishaupt** (Department of Neurology, Ulm)  
Genetics of ALS
- 12:00-12:15 **Julien Courchet** (Neuromyogene, Lyon)  
AMPK related kinase NUA1 haploinsufficiency impairs cortical development and behavior in the mouse
- 12:15-12:30 **Francesca Mattioli** (IGBMC, Strasbourg)  
De novo mutations in NOVA2, a RNA-binding protein, cause intellectual disability with growth retardation
- 12:30-14:00 *Lunch and poster session*
- 13:30-15:00 **Satellite event for students organized by DoctoNeuro**  
Which career with a PhD?
- 14:00-14:45 **Annual General Assembly of the French Neurosciences Society**
- 14:45-15:00 PhD thesis Awards ceremony

## Session 2 - Part I: Molecular mechanisms to pathogenesis

- 15:00-15:45 **Plenary conference**  
**Smita Saxena** (Institute of Cell Biology, Bern)  
Spinocerebellar ataxias: an interplay between genes and cerebellar circuits
- 15:45-16:05 **Erwan Bezaud** (Institut des Maladies Neurodégénératives, Bordeaux)  
Primate-specific susceptibility to neurodegeneration and synucleinopathy induced by patient-derived  $\alpha$ -synuclein extracts
- 16:05-16:25 **Frédéric Saudou** (Institut de Neurosciences de Grenoble)  
Huntingtin: Linking Fast Axonal Transport, Energy Supply and Neurotrophin Signaling to Neurodegeneration
- 16:25-17:00 *Coffee Break*
- 17:00-17:20 **Caroline Rouaux** (Faculty of Médecine, Strasbourg)  
Corticospinal Motor Neurons degeneration in Amyotrophic Lateral Sclerosis: spatiotemporal kinetics and molecular mechanisms
- 17:20-17:40 **Anne-Laurence Boutilier** (LNCA, Strasbourg)  
CBP acetyltransferase-dependent regulations in Alzheimer's disease
- 17:40-17:55 **Boris Rogelj** (Ljubljana, Jožef Stefan Institute)  
Paraspeckle-like properties of G4C2 RNA foci
- 17:55-18:10 **Rafael Alcalá Vida** (LNCA, Strasbourg)  
Striatal super-enhancer signature is conserved across Huntington's disease mouse models and in patients
- 18:10-19:30 *Poster session with snacks and beers*

## Session 2 - Part II: Molecular mechanisms to pathogenesis


- 09:00-09:30 **Ikuo Suzuki** (*Vib-Ku Leuven Center For Brain & Disease Research*)  
Hominin-specific NOTCH2 paralogs expand human cortical neurogenesis through regulation of Delta/Notch interactions
- 09:30-09:50 **Nathalie Spassky** (*IBENS, Paris*)  
Adult neural stem cells and ependymal cells share a common lineage
- 09:50-10:10 **Annette Schenck** (*Donders Institute, Nijmegen*)  
Deficits in Drosophila habituation learning as an endophenotype of intellectual disability/autism disorders – of mechanisms and clinical applications
- 10:10-10:25 **Melissa Stouffer** (*Institut Du Fer À Moulin, Paris*)  
Mitochondrial and Golgi apparatus abnormalities in Doublecortin knockout mice, a neurodevelopmental epilepsy model
- 10:30-11:00 *Coffee Break*
- 11:00-11:15 **Jelena Scekic-Zahirovic** (*Faculty of Medicine, Strasbourg*)  
FTD-like Behavior is Accompanied with loss of ChAT+ neurons in basal forebrain nuclei in a new fus knock-in mouse model of ALS/FTD
- 11:15-11:30 **Melissa Gilles** (*Centre De Recherche Jean-Pierre Aubert, Lille*)  
The effect of Tau-DDX5 interaction in mRNA metabolism
- 11:30-12:30 *Alfred Fessard lecture*  
**Charles Duyckaerts** (*ICM, UPMC, AP-HP, Paris*)  
Alzheimer's disease and its «propagons»
- 12:30-14:00 **Lunch and poster session**

## Session 3 - Towards developing therapeutical approaches

- 14:00-14:45 *Plenary conference*  
**Nicole Déglon** (*University Hospital of Lausanne, Lausanne*)  
Neurodegenerative diseases in the age of genetic engineering
- 14:45-15:05 **Elodie Angot** (*Idorsia Pharmaceuticals, Allschwil*)  
Challenges and opportunities for drug discovery in neurodegenerative diseases
- 15:05-15:25 **Laurent Nguyen** (*GIGA Neuroscience, Liège*)  
Stress-induced unfolded protein response contributes to Zika virus-associated microcephaly
- 15:30-16:00 *Coffee Break*
- 16:00-16:20 **Cemil Kerimoglu** (*DZNE, Gottingen*)  
Neuroepigenetics in Alzheimer's Disease as A Pharmacological Target
- 16:20-16:40 **Hervé Moine** (*IGBMC, Strasbourg*)  
Lipid signaling dysregulation in Fragile X Syndrome pathology and therapy
- 16:40-17:10 **Federica Filice** (*University of Fribourg*)  
17- $\beta$  estradiol increases parvalbumin levels in Pvalb heterozygous mice and attenuates behavioral phenotypes with relevance to autism core symptoms
- 16:55-17:10 **Charline de Montigny** (*IGBMC, Strasbourg*)  
Rapid and complete reversal of sensory ataxia by gene therapy in a novel model of Friedreich ataxia





	<b>Direction de la Recherche Clinique et des Innovations</b>	<i>VQ 1 applicable au :</i> <b>2018-04-30</b>
	<b>FEDERATION HOSPITALO-UNIVERSITAIRE NEUROGENYCS</b>	

Les fédérations hospitalo-universitaires (FHU) sont des structures destinées à réunir les services d'un ou plusieurs Centre Hospitalier Universitaire (CHU) autour de thématiques d'excellence, de la recherche fondamentale au lit du malade.

La FHU NEUROGENYCS labélisée par AVIESAN en février 2015 est dédiée à l'étude des maladies neurologiques, neuropsychiatriques et de génétiques neurosensorielles. Conçue dans le but d'unifier et de développer le potentiel commun des équipes de recherche des Hôpitaux Universitaires de Strasbourg (HUS) et du CHU de Nancy dans le domaine des neurosciences et de la génétique humaine, la FHU NEUROGENYCS associe de nombreux acteurs de la recherche.

Portée, pour les Hôpitaux Universitaires de Strasbourg, par les Professeurs Hélène DOLLFUS (PU-PH génétique médicale - Directrice de l'UMR S1112) et Jérôme DE SEZE (PU-PH Neurologie - Responsable du Centre d'Investigation Clinique des Hôpitaux Universitaires de Strasbourg), la FHU NEUROGENYCS regroupe en effet de nombreux services cliniques (neurologie, psychiatrie, génétique médicale, ophtalmologie et imagerie), ainsi que des laboratoires de recherche de l'INSERM, du CNRS et de la Faculté de médecine, regroupés au sein de la Fédération de Médecine Translationnelle de Strasbourg (FMTS) mais aussi des instituts du campus strasbourgeois (IGBMC, IBMC, IGMA).

La FHU NeurogenyCS a comme objectifs opérationnels :

- de préciser les connaissances mécanistiques des maladies neuropsychiatriques communes et rares en particulier des maladies génétiques sensorielles, des maladies neuromusculaires à expression précoce, de la sclérose latérale amyotrophique, ainsi que l'autisme et des autres déficits intellectuels.
- de déterminer des marqueurs diagnostiques.
- d'identifier de nouvelles cibles thérapeutiques.
- d'améliorer la connaissance et la formation dans ces domaines des neurosciences et de la génétique.



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# Speakers Abstracts

## In vivo modeling of complex genetic disorders

### Christelle Golzio

*IGBMC, Département Médecine Translationnelle et Neurogénétique, CERBM-GIE, 1 Rue Laurent Fries, Illkirch*

The increased resolution of aCGH has catalyzed the hyper-acceleration of copy number variants (CNV) discovery and recent advances in exome and genome sequencing analyses are likely to increase the pace of CNV discovery even further. However, in the midst of this progress, a profound interpretive problem has arisen that is akin to the difficulty of assigning pathogenic potential of rare point mutations. First, similar to point mutations, the rarity of most CNVs precludes their statistical analysis with regard to causality of clinical phenotypes. Second, CNVs typically affect multiple transcripts, exacerbating the problem of assigning causality to a particular subset of transcripts within a given CNV. This problem is complicated further by the documented non-penetrance and variable expressivity of CNVs. In some instances, however, the identification of rare point mutations in genes within a CNV has aided the dissection of the effect. We chose an orthogonal approach to this challenge and we utilized the zebrafish embryo as an in vivo model to screen in a medium throughput manner the genes within these rearrangements to identify potential phenotypic drivers for the neuroanatomical defects associated to these CNVs.

## Corpus callosum malformations and microtubule associated proteins

### David Keays

*Research Institute of Molecular Pathology, Campus Vienna Biocenter 1, Vienna Biocentre (VBC), Vienna 1030, Austria.*

Corpus callosum malformations are associated with a broad range of neurodevelopmental diseases. We report that de novo microdeletions in MAST1 cause mega-corpus-callosum syndrome with cerebellar hypoplasia and cortical phenotypes (MCC-CH-CP) in the absence of megalencephaly. We demonstrate that MAST1 is expressed in post-mitotic neurons, is a microtubule associated protein, and that patient specific mutations alter the affinity of the protein for microtubules. We further show that Mast1 null animals are phenotypically normal, whereas the deletion of a single amino acid (Leu278del) recapitulates the distinct neurological phenotype observed in patients. In animals harboring Mast1 microdeletions we find that the PI3K/AKT3/mTOR pathway is unperturbed, whereas Mast2 and Mast3 levels are diminished, indicative of a dominant negative mode of action. Finally, we report that de novo MAST1 substitutions are present in patients with autism and microcephaly, raising the prospect that mutations in this gene give rise to a spectrum of neurodevelopmental diseases.

## Genetics of intellectual disability

### Han G. Brunner

*Radboud UMC, Department of Human Genetics and Donders Institute for Brain, Cognition and Behaviour, PO Box 9101, 6500HB Nijmegen  
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Maastricht University Medical Center, GROW School for Oncology and Developmental Biology, Maastricht, The Netherlands*

Severe intellectual disability with an IQ of less than 50 affects approximately 1 in 200 newborns. Recent technological advances have clarified the genetics of ID: There are at least 1000 genes involved in causing ID. While autosomal recessive ID predominates in inbred populations, new mutations are by far the most common cause of ID in outbred populations. Whole exome trio sequencing and array analysis for structural variants can clarify up to 60% of all cases of severe ID in the Dutch population, with the majority being due to de novo events. This has implications for our ability to predict and prevent such events. Studies of spontaneous new mutations in humans show that paternal mutations predominate by about 4:1. There is an increase in mutations with age, which is most marked in males. Also, the types of mutations that occur are slightly different between males and females. Our recent work and that of others has shown that new mutations in a wide variety of genes that are functionally linked to MTOR signalling tend to cause ID and brain overgrowth. Common variants in the same set of ~100 genes affects intracranial volume in the population, and may also associate with autism risk. Taken together, a large community of MTOR related genes governs human brain volume, by either rare disruptive events causing hyperactivation of the pathway, or through the collective effects of common alleles.

## Genetics of Alzheimer's Disease: A field Still in motion

### Jean-Charles Lambert

*Inserm, Institut Pasteur de Lille, Univ. Lille,  
LabEx DISTALZ-UMR1167 - RID-AGE - Risk factors and molecular determinants of aging-related diseases,  
Epidemiology and Public Health Department, Lille*

Alzheimer's disease (AD) is the leading cause of neurodegenerative diseases worldwide. A strong genetic predisposition (60%–80% of the attributable risk) is present in AD and in view of this major genetic component, identification of the genetic risk factors has been a major objective in the AD field, with the ultimate aim to better understand the pathological processes. However, the characterization of these genetic determinants proved to be more difficult than initially hoped. Fortunately, as for other multifactorial diseases, AD has

benefited from the advent of high throughput genomic approaches. The application of these technologies has and still continues to strongly modify our knowledge of the genetic determinants of AD. This new landscape is dramatically changing our understanding of the pathological processes responsible for the development of the disease.

## Genetics of ALS

### Jochen Weishaupt

*Department of Neurology, Ulm University, Germany*

Amiotrophic lateral sclerosis (ALS) is a neurodegenerative disease where primarily motor neurons are affected. Although most ALS cases occur sporadically, ALS genetic research has revealed that mutations in approximately two dozens of genes can cause familial ALS, mostly with an autosomal-dominant pattern of inheritance. Several novel ALS disease genes have been recently discovered by use of high throughput sequencing techniques. Although very heterogeneous at first glance, many ALS genes share common functional denominators and together point towards a few overarching pathways in ALS pathogenesis. Several ALS genes, for example, accumulate in pathways regulating protein homeostasis, RNA processing or cytoskeletal dynamics. Nevertheless, a precise picture of how various cellular processes cause neuronal death, or how different routes leading to ALS are possibly functionally connected are just emerging. Here we present an overview of ALS genetics and highlight some of the most recent findings in the field, and discuss the consequences for the understanding of the biology and molecular pathogenesis of this devastating disease.

### **AMPK related kinase NUA1 haploinsufficiency impairs cortical development and behavior in the mouse**

COURCHET Virginie (1), ROBERTS Amanda (2), LEWIS Tommy L (3), POLLEUX Franck (3), **COURCHET Julien** (1)

*(1) Institut NeuroMyoGene, CNRS/INSERM/Université Claude Bernard Lyon 1, Lyon, France, (2) The Scripps Research Institute, San Diego, CA, (3) Columbia University Medical School, New York, NY*

Numerous rare de novo mutations have recently been identified in children diagnosed with autism spectrum disorders (ASD). However, despite the predicted loss-of-function nature of some of these de novo mutations, the affected individuals are heterozygous carriers, which would suggest that most of these candidate genes are haploinsufficient and/or that these mutations lead to expression of dominant-negative forms of the protein. We tested this hypothesis with the gene Nuak1 recently identified as a candidate ASD gene and that we previously identified for its role in the development

of cortical connectivity. We now present evidence that Nuak1 is haploinsufficient for mouse cortex development and cortical axon branching in vitro and in vivo. The inactivation of one allele of Nuak1 results in a complex phenotype including growth retardation, lateral ventricles enlargement and thinning of the cortex. Nuak1<sup>+/-</sup> mice show a combination of abnormal behavioral traits ranging from defective memory consolidation in a spatial learning task, defects in social novelty (but not social preference) and abnormal sensorimotor gating and prepulse inhibition of the startle response. Finally we adopted a gene-replacement strategy to validate in vitro some ASD-linked mutations identified in Nuak1. Overall, our results demonstrate that Nuak1 haploinsufficiency leads to defects in the development of cortical connectivity and a complex array of behavioral deficits compatible with ASD, intellectual disability and schizophrenia.

### **De novo mutations in NOVA2, a RNA-binding protein, cause intellectual disability with growth retardation**

**Mattioli F** (1), Isidor B(2), Hinckelmann-Rivas MV(1), Tran Mau-Them F(3), Nambot S(3), Jean N(3), Telegraphi A(4), Boughton A(5), Gamble C(5), Cho M(4), Shad Z(6), Kaplan E(6), Dineen R(6), Goldman A(7), Mandel JL(1,8) & Piton A (1,8)

*(1) Department of Translational Medicine and Neurogenetics, IGBMC, Illkirch; (2) Service de Génétique Médicale, CHU de Nantes, Nantes, France; (3) Service de Génétique des Anomalies du Développement, Dijon, France; (4) Genedx, Gaithersburg, USA; (5) Cook Children's Genetics Fort Worth, Texas, USA; (6) University of Illinois at Chicago; (7) Department of neurology, Baylor college of medicine, Houston, USA; (8) Laboratoire de diagnostic génétique, Hôpitaux Universitaires de Strasbourg*

Monogenic forms of intellectual disability (ID) are characterized by an extreme heterogeneity, with more than 700 genes now implicated. The most frequent cause of monogenic ID - the fragile X-syndrome- is due to the absence of the RNA-binding protein (RBP) FMRP. Many other ID genes involved in RNA metabolism have been recently identified. About 5% (40/721) of the ID-associated genes play a role in the posttranscriptional regulation of gene expression by regulating mRNA splicing, nuclear export, degradation or translation.

We identified 5 de novo frameshift variants in NOVA2 in patients with ID, growth retardation, microcephaly and ataxia. This gene encodes for a neuron specific RNA-binding protein that regulates alternative-splicing events during brain development. Previous studies on knockout mice for this gene revealed that Nova2 specifically controls the formation of alternative transcripts of known axon-guidance genes (Saito et al. 2016).

The 5 mutations cluster in a GC and repeat-rich interval that is poorly covered in most exomes, thus eventual mutations may have been missed in large scale projects. All the mutations lead to the addition of the same 134aa, suggesting a dominant negative mechanism.

We showed that the mutations lead to dysfunctional truncated proteins not able to regulate specific splicing events like the NOVA2 wild-type. Moreover, the inactivation of NOVA2 by siRNA in differentiated N2A cells alter neurite outgrowth.

Overall, our study shows for the first time that truncating mutations in NOVA2 cause a syndromic form of ID with Angelman-like features, highlighting the importance of alternative-splicing regulation during brain development.

## **Spinocerebellar ataxias: an interplay between genes and cerebellar circuits**

Pilotto F. (1,2,3), Ruegsegger C. (3), Stucki D.M. (3), **Saxena S. (1,2)**

(1) *Center for Experimental Neurology, Department of Neurology, Inselspital, Bern, Switzerland*

(2) *Department of Biomedical Research University of Bern, Bern, Switzerland*

(3) *Graduate School for Cellular and Biomedical Sciences, University of Bern, Bern, Switzerland*

Spinocerebellar ataxia type 1 (SCA1) is caused by a polyglutamine or CAG nucleotide repeat expansion in the ATXN1 gene. This is rare disorder, causes progressive ataxia, motor incoordination, oculomotor impairments, dysarthria and dysphagia. The genetic cause for majority of SCAs have been identified, nevertheless how mutations in genes, which are ubiquitously expressed lead to the degeneration of cerebellar Purkinje cells (PCs), remains enigmatic. Using preclinical mouse model of SCA1, we identified the unique proteomic signature of mutant PCs at early stage of disease. This strategy highlighted extensive alterations in proteins associated with synaptic functioning, maintenance and transmission. We then focused on one of those alterations, the decline in the expression of Homer-3; a PC-specific and enriched scaffold protein regulating neuronal activity. Mechanistically, decline in Homer-3 expression was due to impaired excitatory climbing fibre-mediated synaptic transmission, which concomitantly diminished activity dependent mTORC1 signaling. Pharmacological inhibition of mTORC1 identified Homer-3 as its downstream target. mTORC1 knockdown in SCA1 PCs exacerbated and accelerated pathology. Reinstating Homer-3 expression in SCA1 PCs attenuated cellular dysfunctions and improved motor deficits, thereby implicating mTORC1 and Homer-3 in the pathology.

We are currently investigating how neuronal circuits drive the process of neurodegeneration, mainly due to sub-optimal functioning of the presynaptic climbing fiber inputs. Moreover, we are investigating how Excitation-Inhibition (E/I) balance might be perturbed and we aim to restore the E/I balance, thereby ameliorating the pathology. In our work, we would like to understand the pathways from genes to clinical symptoms, discovering targets for drug development.

## **Primate-specific susceptibility to neurodegeneration and synucleinopathy induced by patient-derived $\alpha$ -synuclein extracts**

**Erwan Bezard**

*Univ. de Bordeaux, Institut des Maladies Neurodégénératives, UMR 5293, Bordeaux*

Intracellular  $\alpha$ -synuclein ( $\alpha$ -syn)-rich protein aggregates termed Lewy pathology and neuronal death are commonly found in the brains of Parkinson's disease (PD) patients. Clinical, neuropathological and experimental evidences strongly suggest that  $\alpha$ -syn plays a role not only as a trigger of pathological processes at disease inception, but also as a mediator of pathological spreading during disease progression. These properties of  $\alpha$ -syn have been described in rodents and non-human primates, but still remain controversial. Building up on this recent literature, we here used an unbiased machine learning-based approach to unravel unique signatures of degeneration induced by distinct  $\alpha$ -syn assemblies derived from PD patients in non-human primates. Our results pinpoint the long anticipated, yet unproved, primate-specific susceptibility to  $\alpha$ -syn toxicity thus reinforcing the need of preclinical research in this species. Furthermore, our results provide evidence supporting the true multifactorial nature of PD as multiple causes can induce similar outcome regarding dopaminergic degeneration.

## **Huntingtin: Linking Fast Axonal Transport, Energy Supply and Neurotrophin Signaling to Neurodegeneration**

**Frédéric Saudou (1,2,3)**

(1) *Grenoble Institute of Neurosciences, Univ. Grenoble Alpes*, (2) *INSERM Research center U1216, Grenoble*, (3) *Grenoble University Hospital CHUGA, Grenoble, France*

Huntington's disease is caused by the abnormal polyglutamine expansion in the N-ter part of huntingtin (HTT), a large protein of 350kDa. Over the past years, we proposed that HTT acts a scaffold for the molecular motors and through this function, regulates the efficiency and directionality of vesicular transport along microtubules in neurons. HTT controls the microtubule-based fast axonal transport (FAT) of neurotrophic factors such as BDNF. HTT function in transport is modulated by direct phosphorylation/dephosphorylation via specific signaling pathways. Importantly, polyQ expansion in HTT alters this function, leading to a decrease in neurotrophic support and death of striatal neurons. The defect in transport might not be restricted to axons but could also involve defects in the retrograde transport of TrkB in striatal dendrites. In addition to the role of HTT in scaffolding the molecular motors both in cortical and striatal neurons, we found that HTT scaffolds GAPDH on vesicles and that vesicular GAPDH is necessary to propel vesicles in GAPDH deficient neurons. Here we will extend these findings and

discuss how HTT by specifically localizing the glycolytic machinery on vesicles may supply constant energy for the transport of vesicles over long distances in axons. We will also discuss how this machinery is altered in disease situation using new approaches that allow the study of defective networks in vitro through the development of microfluidic systems compatible with high-resolution videomicroscopy and the use of biosensors to reconstitute and identify each component of the corticostriatal network.

## **Corticospinal Motor Neurons degeneration in Amyotrophic Lateral Sclerosis: spatiotemporal kinetics and molecular mechanisms**

Marques C (1), Burg T (1), Fischer M (1), Scekcic-Zahirovic J (1), Keime C (2) and **Rouaux C (1)**

(1) *Université de Strasbourg, Inserm U1118, Strasbourg, France*, (2) *Université de Strasbourg, CNRS UMR 7104, Inserm U964, IGBMC, Strasbourg, France*

Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease that arises from the combined degeneration of two neuronal populations: the corticospinal and corticobulbar motor neurons (CSMN) along with the bulbar and spinal motor neurons (SMN). While a growing body of evidence points to the cerebral cortex as the potential initiation site of ALS, little is known about the spatiotemporal dynamics of CSMN degeneration, and the molecular pathways involved. In the classical rodent model of the disease, the Sod1G86R mice, we combined retrograde labelling with rigorous sampling and counting of either the whole CSMN population or only the lumbar-projecting CSMN and showed that CSMN loss occurs in a somatotopic manner and precedes motor symptom appearance and SMN degeneration. To gain insights into the molecular mechanisms that selectively trigger CSMN degeneration, we purified adult CSMN from the cerebral cortex of healthy or diseased mice and conducted a time-course of RNAseq analysis from early pre-symptomatic ages to end stage of the disease. The results identify new and early molecular players in ALS, and provide a foundation for the development of therapeutic approaches based on the maintenance of a healthy and functional population of CSMN.

## **CBP acetyltransferase-dependent regulations in Alzheimer's disease**

**Anne-Laurence Boutillier**

*Laboratoire de Neurosciences Cognitives et Adaptatives (LNCA), UMR7364 CNRS & University of Strasbourg, Strasbourg.*

Alzheimer's disease (AD) is characterized by a progressive loss of plasticity and memory functions, further leading

to neuronal loss and dementia. Epigenetic changes, including histone acetylation, have emerged as important contributors of AD. In the adult brain, histone acetylation is associated with activity-regulated transcriptional changes required for synaptic plasticity and memory, of which the CBP/p300 acetyltransferases (HAT) play an important role. We have recently produced the first permeant CBP/p300 HAT activator molecule, CSP-TTK21, that acetylates nuclear chromatin in mice brain and improves spatial memory (WO2013160885A1). We demonstrate that deficient synaptic plasticity and long term spatial memory can be restored by a treatment with CSP-TTK21 in an AD mouse model presenting neurofibrillary tangles (THY-Tau22 mice). Genome wide screenings (ChIP-seq) showed that H2B acetylation was significantly reduced in the hippocampus of THY-Tau22 mice. Interestingly, CSP-TTK21 partly re-established H2Bac levels, particularly at H3K27ac-enriched genomic regions within gene profiles (super-enhancers) associated with the control of cellular identity. Transcriptomic studies (RNA-seq) revealed that CSP-TTK21 treatment rescued induction of immediate early genes (egr-1, cFos, Arc...) in response to learning, as well as memory formation associated genes (e.g. Klotho). Moreover, CSP-TTK21 down-regulated the expression of genes bearing the H3K27ac/H2Bac signature, as seen in response to learning in WT mice, suggesting that the molecular changes leading to neuronal activation and plasticity might be associated with a partial loss of identity gene expression in a population of hippocampal cells. Altogether, we evidence CBP/p300-dependent epigenetic regulations as important therapeutic targets to counteract behavioral deficits associated with AD lesions in mice.

## **Paraspeckle-like properties of G4C2 RNA foci**

**Rogelj B.** (1, 2, 3)

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The expansion mutation of the GGGGCC repeat in the gene C9ORF72 is the most common genetic cause of FTL and ALS. It is transcribed both from the sense and the antisense strands leading to the formation of nuclear RNA foci, which may sequester specific RNA binding proteins and affect various steps of post-transcriptional gene regulation. Core paraspeckle proteins SFPQ, NONO and PSPC1 bind to (G4C2)<sub>n</sub> repeat RNA in vitro, and colocalize with nuclear RNA foci in transfected cells and brain tissue of C9ORF72 mutant carriers at post-mortem. G4C2 RNA foci lead to an increased number of SFPQ-stained subnuclear bodies, which form independently of the known paraspeckle platform long non-coding RNA NEAT1. Furthermore, (G4C2)<sub>72</sub> RNA foci also colocalized with paraspeckle-associated associated Alu repeat-containing RNAs, indicating that (G4C2)<sub>n</sub> RNA foci might replace NEAT1 as scaffold of paraspeckle-

like structures. Our results suggest that (G4C2)<sub>n</sub> RNA foci form paraspeckle-like structures, which function in similar fashion as paraspeckles and modulate nuclear compartmentalization of paraspeckle-bound RNAs.

## **Striatal super-enhancer signature is conserved across Huntington's disease mouse models and in patients**

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Huntington's disease (HD) is a progressive, neurodegenerative disease affecting primarily the striatum. It is believed that striatal transcriptional dysregulation contributes to HD progression, though the underlying mechanism is unclear. Using ChIPseq and RNAseq techniques on the striatum of HD R6/1 transgenic mice, we showed that down-regulated genes were enriched in striatal identity genes, controlled by a super-enhancer. Moreover, H3K27 acetylation (H3K27ac), enhancer transcription and recruitment of RNA polymerase II (RNAPII) were selectively reduced at R6/1 striatal super-enhancers. To investigate the relationship between super-enhancer activity and transcription of striatal identity genes, we performed 4Cseq experiments. We found altered promoter ? super-enhancer interaction at striatal super-enhancer-regulated gene Pde10a in R6/1 mice, suggesting disruption of chromatin 3D architecture could contribute to altered striatal super-enhancer activity. To investigate functional consequences of HD striatal super-enhancer signature, R6/1 mice were trained to learn striatum-dependent cognitive task. In contrast to wild-type (WT) animals, R6/1 mice were impaired in this task. ChIPseq data generated using the striatum of "trained" and "home cage" mice showed a specific increase of H3K27ac and RNAPII at genes implicated in synaptic plasticity in trained vs home cage WT animals. However, this "plasticity" signature was absent in trained R6/1 mice, suggesting aberrant RNAPII dynamics and inadequate histone acetylation in R6/1 mice preclude synaptic plasticity and contribute to behavioural deficits. Finally, we generated ChIPseq data using the striatum of HD patients and knock-in mice. HD striatal "super-enhancer" signature was conserved across models and our analyses further revealed that it established at presymptomatic stage.



## Hominin-specific NOTCH2 paralogs expand human cortical neurogenesis through regulation of Delta/Notch interactions

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The human cerebral cortex has undergone rapid expansion and increased complexity during recent evolution. Hominid-specific gene duplications represent a major driving force of evolution, but their impact on human brain evolution remains unclear. Using tailored RNA sequencing (RNAseq), we profiled the spatial and temporal expression of Hominid-specific duplicated (HS) genes in the human fetal cortex, leading to the identification of a repertoire of 35 HS genes displaying robust and dynamic patterns during cortical neurogenesis. Among these we focused on NOTCH2NL, previously uncharacterized set of four HS paralogs of NOTCH2. NOTCH2NL promote the clonal expansion of human cortical progenitors, ultimately leading to higher neuronal output. NOTCH2NL function by activating the Notch pathway, through inhibition of cis Delta/Notch interactions. Our study uncovers a large repertoire of recently evolved genes linking genomic evolution to human brain development, and reveals how human-specific NOTCH paralogs may have contributed to the expansion of the human cortex.

## Adult neural stem cells and ependymal cells share a common lineage

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Adult neural stem cells (NSCs) (B1 cells) and post-mitotic multiciliated ependymal cells (E cells) are glial cells composing the neurogenic niche in the mammalian brain. Although both cells originate from radial glial progenitors

(RGPs) at late embryonic stages, the mechanism of their production is unknown. Using clonal analysis of large numbers of RGPs using the Nubow strategy or single-cell resolution of progenitor division patterns and fate, we show that the vast majority of B1 and E cells are sister cells generated through sequential symmetric and asymmetric divisions. Overexpression of Geminin family members, initially identified as regulators of DNA replication can modify the relative numbers of B1 and E cells in the resulting clones. These results suggest that gliogenic progenitor behavior in the walls of the lateral ventricles (ventricular-subventricular zone V-SVZ) is controlled by cell cycle regulators.

## Deficits in Drosophila habituation learning as an endophenotype of intellectual disability/autism disorders – of mechanisms and clinical applications

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Intellectual Disability (ID) disorders are a major unmet socioeconomic problem. More than 1000 causative genes ("ID genes") have been reported, providing unique stepping stones into the molecular basis of cognition. However, the role of most ID genes in the nervous system is poorly understood, and so are the pathogenic consequences of deleterious mutations and their potential reversibility later in development. A highly efficient model organism is needed to make use of the available genetic information to advance our fundamental knowledge, and diagnostic & therapeutic approaches in this field.

Recently, we have phenotyped *Drosophila* models of ID and of clinically & genetically overlapping Autism Spectrum Disorders (ASD) in large scale. I will present our work on the role of these disease genes in habituation, one of the most fundamental and ancient forms of learning. We found that habituation deficits are very common in *Drosophila* models of ID and particularly highlight ID genes with synaptic function and associated autistic features. We propose that defective habituation is a widely affected mechanism underlying cognitive and behavioral problems in ID/ASD. With our *Drosophila* habituation assay we provide an experimental platform that supports testing scientific hypotheses and drugs in

a high-throughput manner. In parallel, we work together with our collaborators towards implementing similar habituation paradigms in humans as objective and quantitative outcome measures for clinical trials, another urgent completely unmet need in the field. Together, our cross-species efforts open conceptually novel avenues for improved translational research and treatment of cognitive and behavioral deficits in ID/ASD disorders.

## **Mitochondrial and Golgi apparatus abnormalities in Doublecortin knockout mice, a neurodevelopmental epilepsy model**

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Human doublecortin (DCX) mutations are associated with severe brain malformations leading to intellectual disability and epilepsy. Hippocampal pyramidal neurons in Dcx knockout (KO) mice show abnormal morphologies, hyperexcitability and disorganization, and Dcx KO mice also exhibit spontaneous epileptic activity originating in the hippocampus. Dcx plays a key role in neuronal migration, interacting with microtubules. Regulation of mitochondrion and Golgi apparatus (GA) form and function are critical during neurodegenerative processes, although abnormalities in these organelles are not frequently associated with neuronal migration disorders. Using electron microscopy, we first showed abnormal organelle ultrastructure in early postnatal Dcx KO hippocampal neurons, which included damaged and swollen mitochondria and fragmented GAs with excessive vesicles. Transcriptome analyses of CA3 neurons from postnatal hippocampi revealed abnormal gene expression confirming mitochondrial and GA abnormalities, and identifying increased cell stress, in KO compared to WT neurons. More recently, we have found that ultrastructural and genetic abnormalities related to these organelles are still present in the adult Dcx KO hippocampus, hence lasting beyond the period of normal developmentally-regulated Dcx expression. Using in utero electroporation and primary cultures, we further show abnormal mitochondrial number and localization, as well as abnormal GA form and distribution in Dcx KO hippocampal neurons, which correlate with aberrant neuron morphology. These novel results involving deregulated processes associating mitochondria, GA and microtubules may suggest transport abnormalities underlying neuronal dysfunction in neurodevelopmental disorders, therefore underlining certain similarities with neurodegeneration phenotypes. Targeting such defects postnatally may prove promising for neuronal migration disorders.

## **FTD-like Behavior is Accompanied with loss of ChAT+ neurons in basal forebrain nuclei in a new fus knock-in mouse model of ALS/FTD**

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Amyotrophic lateral sclerosis (ALS) and Frontotemporal dementia (FTD) are now considered as a unique clinicopathological spectrum referred to as ALS/FTD. A subset of ALS/FTD patients develop fused in sarcoma (FUS) protein pathology. To unravel the role of mutant FUS in the disease pathogenesis, we created a knock-in mouse expressing a truncated FUS without nuclear localization signal (NLS) in the endogenous mouse Fus gene. Our data showed that relocation of truncated FUS protein from nucleus to cytoplasm within spinal motor neurons, led to motor neuron degeneration via toxic gain of function and triggered key features of ALS in Fus $\Delta$ NLS/+ mice. Since FUS pathology is also present in a subset of FTD patients, we asked here whether Fus $\Delta$ NLS/+ mice might develop FTD-like phenotype. Our results indicated progressive defect, starting early in the age, in social interaction, including social disinhibition, increased aggressive behavior and spontaneous activity and therefore recapitulating some of the clinical symptoms of bvFTD. Furthermore Fus $\Delta$ NLS/+ mice, despite normal task acquisition, displayed precocious and progressive cognitive dysfunction, a spatial memory loss in the Morris water maze suggesting disrupted (fronto) cortico-hippocampal dialog. Consistently, we observed significant progressive frontotemporal lobe atrophy, which was not accompanied with a major loss of either inhibitory or excitatory neuronal populations within cortex. Interestingly, we detected loss of ChAT+ neurons in basal forebrain nuclei and decreased density of ChAT+ fibers projecting to layers V-VI. Pharmacological experiments targeting relevant cholinergic receptors are currently ongoing to identified possible causative relation between FTD-like behavior and impaired cholinergic system.

### The effect of Tau-DDX5 interaction in mRNA metabolism

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Tauopathies are neurodegenerative disorders characterized by the aggregation of hyper-phosphorylated Tau proteins. Tau proteins are mainly expressed in axons where they promote stabilization of microtubules. However, it has been shown that Tau displays additional cellular localization where it may regulate many other functions. Here, we used tandem-affinity purification methodology coupled to mass spectrometry to identify novel interaction partners. We found that Tau interacts with DDX5, a DEAD box RNA helicase involved in several RNA metabolic processes such as, splicing and nonsense-mediated mRNA decay (NMD) pathway.

Tau/DDX5 interaction has been confirmed in vitro by GST-pulldown assay and in cellulo by immunoprecipitation and PLA (Proximity Ligation Assay). We also identified that Tau binds to DDX5 through its proline rich domain in a RNA dependent-manner and the presence of DDX5's known partner, DDX17, in the complex. Using reporter system, we further demonstrated that Tau contributed to NMD and pre-mRNA splicing regulation in a DDX5 dependent manner. Interestingly, we also found that P301S pathological mutation of Tau increases its positive regulation on NMD pathway.

Altogether, our results highlight a link between Tau and the DEAD box RNA helicase DDX5 and demonstrated an unexpected role of Tau in regulating NMD and pre-mRNA splicing. Our findings suggest that a loss of Tau functions may participate directly to the splicing and NMD target genes misregulation observed in Tauopathies.

### Alzheimer's disease and its "propagons"

#### Charles Duyckaerts

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Alzheimer disease (AD) is characterized by the extracellular accumulation of A $\beta$  peptide, especially in the amyloid core of the senile plaques and in the vessel walls, and by the intracellular aggregation of tau protein, particularly in neurofibrillary tangles and in neuropil threads. The relationship between the two lesions has

been debated for decades. The finding of AD genetic cases seemed to have settled the question: all the mutations were indeed located on the genes coding for proteins directly involved in A $\beta$  metabolism and all of them appeared to increase the production of A $\beta$  or at least of A $\beta$ 42, its long and less soluble isoform – hence the multiple therapeutic attempts to reduce its accumulation, either by inhibiting the enzymes involved in its production or by using antibodies to increase its clearance. These attempts have up to now failed.

It was demonstrated 25 years ago that the intracerebral injection of brain homogenates from one Alzheimer disease patient into marmosets induced the development of amyloid angiopathy and of senile plaques several years later. Similarly, the injections into transgenic mice bearing the human mutated APP gene also "seeded" the amyloid pathology and accelerated its propagation. In the human, the deposition of A $\beta$  in the vessel walls (cerebral amyloid angiopathy) and in the parenchyma has been observed in young patients treated by cadaver derived growth hormone (GH) or having received a cadaver derived dural graft. A $\beta$  aggregates have been detected in the GH preparation and A $\beta$  deposits have been seen in the contaminated dura. Long contact of the brain with A $\beta$  aggregates, however, did not induce tau pathology. Injection of AD human brain homogenates into tau transgenic mice has induced tangle pathology. Moreover, there is some disputable evidence that tau pathology could also have been transmitted in man. The propagation of tau pathology follows connections. In the well-known subiculo-mammillary system of connections we were able to show the transport of aggregated tau in the axons of the subicular neurons and the secondary involvement of the mammillary body. The propagation of A $\beta$  pathology does not require connections. Finally, the crossing of tau and APP transgenic mice has shown that amyloid pathology enhanced tau pathology, while the opposite is not true. In conclusion, recent data have brought a change in paradigm: the pathogenic mechanism appears related, rather than to an increase in A $\beta$  production, to a "prion-like" protein misfolding. The misfolding propagates within molecules, tissue or a whole organism as an epidemic – hence the name "propagon" that has been proposed. Tau and A $\beta$  propagons do not appear to be linked by causality as suggested in the cascade hypothesis but rather by an asymmetric synergy: Alzheimer disease seems to be an amyloid promoted primary tauopathy.

### Neurodegenerative diseases in the age of genetic engineering

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Genome editing with the CRISPR/Cas9 system is making possible to modify the sequence of genes linked to these diseases in the adult brain. Here, we developed the kamiCas9 self-inactivating CRISPR/Cas9 system. This system was designed for a transient expression of the Cas9 nuclease while preserving high editing efficiency. In the first application of this technology to neurodegenerative disorders, the gene responsible for Huntington's disease (HD) was targeted in adult mouse neuronal and glial cells. Mutant huntingtin (HTT) was efficiently inactivated in mouse models of HD, leading to an improvement in key markers of the disease. Sequencing of potential off-targets with the constitutive Cas9 system in differentiated human iPS cells, revealed a very low incidence with only one site (OT1) above background level. Importantly, OT1 off-target frequency was drastically reduced with the kamiCas9 system. These results demonstrate the potential of the self-inactivating CRISPR/Cas9 editing for applications in the context of neurodegenerative diseases.

## Challenges and opportunities for drug discovery in neurodegenerative diseases

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The considerable progress in health care over the last decades resulted in prolonged life expectancy. However, this has at the same time increased the prevalence of neurodegenerative diseases, the most common being Alzheimer's Disease (AD). In 2015, 46,8 million people worldwide were living with dementia, representing a huge challenge for the pharmaceutical industry. The mean duration for developing a disease modifying treatment in AD is around 9 years for a cost estimated at \$5.7 billion. Knowing that 99% of drugs tested in AD between 2002 and 2014 failed to show efficacy, the way we conduct drug discovery in AD today, and more generally in neurodegeneration, has to be questioned. To shorten the duration of clinical development and thus reduce the cost while increasing the chance of success, pharmaceutical companies are developing new concepts in clinical trial design which I will discuss in this talk. The first prevention trials have started in AD, in prodromal, still cognitively well-functioning people. Precision medicine, targeting a genetically defined group of patients, is a hot topic in Parkinson's Disease. The importance of target engagement biomarkers in early phases of the clinical development was recently illustrated in a Phase 1/2 trial of antisense therapy for Huntington's disease reporting a decrease of Huntingtin protein. Finally, I will present the impact of these innovative clinical approaches on the way preclinical studies are currently designed and conducted to support entry into man decisions.

## Stress-induced unfolded protein response contributes to Zika virus-associated microcephaly

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Accumulating evidence support a causal link between Zika virus (ZIKV) infection during pregnancy and congenital microcephaly. However, the mechanism of ZIKV-associated microcephaly remains unclear. We combined analyses of ZIKV-infected human fetuses and cultured human neural stem cells with mouse embryos to understand how ZIKV induces microcephaly. After intracerebral and intraplacental inoculation of ZIKV in mouse embryos, we show that it triggers endoplasmic reticulum stress in embryonic brains in vivo. This perturbs a physiological unfolded protein response within cortical progenitors that controls neurogenesis. Thus, ZIKV-infected progenitors generate fewer projection neurons that eventually settle in the cerebral cortex whereupon sustained ER stress leads to apoptosis. Furthermore, we demonstrate that administration of pharmacological inhibitors of UPR counteracts these pathophysiological mechanisms, and prevents microcephaly in ZIKV-infected mouse embryos. Such defects are specific to ZIKV as they were not observed upon intraplacental injection of other related flaviviruses in mice.

### Neuroepigenetics in Alzheimer's Disease as A Pharmacological Target

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There is accumulating evidence that epigenetic mechanisms in the form of histone modifications play an important role in cognitive function. Their impairment, in turn, has recently been implicated in age-related cognitive decline and Alzheimer's disease. Recent studies from our group especially implicate aberrant histone acetylation and histone methylation to be critically involved in these processes. Evidence suggests that recovering these modifications during aging or progression of Alzheimer's disease can relieve the cognitive symptoms and can therefore serve as a suitable therapeutic target.

### Lipid signaling dysregulation in Fragile X Syndrome pathology and therapy

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Fragile X syndrome (FXS) is the most frequent cause of inherited intellectual disability and autism. FXS is due to the silencing of FMR1 gene and/or the loss of function of its protein product FMRP. The lack of FMRP causes an excessive translation of neuronal proteins associated with glutamatergic synapse defects. Little is known about how ubiquitous FMRP is able to impact protein translation specifically in neurons and what are the precise molecular mechanisms underlying the pathology. To elucidate the function of FMRP, we developed a

crosslinking-immunoprecipitation strategy that enabled us to identify that the master regulator of lipid signaling, DGKk (diacylglycerol kinase kappa), is a main mRNA target of FMRP in neurons. The absence of FMRP impairs both DGKk translation and mGluRI-dependent conversion of DAG (diacylglycerol) to PA (phosphatidic acid), leading to an accumulation of DAG in the brain of Fmr1-KO mice and of FXS patients. Knockdown of DGKk in a wild type mouse recapitulates FXS phenotype, while its re-expression in Fmr1-KO neurons corrects their abnormal dendritic spines. Our data support a novel pathomechanism where the dysregulation of DGKk activity and its resulting abnormal lipid signaling account for major alterations underlying FXS. Based on this new model, we tested whether an increase of DGK activity could rescue FXS phenotypes. In cells, PPAR-gamma agonist pioglitazone corrects excessive eIF4E phosphorylation and protein translation. In Fmr1-KO mice, pioglitazone rescues memory defect, stereotypies, social interactions and macroorchidism. Altogether our data suggest that DGK activity is a promising therapeutic target for FXS.

### 17- $\beta$ estradiol increases parvalbumin levels in Pvalb heterozygous mice and attenuates behavioral phenotypes with relevance to autism core symptoms

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Autism spectrum disorder (ASD) is characterized by impaired social interaction and communication, and restricted, repetitive behaviors and interests. Although the pathophysiology of ASD is not yet fully understood, due to a plethora of genetic and environmental risk factors that might be associated with or causal for ASD, recent findings suggest that a common final endpoint for some forms of ASD might be the downregulation of the calcium-binding protein parvalbumin (PV). In fact, PV-deficient mice (PV<sup>-/-</sup>, PV<sup>+/-</sup>), as well as Shank1<sup>-/-</sup>, Shank3<sup>-/-</sup>, and VPA mice, which show behavioral deficits relevant to all human ASD core symptoms, are all characterized by lower PV expression levels.

Based on the hypothesis that PV expression might be increased by 17- $\beta$  estradiol (E2), PV<sup>+/-</sup> mice were treated with E2 from postnatal days 5–15 and ASD-related behavior all tests were performed between postnatal days 25 and 31.

PV expression levels were significantly increased after E2 treatment and, concomitantly, sociability deficits in PV<sup>+/-</sup> mice in the direct reciprocal social interaction and the 3-chamber social approach assays, as well as repetitive behaviors, were attenuated. Our results suggest that the

E2-linked amelioration of ASD-like behaviors is specifically occurring in PV+/- mice, indicating that PV upregulation is required for the E2-mediated rescue of ASD-relevant behavioral impairments.

## **Rapid and complete reversal of sensory ataxia by gene therapy in a novel model of Friedreich ataxia**

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Friedreich Ataxia (FA) is a rare mitochondrial disease characterized by sensory and spinocerebellar ataxia, hypertrophic cardiomyopathy and diabetes for which there is no treatment. FA is caused by reduced levels of frataxin (FXN), an essential mitochondrial protein involved in the biosynthesis of iron-sulfur (Fe-S) clusters. Despite significant progress in recent years, to date, there are no good models to explore and test therapeutic approaches to stop or reverse the ganglionopathy and the sensory neuropathy associated to frataxin deficiency. Here, we report a new conditional mouse model with complete frataxin deletion in parvalbumin positive cells which recapitulate the sensory ataxia and neuropathy associated to FA, albeit with a more rapid and severe course. Interestingly, proprioceptive neurons can survive for many weeks without frataxin, although fully dysfunctional. Furthermore, we demonstrate that post-symptomatic delivery of frataxin-expressing AAV allows for rapid and complete rescue the sensory neuropathy associated with frataxin deficiency, thus establishing the preclinical proof of concept for the potential of gene therapy in treating FA neuropathy.



The **International Society for Developmental Neuroscience (ISDN)** is an organization of basic and clinical scientists interested in the development of the nervous system in the broadest sense. The society aim is to promote research and knowledge concerning the development of the nervous system and support the effective application of this knowledge for the improvement of human health.

The society publishes a journal in cooperation with Elsevier called the **International Journal of Developmental Neuroscience (IJDN)** <https://www.journals.elsevier.com/international-journal-of-developmental-neuroscience/>. IJDN publishes original research papers, reviews and communications on both basic and clinical aspects of the developing nervous system, ranging from simpler invertebrate systems and in vitro neural models to models of regeneration and neurological diseases of developmental origin. The journal encourages the publication of Special Issues dealing with topics at the cutting edge of research, edited by Guest Editors appointed by the Editor in Chief. The main aim of the journal is to facilitate the transfer of basic information to clinical applications and to promote an understanding of the fundamental mechanisms of neural growth, development and pathology.

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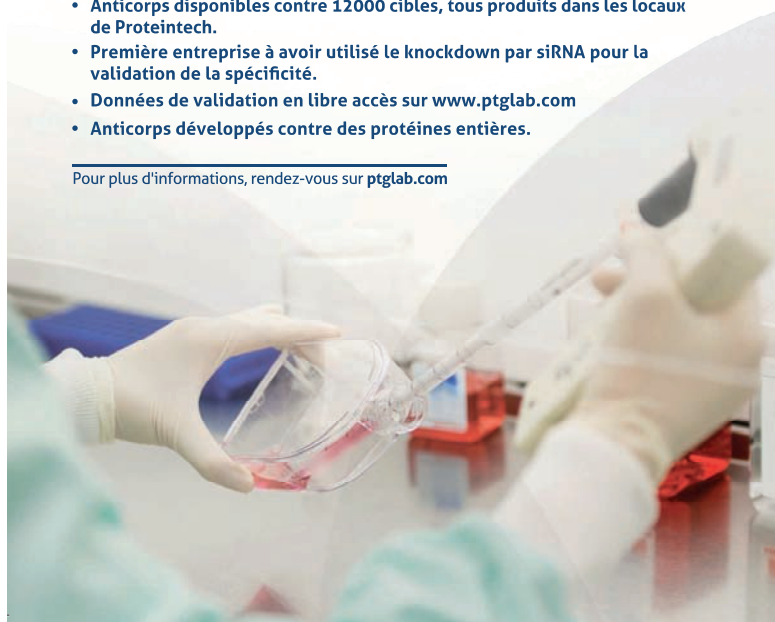


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# Posters

# Genetics of neurological diseases

Les posters doivent rester affichés les deux jours mais il est demandé aux auteurs d'être présents à leur session uniquement.  
Le numéro mentionné avant le titre du résumé correspond au numéro du panneau poster.

01

## The kinesin KIF21B modulates neuronal migration in the developing cerebral cortex both in mice and human

Asselin L. (1,2,3,4), Tilly P. (1,2,3,4), Heide S. (5), Héron D. (5), Depienne C. (6), Yalcin B. (1,2,3,4) and Godin J. (1,2,3,4)

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During development, microtubules (MT) act in concert with microtubule associated proteins (MAPs) and molecular motors to carry out the structural changes that underlie key developmental events such as neurogenesis, neuronal migration, axon pathfinding and synapse formation. Over the years, several human genetic mutations in genes encoding tubulin, MAPs and motors have been associated to malformation of cortical development (MCD) such as microcephaly or lissencephaly highlighting the critical role of MT cytoskeleton in brain development.

In a search of key regulators of cortical development, we identified KIF21B, a member of the kinesin superfamily. Interestingly, KIF21B is essential for brain morphogenesis in young adult mice. Combining in utero electroporation (IUE) of shRNA in mouse embryos with time lapse recording on live cortical slices, we demonstrated that KIF21B regulates neuronal migration of projection neurons through the tight control of both locomotion and neural shape. Rescue experiments with different truncated forms of KIF21B allowed us to decipher precisely the cellular mechanisms involved in the migration phenotype. Furthermore, we recently identified missense mutations in the KIF21B gene, in four different families presenting either microcephaly or corpus callosum (CC) agenesis in combination with intellectual disabilities. Overexpression of the mutated human KIF21B by IUE revealed that these mutations lead to severe radial migration delay in mice. We are currently performing further functional analysis to uncover how KIF21B mutations lead to microcephaly and CC agenesis. Overall, our results clearly identified KIF21B as a novel key regulator of cortical development both in mouse and human.

02

## Working memory and cognitive flexibility deficits related to aging in the mouse

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The interpretation of aged-related cognitive decline in preclinical studies is complicated by deterioration in motor skills that accompany aging. Motor dysfunction can significantly impact the performances of mice evaluated in cognitive tasks involving navigation, such as the Morris water maze (MWM) test. In the present study, 2 month, Young, and 18 month, Aged, C57BL/6J mice were tested in 4 sequential protocols of the MWM test: The spatial learning basic protocol, spatial reversal learning, delayed-matching-to-place (DMTP) and cued learning protocols. Locomotor activity and motor coordination were also evaluated using the activity meter and rotarod tests, respectively.

Aged mice displayed an almost normal acquisition of the initial place of the hidden platform. However, aged mice were not able to learn the new position of the hidden platform, as shown during the probe test following the reversal phase (% of distance swum in the target quadrant not different from the chance level). A marked deficit was observed in the DMTP protocol (+40 % of the mean distance swum in the last daily trial,  $P < 0.05$ , as compared with young mice). Age did not affect average speed, total distance swum over all sessions, or distance swum to reach the visible platform.

Aged mice displayed specific deficits in cognitive flexibility and working memory. These deficits cannot be attributed to motor dysfunction since aged mice displayed normal learning of the initial place of the hidden platform and reference memory performance. The mouse may therefore be an appropriate model for studying age related memory deficits.

03

## Identifying the MVP/vault neuronal function at the autism-associated 16p11.2 locus

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Copy Number Variation (CNVs) causes genomic variations that can lead to syndromes involving macro- and microcephaly associated with cognitive disorders such as intellectual disability (ID) and autism spectrum disorders (ASDs). The 16p11.2 deletion underlying 30 genes has a prevalence of ~0.05% in the general population and is one of the most frequent known aetiologies of ASDs and related neurodevelopmental disorders. Yet the specific gene(s) affecting brain function in this locus remain(s) to be identified.

Neuroanatomical characterization of candidate genes at the autism-associated 16p11.2 locus identified Major Vault Protein (Mvp) as the main driver of brain size

phenotypes associated to the 16p11.2 syndrome. Here we describe the function of MVP, the main component of the vault organelle, in the central nervous system and its potential implication in the ERK pathway using double knock-out mice.

Neuroanatomical phenotypes, which are characterized by a reduction of the size of corpus callosum, hippocampus and cingulate and somatosensory cortices, are specific to male mice and appear only postnatally. A decrease of cell size is observed both in cortical and hippocampal neurons, as well as a reduction of the size of the growth cone. Moreover the morphological abnormalities are reduced in Mvp+/- Erk1+/- double-heterozygous mouse models, while revealing behavioral phenotypes not present in single genes mutants.

To conclude, these data unravels the role of the MVP/vault in neurons and its functional interaction with Erk1, which opens up new mechanistic insights in understanding the 16p11.2 genes interaction and pathophysiology of autism spectrum disorders.

## 04

### **RAT: a new genetically modified model to decipher intellectual disabilities in MRD7 syndrome**

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Dyrk1a gene (Dual Specificity Tyrosine(Y) Regulated Kinase 1A), is located on human chromosome 21 (Hsa21), code for a serine-threonine kinase. Dyrk1a haploinsufficiency leads to a severe mental retardation syndrome associated with microcephaly, memory impairments, ASD symptoms and epileptic seizures (MRD7; MIM614104). The study of a mouse model carrying the deletion of one allele of Dyrk1a (Arqué et al. 2008) described phenotypes mimicking human symptoms, in particular recognition memory and spatial learning defects. However, the use of mouse model showed limitations in terms of cognitive approach and sociability; as a consequence, we moved towards the development of rat genetically modified. To engineer this model, because no ES cells were available for the Rat, we developed a new method, called Crismere, to

rearrange large genetic loci such as deletion, inversion and duplication in less than 6 months (Birling et al., 2017), and we obtained rapidly and efficiently the Del rat. Our model passed through a behavioural pipeline to evaluate locomotion, circadian rhythm, vision, memory, learning (to compare the relevance of our model to mouse) but also sociability paradigm and empathy. In our work, we demonstrated that rat deleted for one copy of Dyrk1a recapitulated some of the phenotypes observed in the mouse model, and new phenotypes which could be only observed in rat. Supporting, among others, by our results, the emergence of genetic manipulation in rat pave the way to a better comprehension of complex neurodevelopmental and psychiatric disorders.

## 05

### **Transdifferentiation of fibroblasts of patients with genetic defects of intracellular metabolism of vitamin B12 into neurons for the study of neurological disorders**

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(3) *CHRU Brabois, Vandoeuvre-lès-Nancy*

The main clinical symptoms observed in patients with genetic defects of intracellular metabolism of vitamin B12 are hematological and neurological. In some patients, treatment with vitamin B12 can correct biochemical parameters and hematological symptoms. However, the efficiency of treatment does not affect neurological, neuropsychiatric and neurocognitive disorders. The study of the mechanisms underlying these pathologies would benefit from the use of neurons as a more appropriate cellular model than patient fibroblasts.

The aim of this study is to transdifferentiate fibroblasts of patients with genetic defects of intracellular metabolism of vitamin B12 into neurons that will be used for the study of the associated neurological disorders.

The technique used, (Xue and al, Cell, 2013), relies on the inhibition of the PTBP1 gene by infecting fibroblasts with lentiviral particles containing a plasmid encoding a shRNA. PTBP1 exists in two forms: a basal and a specific neuronal form. Inhibition of basal PTB leads to expression of the neuronal form, which promotes the expression of neuronal genes. Incubation of the transfected cells with neurogenic growth factors contribute to neuronal differentiation and maturation.

Our results show that this method leads to modifications of the morphology of transdifferentiated cells. Immunolabeling and confocal microscopy shows that these cells express the neuronal-specific proteins NeuN, MAP2, TUJ1 and SYN1. Thus, our results indicate that

# Genetics of neurological diseases

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we successfully transdifferentiated patient fibroblasts into neurons. This novel cellular model will be used to investigate the molecular mechanisms underlying the neurological disorders associated with inherited defects of vitamin B12 metabolism.

06

## Mutations in the netrin-1 gene cause congenital mirror movements

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Netrin-1 is a secreted protein first identified 20 years ago as an axon guidance molecule regulating midline crossing in the central nervous system. It has since been shown to play critical roles in various tissues throughout development as well as in tumorigenesis and inflammation in adulthood. Despite extensive studies, no inherited human disease has been directly associated with mutations in NTN1, the gene coding for netrin-1. Here we show mutations in exon 7 of NTN1 in two unrelated families and one sporadic case with isolated congenital mirror movements (CMM). CMM is characterized by involuntary movements of one hand that mirror intentional movements of the opposite hand. Given the numerous roles of netrin-1, the absence of manifestations other than mirror movements is unexpected. With multimodal approaches, we show that the anatomy of the cortical spinal tract (CST) is abnormal in NTN1-CMM patients. When expressed in HEK293 or HeLa cells, the 3 mutated proteins were almost exclusively detected in the intracellular compartment, contrary to wild-type netrin-1 (detected both in intracellular and extracellular compartments). Since netrin-1 is a diffusible extracellular cue, the pathophysiology likely involves loss of function and subsequent disruption of axon guidance with abnormal decussation of the CST.

07

## NEUROLOGICAL AND COGNITIVE PHENOTYPE IN 22q11 MICRODUPLICATION

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The 22q11.21 region is susceptible to chromosomal rearrangements, leading to various types of congenital malformation and intellectual disability (ID). We describe two adult male carriers of proximal 22q11 duplication. The patients have been evaluated from clinical, instrumental and psychometric point of view, conventional cytogenetic and FISH and ARRAY-CGH testing.

Case 1: M 27 years old. Motor developmental milestones delayed.

Clinical examination: facial dysmorphic features, congenital facial diplegia and immunologic anomalies (ocular rhinitis

and allergic dermatitis). Right renal agenesis.

MRI brain: thinning of the posterior third of the corpus callosum.

Cognitive phenotype: IQ borderline at WAIS (TIQ= 72; VIQ=78; PIQ= 68).

Array-CGH tetrasomy of about 4 Mb on chromosome 22q11 (first amplified oligo: 15.471 Mb; last trace amplified : 19.707; first oligo normal: 20.123 Mb). karyotype was 47, XY, invdup (22)(q11).

Case 2: M 29 years old, At birth a cardiac total anomalous pulmonary venous connection was diagnosed. Developmental milestones severe delayed: no development of language . Since childhood focal seizures, refractory to treatment.

Clinical examination: turricephaly, spastic tetraparesis.

MRI brain: thinning of the corpus callosum, hypomyelination of the oval centers. EEG: spikes and polyspikes and waves more marked during sleep.

Cognitive phenotype: IQ undetectable for severity.

Array-CGH tetrasomy of about 1,55 Mb on chromosome 22q11.1q11.21, due to the presence of a bisatellited small dicentric supernumerary chromosome, as demonstrated by karyotype and FISH analysis.

Conclusion

ID of different severity may be associated to 22q11 proximal duplication.

Together with the cardiac and renal disorders, different levels of neurological compromise emerged.

# Molecular mechanisms to pathogenesis

Les posters doivent rester affichés les deux jours mais il est demandé aux auteurs d'être présents à leur session uniquement.  
Le numéro mentionné avant le titre du résumé correspond au numéro du panneau poster.

08

## Cellular prion protein protects neuronal cells from TNF $\alpha$ -mediated inflammation

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Although cellular prion protein (PrP<sup>C</sup>) is mainly known for its implication in prion diseases, its function(s) remain(s) elusive. PrP<sup>C</sup> recently emerged as a regulator of the inflammation process able to modulate the release of pro-inflammatory factors by microglia and astrocytes. Whether PrP<sup>C</sup> also displays the capacity to adjust the cell response to the pro-inflammatory TNF $\alpha$  cytokine remains unknown. To address this issue, we exploit the 1C11 neuronal cell line and primary cultures of cerebellar granule neurons. We show that PrP<sup>C</sup> protects neurons against TNF $\alpha$ -associated inflammation by controlling the level of TNF $\alpha$  Receptor type 1 (TNFR1) at the plasma membrane. Through its coupling to the NADPH oxidase-TACE  $\alpha$ -secretase signaling pathway, PrP<sup>C</sup> promotes TACE-mediated cleavage of transmembrane TNFR1 and limits the sensitivity of neurons to TNF $\alpha$ . We further demonstrate that PrP<sup>C</sup> protection against TNF $\alpha$  also depends on a PrP<sup>C</sup> control of TACE  $\alpha$ -secretase bioavailability at the plasma membrane in an active state for TNFR1 shedding. In PrP<sup>C</sup>-depleted cells, TACE is internalized, which diverts TACE activity away from TNFR1 and renders PrP<sup>C</sup>-depleted cells highly vulnerable to TNF $\alpha$ . Such PrP<sup>C</sup> control of TACE localization depends on PrP<sup>C</sup> capacity to negatively regulate  $\beta$ 1-integrin signaling and downstream activation of two kinases, ROCK and PDK1. In PrP<sup>C</sup>-depleted cells, antibody-mediated neutralization of  $\beta$ 1-integrins or pharmacological inhibition of ROCK and PDK1 kinases allow TACE to target back the plasma membrane, where it recovers its neuroprotective cleavage activity towards TNFR1.

Our work unravels a novel facet of PrP<sup>C</sup> protective role against TNF $\alpha$ -associated inflammation that would be lost in prion diseases.

09

## Impact of a neuronal upsurge of the adenosine A2A receptor in a Tau mouse model of Alzheimer's disease.

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Neuronal accumulation of hyperphosphorylated/aggregated Tau is correlated with cognitive decline in Alzheimer's disease but mechanisms underlying Tau-induced memory deficits remain unclear. Caffeine consumption reduces AD risk and associated cognitive deficits. These effects were ascribed to the blockade of adenosine A2A receptors (A2ARs), found upregulated in the neurons of AD patients in correlation with Tau pathology development and cognitive deficits. To get insights towards this relationship, we evaluated the pathophysiological impact of neuronal A2AR upsurge in a transgenic model of AD-like Tauopathy. To do so, we have developed a conditional model allowing A2AR overexpression in CAMKII-positive neurons. This model was crossed with THY-Tau22 mice, who develop a progressive hippocampal Tau pathology associated with cognitive decline. We found that neuronal A2AR overexpression worsens spatial memory impairments of Tau transgenic mice. This detrimental effect was associated with an increased tau phosphorylation at some epitopes and modified plasticity markers. Interestingly, following RNA sequencing, we uncovered that neuronal A2AR overexpression in Tau mice led to a significant altered hippocampal gene expression mostly ascribed to microglial cell function, underlying a functional link between neuronal A2A dysregulation and microglia in a Tau pathology context. Altogether, these data suggest that neuronal A2AR dysregulation seen in the brain of AD patients contributes to the development of Tau-induced cognitive impairments by modulating the interplay between neurons and glial cells.

10

## Mapping of the residues involved in E6AP - HERC2 ubiquitin ligases interaction

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E3 ubiquitin ligases are main regulators of cellular processes: ubiquitination of a protein can impact its stability, its protein binding features and its subcellular localization. Kühnle et al. have shown direct interaction between residues 150-200 of E6AP and the second RLD domain of HERC2. E6AP is the founding member of HECT ubiquitin ligase family (homologous to E6AP C-terminal). HERC2 is also a HECT ubiquitin ligase and contains and three RCC1-like domains (RLD). The inactivation or loss of function of both E6AP and HERC2 by mutations in their respective genes has been reported to cause the development of the Angelman syndrome, a neurodevelopmental disorder. Thus, both genes are implicated in the same disease and the corresponding proteins bind to each other. We confirmed the physical interaction and further mapped the residues from E6AP involved in physical interaction with RLD2 domain. After a first screen by HoldUp (inhouse quantitative interaction assay) and further characterization by surface-plasmon resonance, we identified 15 residues determinant for the interaction by testing overlapping peptides of E6AP binding region with RLD2 domain. In addition, X-ray crystallography trials have been started to solve the structure of RLD2 in complex with E6AP 15 binding residues. Our data bring new knowledge on the molecular aspects ruling E6AP-HERC2 interaction, with both quantitative and structural analysis.

Kühnle, S., Kogel, U., Glockzin, S., Marquardt, A., Ciechanover, A., Matentzoglou, K., and Scheffner, M. (2011). Physical and Functional Interaction of the HECT Ubiquitin-protein Ligases E6AP and HERC2. *Journal of Biological Chemistry* 286, 19410-19416.

## 11

### Increased N-homocysteinylation of tau and MAP1 may contribute to the pathogeny of Alzheimer-type dementia

Bossenmeyer-Pourié C. (1), Smith DA (2), Lehmann S (3), Deramecourt V.(4), Sablonnière B (4), Jean-Michel Camadro (5) JM, Pourié G. (1) Kerek R.(1), Helle D. (1), Umoret R. (1), Guéant-Rodriguez RM. (1), Rigau V. (3), Gabelle A. (3), Siqueiras JM (6), Quadros EV (6), Daval JL. (1), Guéant JL. (1).

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Despite evidence of the influence of folate/vitamin B12 deficiency and hyperhomocysteinemia in neurodegenerative diseases, nothing is known about homocysteinylation of microtubule-associated proteins (MAPs) in the brain. We investigated this mechanism in brains of patients with Alzheimer's disease or cerebrovascular dementia and in animal and cell models, including rats depleted in folate and vitamin B12, Cd320 KO mice with selective B12 brain deficiency and H19-7 neuroprogenitors lacking folate.

We demonstrated that tau, MAP1a and MAP4 are homocysteinylation and accumulate in protein aggregates in cortex, hippocampus and cerebellum of patients and animals, compared with controls. N-homocysteinylation dissociates tau and MAPs from  $\beta$ -tubulin by targeting lysine residues. This was correlated with higher homocysteine levels and higher expression of Methionine tRNAsynthetase (MARS), required for the synthesis of the substrate of N-homocysteinylation. In H19-7 neuroprogenitors, inactivation of MARS prevents homocysteinylation and dissociation of tau and MAPs from  $\beta$ -tubulin and MAP1a from PSD95.

In conclusion, increased N-homocysteinylation of tau and MAP1 in brain tissues of patients with AD or CVD is an irreversible and cumulative age-related change which depends on Hcy concentration and expression of MARS enzyme, and triggers a decreased interaction of MAPs with their partner proteins, contributing to cognitive decline. Trials should be designed to prevent this irreversible mechanism in the early step of cognitive decline, in particular in subjects with hyperhomocysteinemia.

## 12

### Development of the astrocyte perivascular MLC1/GlialCAM complex defines a temporal window for the postnatal gliovascular unit maturation

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Astrocytes are morphologically complex glial cells of the central nervous system. They display numerous processes interacting with synapses and blood vessels. At the vascular interface, astrocyte endfeet-terminated processes almost entirely cover the blood vessel surface and participate to the gliovascular unit where important vascular properties of the brain are set such as the blood-brain barrier (BBB) integrity. How the specific

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morphological and functional interaction between astrocytes and the vascular compartment develops has not been fully investigated. Here, we characterized the postnatal expression of MLC1 and GlialCAM, two transmembrane proteins forming a complex enriched at the junctions between mature astrocyte perivascular endfeet. Performing immunodetection on purified gliovascular units, we showed that MLC1 and GlialCAM were enriched and formed mature complexes in astrocyte endfeet between postnatal days 10 and 15. These events correlated with the increased expression of Claudin-5 and P-gP, two endothelial-specific BBB components. These results suggest that astrocyte endfeet and BBB mature in concert between postnatal days 10 and 15. Moreover, the formation of the astrocyte endfeet MLC1/GlialCAM complex might thus be a key event in the gliovascular unit maturation.

13

## Role of Raldh1 in the control of animal behavior and dopaminergic signaling

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Retinoic acid (RA) is an active form of vitamin A that binds to retinoic acid receptors (RARs) and retinoid X receptors (RXRs) to act as transcription factors and control gene expression. Whereas RA signaling is best known for its critical role in developmental of different organs including brain, its functions in control of brain physiology only start being identified. There are several lines of evidence that RA signaling is involved in the physiopathology of neurodegenerative disorders. In particular, reduced signaling of RA is observed during aging and can be exacerbated during neurodegeneration. Compromised activity of Raldh1, one of three enzymes involved in RA synthesis has been suggested to be a causal factor of Parkinson disease (PD) in human. Here using mice lacking Raldh1 (Raldh1<sup>-/-</sup>), we identify behavioral deficits consistent with some of the key symptoms of PD including age-dependent motor coordination and dexterity deficits. Our molecular and histological data point to dysfunction of mitochondrial functions in the striatal dopamine-sensitive neurons as potential mechanism of such deficits. Similar phenotypes have been observed in mice lacking RARb (RARb<sup>-/-</sup>), the main RAR in the striatum. Globally, obtained data point to relevance of studies of retinoid signaling for research into PD, but also into other neurodegenerative diseases suggesting also potential prevention strategies.

14

## Study of the mechanisms leading to immune disorder in C9orf72 deficient mice

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An expansion of GGGGCC repeats in the first intron of C9ORF72 gene is the most common genetic cause of Amyotrophic Lateral Sclerosis associated to Frontotemporal Dementia (ALS/FTD). As a decreased expression of C9ORF72 is observed in patients carrying expansions, we created a C9orf72 deficient mice to assess whether C9ORF72 haploinsufficiency could induce an ALS phenotype. However, those KO mice developed a splenomegaly and lymphadenopathy. Sera analysis and histopathology revealed an elevation of autoantibodies and a glomerulonephropathy, leading to reduced mice longevity.

In order to investigate further this phenotype, we crossed C9orf72 flox mice with Cre lines specific of the main immune cell populations: dendritic cells (CD11c Cre), macrophages (LysM Cre), B cells (Mb1 Cre) and T cells (CD4 Cre). Interestingly, C9orf72 flox X CD11c Cre mice developed massive splenomegaly and lymphadenopathy. In contrast, deletion of C9orf72 in B cells, T cells or macrophages did not induce any phenotype. These results indicate a major role of C9orf72 in dendritic cells. Immunophenotyping of the DC lineage, from the myeloid precursor to conventional DCs and plasmacytoid DCs (pDC) of C9orf72 knockout mice demonstrated a specific alteration of the pDCs, which are more numerous and immature compared to control mice. Plasmacytoid dendritic cells are specialized immune cells dedicated to respond to viral infection by massive secretion of interferon.

Overall, these results suggest a crucial function of C9ORF72 in dendritic cells. Hopefully, this study will help to better assess the molecular and cellular functions of C9ORF72 and better understand its implication in amyotrophic lateral sclerosis.

15

## Primary cilium : a new target for remyelination?

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The primary cilium (PC) is considered as a cellular sensory antenna present at the surface of many cell types.

It coordinates several molecular pathways that control cellular proliferation and differentiation. In the central nervous system (CNS) the presence and the role of primary cilia have been documented in neurons and astrocytes ; however very little is known about PC in oligodendrocytes, the myelinating cells in the CNS. Oligodendrocytes originate in the ventricular zone from oligodendrocyte precursors cells (OPCs) before differentiating in myelinating cells. In neurons, PC length is modulated by extracellular cues and as well as by drugs, such as Lithium Chloride (LiCl).

Our aim was then: 1° to check for the presence of a PC 2° to test the ability of LiCl to modulate PC length in the oligodendroglial lineage.

We worked on an oligodendrocytic cell line (158N) and on OPCs purified from mixed glial cell cultures established from neonatal plp-eGFP mouse cortices. Cultures were treated with LiCl at different times and PC was observed by double Arl13b/ $\gamma$ -tubulin immunostaining and by electron microscopy.

We show that a PC is present on 158N cells and only on OPCs of the native oligodendroglial lineage. LiCl elongates primary cilia in oligodendrocytic cell lines as well as in OPCs.

This study opens a new field of investigation to increase the ability of OPCs to remyelinate in demyelinating diseases such as multiple sclerosis. Accelerating remyelination and preventing axonal and neuronal degeneration is currently an important issue in this pathology.

## 16

### **Congenital mirror movement disorder provides new insights into the role of RAD51 in the development of the nervous system**

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Congenital mirror movement (CMM) disorder is a neurodevelopmental disease characterized by involuntary movements of one hand during voluntary movements of the opposite hand. In CMM patients, midline crossing of the cortico-spinal tract (CST) at the decussation is impaired. Mutations in genes encoding the Netrin-1 axonal guidance cue and its receptor DCC can cause CMM.

Our team and others showed that RAD51 mutations can also account for some CMM cases, which was totally unexpected. Indeed, the role of RAD51 has been largely investigated in homologous recombination during DNA repair and meiotic division.

We previously found that CMM patients with a heterozygous truncating mutation of RAD51 (R254\*) had decreased RAD51 mRNA levels likely due to the nonsense mediated mRNA decay. Recently, we analyzed RAD51 expression by western blot in the same CMM family: interestingly, only the affected individual with RAD51 mutation showed a decrease in RAD51 expression as compared to a healthy relative (no RAD51 mutation) or an asymptomatic carrier (same RAD51 mutation but no MM). This data strongly suggests that RAD51 haploinsufficiency (loss of function) causes CMM in humans. In mouse, the RAD51 protein is detected in the cytoplasm of CTIP2+ cortical neurons, and at the decussation at the time of CST midline crossing. We now focus our study on this new cytoplasmic role of RAD51, taking advantage of a non-truncating CMM mutation of RAD51 (R250Q) and investigating its impact on the protein biochemical and cellular properties.

## 17

### **Modification of neural stem cell differentiation following glufosinate-ammonium herbicide exposure**

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In vertebrates, neurogenesis persists in two distinct areas, the ventricular-subventricular zone (V-SVZ) of the lateral ventricle wall and the subgranular zone (SGZ) of the hippocampal dentate gyrus. The V-SVZ is the largest neurogenic niche and contains four cellular types as defined by their morphology, ultrastructure and molecular markers. Neural stem cells of the V-SVZ or B1 cells give rise to transit-amplifying intermediate progenitors (C cells) which in turn generate neuronal lineage or glial lineage. Moreover, the V-SVZ is separated from the ventricular lumen by a multiciliated ependymal cells (E cells) in direct contact with the cerebrospinal fluid. Glufosinate-ammonium (GLA), the active substance of a worldwide organophosphorus herbicide, targets the central nervous system due to its structural analogy of glutamate and thus interferes with glutamatergic system. In mouse prenatal exposure, we previously showed a potential link between GLA exposure and the onset of autism spectrum disorder-like symptoms associated with a defective neurogenesis in the V-SVZ. Here, we characterized the cellular effects of GLA on the differentiation into E cells and SVZ cells. In our in vitro model, we observed a disturbance of the ependyma with a decrease in the number of multiciliated

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tuft and the loss of cell-cell adhesion between ependymal cells following GLA exposure. Thereafter, we quantified an impairment of the neuro-glial differentiation of B1 cells through a modification of their cell fate. Our data revealed that GLA disrupted the V-SVZ homeostasis and gave a novel insight into the cellular mechanism potentially involved in previous in vivo observations.

18

## Retinal alterations and visual dys-sensibility in the Fragile X syndrome

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Fragile X syndrome (FXS) is the most common monogenic intellectual disability (ID) in men (1/3000 births). In addition to ID, patients present autism spectrum disorders as well as sensory disturbances, including impaired visual functions. Indeed, they display a decreased sensitivity to contrasts, textures and motions. The FXS is caused by the absence of the FMRP protein, regulator of neuronal and glial protein translation, due to the silencing of the FMR1 gene. At the molecular and cellular levels, the cerebral loss of FMRP induces structural and functional synaptic abnormalities, considered as the origin of the clinical phenotype of ID but also anomalies of integration of visual functions.

However, we have recently shown that Fmrp is also expressed in the retina, the key structure of the visual system responsible for visual perception. The retina of the murine model of the FXS (the Fmr1 KO mouse) displays major electrophysiological alterations, in association with our observations of protein deregulation and neuronal immaturity similar to those observed in brain. Moreover, the behavioral response of Fmr1 KO mice to visio-spatial tests, involving both perception and integration of visual stimuli, is impaired.

Thus, the whole of our results indicate that the peripheral part of the visual system is altered, as well as its central part. Therefore, it becomes necessary to understand the

involvement of each of these two parts in the visual clinical phenotype.

19

## Corticospinal motor neuron degeneration precedes spinal motor neuron degeneration and involves a new set of molecular players.

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Amyotrophic Lateral Sclerosis (ALS) is clinically defined as the combined degeneration of corticospinal motor neurons (CSMN) and spinal motor neurons (SMN). However, little is known about CSMN degeneration.

To characterize the spatiotemporal dynamics of CSMN degeneration, we performed retrograde labelling either from the cervical (total population, CSMNTot) or the lumbar (CSMNLomb) part of the spinal cord of wild-type and Sod1G86R mice. The quantification reveals a progressive and significant loss of CSMN in Sod1G86R mice. Importantly, CSMNLomb are affected earlier and to a greater extent than the whole CSMNTot. Given that Sod1G86R mice present with first motor symptoms in the hind limbs and display a pronounced SMN degeneration in the lumbar spinal cord, the data support a somatotopic relationship between the cortical and spinal insults, similar to what was reported in patients. Finally, CSMN loss precedes by far SMN degeneration, suggesting that loss of CSMN could be detrimental to downstream SMN's integrity, and supporting a cortical origin of the disease and a corticofugal propagation.

To unravel the molecular mechanisms underlying CSMN degeneration, we developed an approach to purify, for the first time, CSMN from the cerebral cortex of adult wild-type and Sod1G86R mice. RNAseq analyses conducted at 4 time-points reveal early alterations of CSMN and unravel a new set of molecular players in ALS. The work is intended to inform the development of alternative strategies, based on the maintenance of a healthy and functional pool of CSMN.

20

## KIF2A conditional mutant knock-in mouse: a flexible model to study cortical malformations

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Development of the human cerebral cortex is based on three major, highly regulated processes: progenitor's proliferation, following by migration of post-mitotic neurons to reach the cortical plate and finally their differentiation. Alteration of one of these processes can lead to malformations of cortical development (MCD), often associated with intellectual disability and pharmaco-resistant epilepsy. Our team has previously identified mutations in KIF2A gene in patients with MCD diagnosed by MRI sequences as posterior pachygyria and microcephaly (Poirier et al., 2013).

In order to better understand the in vivo implications of KIF2A mutations in the pathophysiology of MCD, we have designed and engineered, in collaboration with the Institut Clinique de la Souris (ICS), a conditional knock-in expressing the heterozygous human mutation p.His321Asp at physiological level.

We first validated by qPCR and sequencing the proper functioning and expression of the conditional knock-in allele. Then, immunofluorescence analysis on KIF2A knock-in brain slices showed a re-localization of KIF2A protein similar to that observed in patient fibroblasts (Poirier et al., 2013). Neuro-morphological study on adult mice reveal severe heterotopia in hippocampus, dysmorphic corpus callosum and enlarged lateral ventricle. Further developmental investigations on different embryonic stages showed that KIF2A mutation affect neuronal positioning and radial glia integrity. Altogether, these results show that the important need of cKl could now be addressed and provide a reliable and relevant modelization of KIF2A heterozygous point mutation in order to investigate its effects on brain developmental processes.

## 21

### Uncovering the molecular mechanisms underlying the neuropathology of Friedreich's Ataxia

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Friedreich's Ataxia (FA) is an autosomic recessive neurodegenerative disorder, characterized by a spinocerebellar and sensory ataxia associating cardiomyopathy. The sensory ataxia results mainly from the degeneration of proprioceptive neurons of the dorsal root ganglia (DRG). The major FA-causing mutation corresponds to a GAA expansion in the first intron of the FXN gene, which leads to the reduced expression of frataxin, a mitochondrial protein involved in iron-sulfur (Fe-S) cluster biosynthesis. The study of mouse models bearing heart-specific frataxin depletion showed a primary decrease of Fe-S clusters biosynthesis followed by cellular mitochondrial dysfunction and iron metabolism dysregulation [1]. However, the involvement of

mitochondrial dysfunction in the degeneration of frataxin-deficient DRG sensory neurons has never been fully investigated, due to the complexity of neuronal tissues and the low amount of material available for molecular and cellular analysis. We have established a neurologic cellular model of Friedreich's Ataxia based on mouse primary cultures of DRG sensory neurons depleted for frataxin. My thesis project aims at characterizing this new model at the cellular, molecular and biochemical level, with a particular interest on Fe-S cluster biogenesis and mitochondrial function. This model will allow to characterize the mechanisms underlying neuron degeneration in Friedreich's Ataxia.

## 22

### Alteration of SAGA-related epigenetic marks and loss of photoreceptor cell identity in the SCA7 cone-rod dystrophy.

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Polyglutamine expansion in ATXN7 causes photoreceptor degeneration in SpinoCerebellar Ataxia 7 (SCA7). SCA7 photoreceptors progressively lose their outer segments, a structure essential for phototransduction, which requires daily renewal. The lack of outer segment renewal correlates with decreased expression of photoreceptor-specific genes.

ATXN7 is a subunit of the transcriptional coactivator Spt-Ada-Gcn5 Acetyltransferase (SAGA) complex. SAGA harbors enzymatic activities for acetylation of H3 on lysine 9 (H3K9ac) on gene promoters to initiate transcription, and for deubiquitination of ubiquitinated H2B (H2Bub) on gene bodies to transcription elongation. The role of SAGA in SCA7 pathogenesis remains to be determined.

Here, we determined the role of SAGA in gene expression in mouse retina, and analyzed whether SAGA dysfunction accounts for SCA7 retinopathy. We performed RNA-seq and ChIP-seq analysis of both H3K9ac and H2Bub SAGA-related marks together with active transcription-related marks, H3K36me3 and RNA polymerase II.

We show that H3K9ac and H2Bub occupy, respectively, the gene promoter and gene body of most protein coding genes expressed in wild type retina, in agreement with a broad genome-wide action of SAGA at all transcribed regions. Furthermore, the occupancy of H3K9ac and H2Bub strongly correlate with both the level of RNA polymerase II and the expression level of these retinal genes. Interestingly, in SCA7 retina, the SAGA-related epigenetic marks, are broadly affected, on deregulated

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and non-deregulated genes based on the mRNA steady state level. These results indicate that mutant ATXN7 compromises SAGA epigenetic function. Additional mechanism(s) are ongoing to cause the selective gene deregulation in SCA7 retina.

## 23 TMEM240: a novel transmembrane cerebellar synaptic protein

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**Introduction.** Dominantly inherited spinocerebellar ataxias (SCAs) are heterogeneous neurodegenerative diseases characterized by cerebellar impairment. To date, 38 different loci and 27 genes have been described for the SCAs. Recently, missense mutations and a stop mutation in transmembrane protein 240 (TMEM240) have been reported in spinocerebellar ataxia 21 (SCA21) among 11 French families. SCA21 stands out by its association with severe cognitive impairment and early age onset. Nowadays, TMEM240 function is unknown.

**Objectives.** 1/ Establish a general brain mapping of TMEM240 expression 2/ Determine TMEM240 specific expression in mice cerebellum 3/ Define TMEM240 cellular and subcellular expression.

**Methods.** Immunohistochemistry analyses are performed on mice brain tissues. To establish cellular and subcellular localization, we realized immunohistochemistry on mice brain sections. Immunostaining is studied by confocal microscopy. TMEM240 synaptic expression is analyzed by electron microscopy.

**Results.** Immunostaining shows that TMEM240 is mainly expressed cerebellum and especially in the uvular lobe (IX) and nodulus lobe (X). At a cellular level, TMEM240 is localized in neurons from cerebellar cortex: molecular layer, cerebellar glomeruli in the granular layer and in the soma and dendritic arborization of Purkinje cells. TMEM240 is located among synapses between Purkinje cell and granular cells, and co-localized with synaptic markers as validated by confocal microscopy.

**Conclusion.** TMEM240 protein is expressed in neurons from cerebellar cortex. TMEM240 expression is mainly observed in synapses. TMEM240 could have a synaptic function in cerebellar cortex neuronal network.

**Perspectives.** SCA21 model in zebrafish. Identification of TMEM240 partners.

## 24 Microfluidic Co-Culture System to Expose Fluidically-Isolated Synapses to CHO Cell-Secreted Oligomeric A $\beta$ 42 to Decipher the Role of Pyk2 in Alzheimer's Disease

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**Introduction.** Our genome-wide association studies have identified a number of genetic risk factors for Alzheimer's disease (AD); however, the mechanisms by which these risk factors contribute to the disease are poorly understood. One such gene (PTK2B) expresses Pyk2, a tyrosine kinase closely related to FAK, which regulates synapse function and plasticity in the mouse hippocampus by mediating dendritic spine remodeling.

**Methods.** To specifically analyze Pyk2 at the postsynaptic level, we developed a multi-compartmental microfluidic device that isolates synapses of primary neurons. The device employs microchannels of varying length, thus permitting axons and dendrites, or only axons, emanating from distant chambers, to reach the so-called synapse chamber. The synapse chamber is directly accessible to introduce toxic oligomeric Amyloid- $\beta$  (A $\beta$ ), a hallmark of AD, or potential therapeutic compounds. The synapse chamber is also connected to a fourth chamber, where Chinese Hamster Ovary (CHO) cells over-expressing wild-type APP or APP with London mutation are cultured. CHO cell secretion provides long-term exposure to pathologically-relevant levels of A $\beta$ , thus mimicking disease conditions.

**Results.** Preliminary data obtained from microfluidic cultures suggest that both synthetic and secreted A $\beta$  decreases synaptic connectivity. Phospho-Pyk2 (Tyr402) puncta localize to postsynaptic densities and is associated with synapses resistant to A $\beta$  oligomer toxicity, which affects the relative localization of Homer with respect to Synaptophysin, postsynaptic and presynaptic markers, respectively.

**Discussion.** Experiments where we selectively under- or over-express Pyk2 in postsynaptic neurons to dissect its role in synapse plasticity and failure are under way.

## 25 The LKB1 - NUA1 kinase pathway controls axonal metabolic remodeling in developing cortical neurons

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The growth and branching of the axon is a highly compartmentalized cellular process involved in the

formation of long-range synaptic connections. The precise regulation of the cellular mechanisms underlying axonal morphogenesis is essential to the formation of functional neuronal networks whose disruption is linked to socially-devastating neurodevelopmental disorders. We previously identified a two kinases signaling pathway including the tumor suppressor LKB1 (STK11) and the AMPK-related kinase NUA1 (ARK5) and controlling terminal axon branching in mouse cortical neurons through the control of mitochondria trafficking. This study raised a question pertaining to the local function of mitochondria in the developing axon and the molecular link with collateral branching. Here we focused on the metabolic activity of mitochondria in the developing axon at distinct stages of axonal development. We observed that the inactivation of LKB1 or NUA1 impairs mitochondria function and ATP concentration in the axon. Through seahorse analyses, we observed a dose-dependent reduction in mitochondrial respiration, but not glycolytic capacity, in NUA1 deficient neurons. We subsequently used Chromophore Assisted Light Inactivation (CALI) of mitochondria to correlate branch formation and stabilization with the local presence of functional mitochondria. Finally we developed strategies to upregulate mitochondrial metabolism and observed that metabolic rescue is sufficient to rescue axonal branching in NUA1 deficient neurons. All together our results indicate that a local, mitochondrial-dependent remodeling of the metabolic homeostasis is an important step for axon morphogenesis.

## 26

### Role of altered epigenetic regulations in cognitive deficit of Huntington's disease mice

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Huntington's disease (HD) is a genetic neurodegenerative disorder affecting primarily the striatum, and characterized by motor, cognitive and psychiatric symptoms. Altered H3K27 acetylation (H3K27ac), a target of CBP histone acetyltransferase, and impaired transcription in HD striatum correlate with the progression of behavioral deficits, including cognitive symptoms. However, causative roles of epigenetic and transcriptional mechanisms in HD remain unclear. Here we examined behavioral and molecular consequences of treating HD R6/1 transgenic mice with an activator of CBP, the compound CSP-TTK21. Specifically, R6/1 mice were treated with CSP-TTK21 from presymptomatic to symptomatic stages, through intraperitoneal injections. The effect of CSP-TTK21 on memory was assessed using a new aquatic navigation test, the double-H maze, which allows assessing striatum- vs hippocampus-dependent memories (e.g. procedural vs spatial memories, respectively). R6/1 mice treated with CSP-TTK21 used a procedural memory to solve double-H

behavioral task, like WT mice, but in contrast to control R6/1 mice, which used a spatial memory. Furthermore, transcriptomic analyses using RNAseq showed that CSP-TTK21 normalized the expression of subsets of deregulated genes in R6/1 striatum. Specifically, up-regulated genes in R6/1 striatum, reflecting energy and/or proteotoxic stress, were decreased in the striatum of treated R6/1 mice. Surprisingly however, CSP-TTK21 did not increase the expression of striatal identity genes, which associate with decreased H3K27ac and are down-regulated in R6/1 striatum. Our results suggest that CSP-TTK21 ameliorates striatum-dependent cognitive function of HD mice, improving striatal metabolism and/or stress resistance, but not rescuing striatal identity.

## 27

### Association of a History of Child Abuse With Impaired Myelination in the Anterior Cingulate Cortex: Convergent Epigenetic, Transcriptional, and Morphological Evidence.

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Child abuse (CA) has devastating and long-lasting consequences, considerably increasing the lifetime risk of negative mental health outcomes. Yet the neurobiological processes underlying this heightened vulnerability remain poorly understood. We investigated the hypothesis that epigenetic, transcriptomic, and cellular adaptations may occur in the anterior cingulate cortex as a function of CA. Postmortem brain samples from human subjects and from a rodent model of the impact of early-life environment were analyzed. The human samples were from depressed individuals who died by suicide, with or without a history of CA, as well as from psychiatrically healthy control subjects. Genome-wide DNA methylation and gene expression were investigated using reduced representation bisulfite sequencing and RNA sequencing, respectively. Cell

# Molecular mechanisms to pathogenesis

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type-specific validation of differentially methylated loci was performed after fluorescence-activated cell sorting of oligodendrocyte and neuronal nuclei. Differential gene expression was validated using NanoString technology. Finally, oligodendrocytes and myelinated axons were analyzed using stereology and CARS microscopy.

A history of CA was associated with cell type-specific changes in DNA methylation of oligodendrocyte genes and a global impairment of the myelin-related transcriptional program. These effects were absent in depressed suicide completers with no history of CA, and they were strongly correlated with myelin gene expression changes observed in the animal model. Furthermore, a selective and significant reduction in the thickness of myelin sheaths around small-diameter axons was observed in individuals with history of CA.

The results suggest that CA, in part through epigenetic reprogramming of oligodendrocytes, may lastingly disrupt cortical myelination, a fundamental feature of cerebral connectivity.

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## **The cerebellar pathophysiology of Autosomal Recessive Cerebellar Ataxia 2 (ARCA2)**

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ARCA2, the most common form of primary CoQ10 deficiencies, is caused by loss of function mutations in COQ8 gene (Lagier-Tourenne et al., 2008; Mollet et al., 2008). ARCA2 is characterized by ataxia, cerebellar atrophy, mental retardation, epileptic seizures, exercise intolerance, and CoQ10 deficiency (Lagier-Tourenne et al., 2008; Mollet et al., 2008). The main known function of COQ8A protein is to regulate CoQ10 biosynthesis. COQ8A is a part of a bigger complex whose organization has not been resolved yet and plays a crucial role in stabilizing and regulating it (He, Xie, Allan, Tran, & Clarke, 2014; Tauche, Krause-Buchholz, & Rödel, 2008; Xie et al., 2011). Using a *coq8a* <sup>-/-</sup> mice model, our group described that deletion of COQ8 protein affects the morphology and the function of the Purkinje cells (Stefely et al., 2016). These cells are appearing dark and shrunken, with affected membrane structures and altered electrophysiological activity. To understand the molecular pathways involved in this form of ataxia, we are using laser capture microdissections of the different cell layers of the cerebellum (Purkinje and Granule cell layers) for unbiased transcriptomic and proteomic approaches. In parallel, we are exploring specific candidates which their dysregulation has been already validated, in order to understand their contribution to the pathology. So far, we found that the glutamatergic

neurotransmission and the Golgi apparatus are affected. These results are interesting since the involvement of both has been very well described to be a primary cause of different forms of ataxias.

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## **Behavioral pattern separation deficits have a different origin in a mouse model of Alzheimer's disease and in aged mice**

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Performance in separating overlapping memories is thought to rely on a pattern separation computational process. Older adults show reduced performance in pattern separation demanding recognition tasks using similar objects or object locations. Alzheimer patients also show marked deficits at a very early stage when the medial temporal lobe begins to shrink. This is consistent with several studies suggesting that pattern separation performance depends on the integrity of the dentate gyrus (DG)-CA3 region and its cortical inputs from the temporal lobe. Animal studies further suggest a role for adult-born DG neurons. In a pattern separation task based on subtle changes in object location, we showed a progressive loss of performance between the age of 7 and 21 months in C57BL/6J mice. In the APP SWE model of Alzheimer's disease, performance drops rapidly between 3 and 4 months of age. Brain levels of amyloid peptide are known to increase around this age in APP SWE mice. We hypothesized that pattern separation deficits in APP SWE mice and in aged mice had different origins. Accordingly, chronic treatment with m266 (antibody against amyloid peptide, gift from Boehringer Ingelheim) completely rescued pattern separation performance in APP SWE mice, whereas a deep deficit remained in aged C57BL/6J mice. Preliminary results suggest that performance improvement in APP SWE mice was not mediated through a beneficial effect on quantitative aspects of DG neurogenesis. Our ongoing studies focus on functional activation of neuronal populations thought to participate in pattern separation. Grant from Association France Alzheimer and Groupe Intériale.

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## **Anti-FGFR3 antibodies induce neuronal cell death and NMDA and AMPA receptors expression through MAP kinase pathway and optineurin-mediated autophagy**

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Dysimmune sensitive neuropathies (SSN) was characterized by neuron cell death in dorsal root ganglia



(DRG). We have recently identified FGFR3 antibodies which recognized the intracellular tyrosine kinase domain (TRK) of FGFR3 as a biomarker of a SSN subset patients. We submitted mice cortical neurons cultures to different concentration of a rabbit polyclonal antibody recognizing the FGFR3 TRK domain. FGFR3 antibody induced neuron cell death in a dose dependent manner. The main downstream pathway associated with FGFR3 signaling is the RAS/MAP kinase pathway. In order to decipher molecular mechanism involved in neuronal death induced by FGFR3 antibodies, we submitted neuron cultures to FGFR3 antibodies with and without the presence of the p38 MAPK inhibitor or the ERK1/2 MAPK inhibitor. The expression of FGFR3, NR1, NR2A, NR2B subunit of NMDA receptor and GLUR1, GLUR2 subunit of AMPA receptor were analyzed by RT-qPCR. FGFR3 antibodies treatment increased FGFR3 receptor, NMDA receptor subunits and AMPA receptor subunits expression and this increase was prevented by ERK1/2 or P38 MAPK inhibitor. Treatment of neurons culture cells by Dovinitib, a FGFR3 kinase inhibitor, showed the same profil expression compared to neurons submitted to FGFR3 antibodies. These results suggest that cytotoxicity induced by FGFR3 antibodies increases NMDA and AMPA receptor expression through FGFR3 tyrosine kinase site blocking and RAS/MAP kinase pathway activation. Internalization of certain antibodies enhanced autophagy. We analyzed several autophagy markers expression. We showed that optineurin expression increased in neurons culture submitted to FGFR3 antibodies and this increase was prevented by ERK1/2 and P38 MAPK inhibitor.

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#### Lis1 stem cell mechanisms contributing to cortical malformations

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Human cortical malformations are associated with perturbations of progenitor proliferation, neuronal migration and/or differentiation. Cortical precursors include apical radial glial cells which have processes that connect both the pial and ventricular surfaces, intermediate progenitors and basal radial glial-like cells (bRGs), generally only possessing a basal process. The latter, abundant in primate brains, contribute to the development of gyri and sulci. We study LIS1, coding for a dynein regulator, which is mutated in lissencephaly (smooth brain) and microcephaly in humans. LIS1 was shown to be both important during cell division and neuronal migration. The goal of this work is to investigate the role of Lis1 in bRG-like cells, by first enriching them in the mouse embryonic brain. These can be amplified by the overexpression of TBC1D3, coding for a signaling protein. We overexpressed TBC1D3 in wild-type mouse brain using

in utero electroporation which induced the apparition of Pax6+ bRG-like cells. Similar experiments are now being performed in Lis1 mutant mice. The quantity, morphology and function of mutant bRG-like cells, as well as their progeny, will be assessed using immunohistochemistry and videomicroscopy. Lis1's binding to partners such as Dynein, Nde1 and Ndel1 will also be studied in these cells. These experiments are performed in the framework of an Eranet Neuron project, also exploring the role of wild-type and mutant LIS1 in human cortical progenitors in in vitro models. These combined analyses will shed further light on the role of this lissencephaly gene in bRGs, critical for cortical development.

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#### Exogenous recombinant FUS is able to accumulate in cortical neurons in mouse brain

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Amyotrophic Lateral Sclerosis (ALS) is a neurodegenerative disease which affects primarily upper and lower moto-neurons. 5 major genes for the pathology are: TARDBP, FUS, SOD1, TBK1 and C9ORF72. ALS cases show typical proteinopathy with TDP-43 (encoded by TARDBP gene) aggregates as the major lesion found. In ALS-FUS cases, the FUS protein is cytoplasmically mislocalized and forms aggregates. Recent pathological work suggested that TDP-43 aggregates propagate through monosynaptic tracts from motor cortex to subcortical regions. No evidence that such spreading of protein aggregates occurs in vivo has been provided. Furthermore, there exists, to our knowledge, no evidence of FUS proteinopathy propagation. We produced recombinant FUS-GFP protein that formed insoluble FUS-GFP fibrils after 3 days of incubation at room temperature. Stereotaxic injections of minute amounts of recombinant FUS-GFP in the cerebral cortex of wild type mice demonstrated that these fibrils persisted at injection sites at least thirty days post injection. Here we will describe the fate of these recombinant proteins in the mouse cortex as well as in the hippocampus at 3 and 30 dpi. Importantly, similar results were obtained in wild type mice and in knock-in mice expressing a truncated, partially cytoplasmic endogenous FUS [1]. We are currently exploring whether exogenous FUS recruits endogenous murine FUS in aggregates.

[1] Scekic-Zahirovic J, Oussini HE, Mersmann S, et al. Motor neuron intrinsic and extrinsic mechanisms contribute to the pathogenesis of FUS-associated amyotrophic lateral sclerosis. Acta Neuropathol. 2017 Jun;133(6):887-906.

# Molecular mechanisms to pathogenesis

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## Hippocampal IL-33, deleterious role in cognitive processes associated with neuroinflammatory context amplification

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IL-33, an IL-1 family member, is highly expressed in healthy brain. Extensively described in many neuropathologies, IL-33 has been suggested as a pro- or anti-inflammatory cytokine depending of the model studied. The duality of its effects still misunderstood and controversies. We showed recently in experimental cerebral malaria (ECM) induced by *Plasmodium berghei* Anka, the deleterious role of IL-33 (Reverchon et al, 2017). Indeed, we demonstrated that IL-33 mediated an early and endogenous neuroinflammatory context in the hippocampus, inducing cognitive defects, prior to peripheral immune T cell response and Blood Brain Barrier leakage. We highlighted the IL-33 pathway ability to orchestrate microglia and oligodendrocytes responses, with IL-1 $\beta$  and IL-33 production respectively. To better understand the role of IL-33, in ECM and especially in other neuropathologies, we addressed the role of IL-33 per se in neuroinflammation and cognition. We showed that intra-hippocampal exogenous IL-33 induced a defect in long-term memory, while short-term memory locomotion or anxiety, were spared. These results were associated with a strong IL-1 $\beta$  expression that subsides 48 hours after IL-33 administration, while control mice showed an inflammatory resolution. Moreover, we observed a microgliosis in the hippocampus and analyzed a specific reactive morphological state after IL-33 administration. These findings suggested that hippocampal IL-33-induced a pro-inflammatory, neurotoxic context 'responsible' for a specific cognitive impairment and opened new perspectives to understand its duality.

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## Investigating a causative role for cellular senescence in Fetal Valproate Syndrome

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Valproic acid (VPA) is a drug used to treat epilepsy, bipolar disorder and migraines. However, exposure during pregnancy is associated with an increase in a spectrum of birth defects, referred to as Fetal Valproate Syndrome (FVS). This can include neural tube defects such as spina

bifida or exencephaly, cleft lip, developmental delay, microcephaly and autism. However, the mechanisms by which VPA causes these disorders remains unclear. Several studies have shown that VPA possesses histone deacetylase (HDAC) inhibition activity, thereby activating aberrant transcription. Furthermore, treatment of cells in culture with VPA has been linked to decreased proliferation, increased apoptosis and senescence. Cellular senescence is a form of irreversible cell cycle arrest that has long been associated with cancer and aging. More recently however, the accumulation of senescent cells has been causatively linked with many adult-onset diseases, including osteoarthritis, atherosclerosis, Parkinson's and others. However, to date, senescence has not been linked to the etiology of developmental birth defects. Here we will present our ongoing efforts that make the first association of the induction of cellular senescence with neurodevelopmental defects. To address this, we have established the mouse model reproducing FVS in the embryo, and have identified the induction of many markers of senescence, including senescence-associated beta-galactosidase (SA-B-gal) activity, cell-cycle inhibitor expression and senescence-associated cell-secretion signatures. In addition, we will present our ongoing efforts to recapitulate the phenotype through genetic manipulation of the senescence machinery. Together, our preliminary data suggests a causative link between cellular senescence and developmental birth defects.

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## Parvalbumin interneurons of visual primary sensory cortex in adult mice express Acan and several other genes involved in the making of the PeriNeuronal Net (PNN).

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The PeriNeuronal Net (PNN) in the brain is a specialized extracellular matrix structure forming a mesh-like lattice surrounding neuronal cell bodies. It is found in most areas of the brain. It has been shown to enwrap synaptic terminals synapsing onto cell bodies, and could function as a "fence" blocking movements of pre- and post-synaptic proteins. During brain development, the formation of PNN is associated with the end of the critical period of plasticity. Proteins of PNN are four proteoglycans: aggrecan (Acan), brevican (Bcan), neurocan (Ncan) and versican (Vcan). They include two hyaluronan and proteoglycan link proteins: (Hapln1,4) and one tenascin (Tnr). Polysaccharides of PNN are hyaluronan- and chondroitin-sulfate formed by an array of enzymes encoded by Has1-3, Chst1-15, Csgalnact1-2 and St6galnac1-6.

The present work investigates expression of genes previously implicated in the formation of PNN around parvalbumin (PV) interneurons. We examined the Allen Institute single cell transcriptomics dataset

containing 14301 cells isolated from the primary visual cortex of 56-day old mice (Tasic et al., BioRxiv, 2017, doi:https://doi.org/10.1101/229542) for the expression of PNN genes. Among the 5759 GABAergic neurons, 21% were PV interneurons which could be separated by their expression profiling in 8 clusters. One of these clusters, Pvalb-Tppg (trophoblast glycoprotein), was composed of 391 cells, all expressing Pvalb and 55% expressing Acan, which was restricted to Pvalb-expressing neurons. The other proteoglycans Bcan and Ncan were expressed in most of the cells including glia. Vcan and Tnc were barely detected in PV interneurons. Hapln1 was expressed in most classes of interneurons and glia. Hapln4 and Tnr were expressed in most of the cells except glia. In conclusion PNN genes, including the following polysaccharide-synthesis genes Has1,3; Chst1,2,7,10-12; Csgalnact2; St6galnac2-6 are expressed in PV interneurons while Csgalnact1 and Chst15 are not. Mice KO for these latter key enzymes in the synthesis of chondroitine-sulfate have a prolonged critical period.

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## Effects of early methyl donor deficiency on the ontogeny and the plasticity of hypothalamic networks and energy homeostasis

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The anatomical and functional development of the central nervous system requires the temporal expression of a neurogenic program. Hypothalamic synaptogenesis and maturation occur during the perinatal period. Integration of peripheral signals (Ghrelin, Leptin...) is essential during development for the functional implementation of the hypothalamus regulating energy homeostasis. If it does not occur correctly, there is a disruption of the production of neuropeptides (NPY, AgRP...) that will definitely affect the neuronal projections of the arcuate nucleus to the hypothalamic areas expressing neuropeptide receptors. Previous work in our laboratory has shown that gestational methyl donor (vitamins B9-B12) deficiency (MDD) induced persistent growth retardation and altered brain development. We aimed to assess whether maternal deficiency alters the plasticity of the hypothalamic networks. We also investigated the effects of folate (B9) supplementation during the perinatal period on growth retardation in MDD rats. In addition, the consequences of folate deficiency were studied on two cell lines of hypothalamic embryonic neurons: mHypoE46 (mouse) and rHypoE11 (rat).

Folate deficiency in the cell lines either repressed or stimulated the expression of genes of hypothalamic receptors (NPYR, Ghrelin GHSR, Insulin R, glucocorticoid GR, Leptin R) and neuropeptides (NPY, POMC, AgrP, Ghrelin). These results were confirmed in the animal model, whereas folate supplementation during the

perinatal period improved body weight and restored Ghrelin, Leptin and PYY plasma levels that were affected by gestational deficiency.

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## Regulation of maternal vasoactive intestinal peptide (VIP) levels effect on corticogenesis

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The vasoactive intestinal (neuro)peptide (VIP), produced in placental t-lymphocytes, is involved in the regulation of growth and embryonic development during the early stages of neurogenesis. Several studies have shown that VIP blockade by IP injection of receptor VIP antagonist to pregnant female during early neurogenesis causes cognitive deficits in offspring. However little is known regarding how environmental conditions impact the production of VIP. Here we investigated the role of maternal stress on VIP deficient mice. Compared to WT adults, offspring from VIP null and heterozygous mice display a reduction in cortical thickness and surface area and corpus callosum thickness. This reduction was enhanced when maternal stress was applied during early neurogenesis. Moreover, the effect of VIP levels on the reaction to stress was also characterized through measurements by mass spectrometry of corticosterone levels at both acute and chronic conditions highlighting a susceptibility of the VIP null mice to stress. These results provide a basis for the link between the effect of external stress and VIP levels on neurogenesis.

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## TESTING FOR SYNERGY BETWEEN LOSS AND GAIN OF FUS FUNCTION IN CAUSING MOTOR NEURON DEGENERATION

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FUS is an RNA-binding protein involved in the regulation and transport of proteins from the nucleus to the cytoplasm. Mutations in this gene have been linked to ALS with early onset and short life expectancy. Mutations in the

# Molecular mechanisms to pathogenesis

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FUS gene disrupt FUS nuclear localization and the most severe FUS mutations lead to the C-terminal truncation of the protein thereby deleting the nuclear localization sequence. The analysis of the pathophysiological mechanisms of FUS-ALS is complicated by the severe toxicity of FUS overexpression, and the tight mechanisms of autoregulation of FUS protein levels. To overcome these issues, we have generated and characterized conditional knock-in mice expressing mislocalized cytoplasmic FUS. Using these mice, we have shown that complete FUS cytoplasmic mislocalization leads to motor neuron degeneration, while loss of FUS does not, thus demonstrating that the full toxicity mediated by this mutant truncated FUS requires it to be present in the cytoplasm. To determine whether loss of nuclear FUS contributes to motor neuron degeneration, we crossed our knock-in mice to transgenic mice expressing the human FUS gene (either wild type or carrying an ALS-linked R521H mutation). Both wild type and ALS-linked mutant of FUS rescue the lethality of homozygous knock-in mice expressing cytoplasmically localized FUS. Histological and molecular characterization of these compound transgenic mice are ongoing. These studies have important consequences for potential therapeutics targeting the FUS gene.

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## **BIN1 and MAPT overexpression exacerbates cognitive dysfunction in a mouse model for late-onset Alzheimer's disease**

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**Aim:** While early onset Alzheimer is due to genetic mutations, the etiology of Late Onset Alzheimer Disease (LOAD) remains unclear. GWAS identified BIN1 as a risk factor for LOAD, and accordingly, BIN1 is overexpressed in LOAD brains, and Amphiphysin 2 (encoded by BIN1) directly interacts with the MAP-tau protein. This study aimed to investigate the physiological impact of BIN1 overexpression in tauopathy mouse model with particular attention to Alzheimer phenotypes.

**Methods:** We generated mice overexpressing human BIN1 (TgBIN1), and crossed them with a model overexpressing human MAPT (TgTAU/TgBIN1). Novel object recognition (NOR) was used to study short term memory, and we performed histological analysis to follow the neurodegenerative processes. Additional molecular and cellular experiments were carried out to investigate the pathomechanism of neurodegeneration.

**Results:** TgTAU mice display NOR defect from nine month, and TgTAU/TgBIN1 mice already at 3 months of age. In vivo and ex vivo characterization in TgBIN1 mice revealed structural reticulum abnormalities, and we identified an interaction of Amphiphysin 2 with RTN4/NogoA, a key regulator of endoplasmic reticulum shape. In accordance,

we also found a higher RTN4/NogoA expression level in TgTAU/TgBIN1 brain as well as in LOAD patients.

**Conclusion:** Our results show that the overexpression of BIN1 worsen short term memory defects correlated to TAU overexpression. BIN1 overexpression has an impact on reticulum shape and is responsible for the alteration of neuronal architecture.

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## **THE CRYM-CREERT2 MOUSE LINE TO STUDY THE ROLE OF CORTICOSPINAL MOTOR NEURONS IN ALS**

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While evidence of combined degeneration of spinal and bulbar motoneurons together with corticospinal motor neurons (CSMN) is required to diagnose Amyotrophic Lateral Sclerosis (ALS), preclinical studies have so far mostly left aside the CSMN and their contribution to ALS onset and progression. This seeming disinterest may arise from a lack of tools to selectively label CSMN. To start deciphering the role of CSMN in ALS, we generated a Crym-CreERT2 mouse line, in which the inducible CreERT2 recombinase gene is knocked-in within the endogenous Crym locus, downstream of the gene coding sequence. Crym gene was selected for its almost exclusive expression within the cortical layer V where CSMN reside, and its absence of expression from the spinal cord or the skeletal muscle. The design of the mouse line enables to maintain the endogenous Crym expression, while driving a spatial and temporal expression CreERT2 similar to that of Crym.

To test whether Crym-CreERT2 expression reproduces the endogenous Crym expression, we first revealed CRE protein expression by immunofluorescence, and demonstrated its co-localization with typical cortical layer V markers. Next, we crossed the Crym-CreERT2 mice with the Rosa-tdTomato reporter mice. Within the cerebral cortex, tdTomato-positive cells were detected only in Tamoxifen-injected animals and recapitulated Crym expression. TdTomato-positive cells co-expressed typical corticofugal markers such as CTIP2. Importantly, no tdTomato expression could be detected in the spinal cord of Tamoxifen-injected animals.

Altogether, the data suggest that the Crym-CreERT2 mice represent a potentially useful tool to start investigating the role of CSMN in ALS.

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## **Extensive exploration of a novel rat model of Parkinson's disease using partial 6-hydroxydopamine lesion of dopaminergic neurons suggests new therapeutic approaches**

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Parkinson's disease (PD) is characterized by the degeneration of dopaminergic (DA) neurons constituting the nigrostriatal pathway. Neuroinflammation, related to microglial activation, plays an important role in this process. Exploration of animal models of PD using neuroimaging modalities allows to better understand the pathophysiology of the disease. Here, we fully explored a partial lesion model in the rat in which 6-hydroxydopamine was unilaterally delivered in 3 sites along the striatum. The degenerative process was assessed through in vivo Positron Emission Tomography imaging and in vitro autoradiographic quantitation of the striatal dopamine transporter (DAT) and immunostaining of tyrosine hydroxylase (TH) in the substantia nigra (SN). The microglial activation was studied through in vitro autoradiographic quantitation of the 18 kDa translocator protein (TSPO) in the striatum and CD11b staining in the SN. In addition, a targeted metabolomics exploration was performed in both these structures using mass spectrometry coupled to HPLC. Our results showed a reproducible and moderate decrease in the striatal DAT density associated with a reduction in the number of TH-positive cells in the SN, reflecting a robust partial degeneration of nigrostriatal DA neurons. In addition, we observed strong microglia activation in both the striatum and SN ipsilateral to the lesion, highlighting that this partial degeneration of DA neurons was associated with a marked neuroinflammation. Our metabolomics studies revealed alterations of specific metabolites and metabolic pathways such as carnitine, arginine/proline and histidine metabolisms. These results bring new insights in the PD mechanism knowledge and new potential targets for future therapeutic strategies.

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### Deregulation of tubulin polyglutamylation induced neurodegeneration in mice and humans

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Microtubules are key components of the neuronal cytoskeleton and play pivotal roles in many aspects of neuronal physiology. How different functions of microtubules are regulated in neurons is one of the important questions in neuronal cell biology. One emerging regulator are tubulin posttranslational modifications (PTMs). Here we demonstrate that one of these PTMs, polyglutamylation, plays a key role in neurons, and its deregulation induces neurodegeneration.

Polyglutamylation is generated by glutamylases from the TLL family and removed by deglutamylases from the CCP family. In mice lacking CCP1, polyglutamylation is strongly increased in the cerebellum, and Purkinje cells die rapidly. When we invalidate one of the key tubulin polyglutamylases in brain, TLL1, in Purkinje cells of CCP1-KO mice, Purkinje cells survive. Thus, the degeneration of these neurons in CCP1-KO mice is directly and cell-autonomously caused by tubulin hyperglutamylation.

Because only some regions of the central nervous system of CCP1-KO mice are affected by neurodegeneration, we additionally inactivated a second deglutamylase, CCP6. This caused widespread hyperglutamylation and neurodegeneration, demonstrating that excessive polyglutamylation can cause degeneration of many different types of neurons.

We further discovered biallelic variants of CCP1 in human infantile-onset neurodegeneration and demonstrate that those variants lead to hyperglutamylation in patients, demonstrating that hyperglutamylation is a valid pathogenic mechanism of human neurodegeneration. Considering that CCP1-KO mice replicate the symptoms of the human patients, our results suggest that hyperglutamylation could be involved in a range of neurodegenerative disorders, and that manipulation of enzymes controlling this PTM could become a valid therapeutic option.

# Towards developing therapeutical approaches

Les posters doivent rester affichés les deux jours mais il est demandé aux auteurs d'être présents à leur session uniquement.  
Le numéro mentionné avant le titre du résumé correspond au numéro du panneau poster.

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## Neuroprotective effect of grape seed and skin extract on dopaminergic neurons against 6-OHDA cytotoxicity.

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Parkinson's disease is a neurodegenerative disorder characterized by selective loss of midbrain dopaminergic (mDA) neurons in the substantia nigra pars compacta. Our goal was to evaluate the neuroprotective effect of Vitis vinifera red grape seed and skin extract (GSSE) in a model of Parkinson's disease. GSSE is very rich in phenolic compounds such as flavonoids, anthocyanins, catechins and stilbenes which are distributed in the pulp, seeds, and leaves of the fruit. GSSE is known for its antioxidant properties and has shown beneficial effects against oxidative injury in different organs, such as in kidneys, liver, heart and brain. In this study, we revealed the effect of GSSE on survival of dopaminergic neurons in primary culture in a model of the neurotoxin 6-hydroxydopamine (6-OHDA) which mimics the degeneration of dopaminergic neurons observed in the Parkinson disease. We found that GSSE was effective in protecting dopamine neurons from 6-OHDA toxicity by reducing the apoptosis, the level of reactive oxygen species (ROS) and by reducing inflammation. Furthermore, we found that GSSE treatment was efficient to protect neuronal loss and improve motor function in an in vivo 6-OHDA model of Parkinson's disease (PD). GSSE notably restored the level of antioxidant enzyme superoxide dismutase 1 (SOD1). Altogether our results show that GSSE acts at multiple levels to protect dopamine neurons from degeneration in PD models.

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## Dyneinopathies: from patient fibroblasts to human iPSC-based therapy

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DYNC1H1 gene encodes the heavy chain of cytoplasmic dynein 1, a large multi-subunit motor complex. Human heterozygous DYNC1H1 mutations were identified in neurodevelopmental disorders including brain malformations (MCD) and peripheral neuropathies (SMA-LED). Dynein is responsible for a variety of cellular functions, including neuron-specific functions. Nevertheless, it is unknown whether these distinct phenotypes arise from gain of function, hemizygous loss of function, or a combination of both. Our group has collected the largest cohort of patients with DYNC1H1 mutations, half of them with SMA-LED and the remaining with MCDs with or without peripheral neuropathies. Our preliminary results in fibroblasts derived from patients with either SMA-LED or MCD showed that (i) DYNC1H1 mutations reduced the retrograde, but not anterograde transport of lysosomes in both dyneinopathies, (ii) the compaction of the Golgi apparatus was significantly reduced in SMA-LED fibroblasts at basal level, and Golgi recompaction was not completed in some MCD fibroblasts after depolymerization. Altogether these results suggest that DYNC1H1 mutations may have different effects on dynein functions, resulting in SMALED or MCD. Our objective is to shed light on the different roles of DYNC1H1 and to rescue the biochemical pathways responsible for neurological disorders leading to MCD and SMA-LED. To do so we hold Loa mutant mice with human SMA-LED phenotype and we are currently developing induced pluripotent stem cells (iPSC) derived from DYNC1H1 patients that will be further differentiated into cerebral organoids and motor neurons, a crucial step toward the great promise of human iPSC-based cell therapy aiming to tackle dyneinopathies.

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## Inhibition of B-Glucocerebrosidase activity preserves motor unit integrity in a mouse model of amyotrophic lateral sclerosis.

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Multiple lines of evidence suggest a link between sphingolipid metabolism and the physiopathology of amyotrophic lateral sclerosis [1]. Glucosylceramide, a sphingolipid, is the precursor of gangliosides. And degradation of glucosylceramide is performed by GBA1 and GBA2, two beta-glucocerebrosidases. Our previous

results have shown a benefit for SOD1G86R mice after inhibition of glucosylceramide degradation [2]. Ambroxol hydrochloride is a safe and generic drug known to inhibit GBA2 activity. In SOD1G86R mice, an animal model of amyotrophic lateral sclerosis, ambroxol preserves neuromuscular junctions from denervation, delays disease onset, improves motor function and preserves motor neurons from degeneration. Taken together, our results suggest that GBA2 is a therapeutic target for ALS and that its inhibition preserves motor unit integrity in the SOD1G86R mice. In addition, our results suggest that ambroxol hydrochloride is a candidate drug for this devastating disease.

[1] Henriques et al. 2017 *Frontiers in Mol neuroscience*

[2] Henriques et al. 2017 *Scientific reports*

## 46

### Characterization and optimization of VHH directed against the Tau protein

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Tau is an intrinsically disordered neuronal protein playing a fundamental role in the regulation of tubulin polymerization and microtubule stability. Beyond its major physiological activity, Tau is also involved in a group of diseases called Tauopathies, including Alzheimer disease (AD). It is the principal aggregated component of the paired helical filaments (PHF) that form the intracellular neurofibrillary tangles in AD.

In this context, our goal is to develop and characterize VHHs targeted against the longest isoform of Tau (441 amino-acids). VHH are also called single domain antibodies. They are constituted of an unique chain which corresponds to the variable heavy chain from the Immunoglobulin G. They are produced as recombinant proteins and can easily be modified or optimized for specific uses.

In partnership with Hybrigenics Company, we obtained VHHs against Tau from a synthetic library. The recognition site of these VHHs on Tau was determined using NMR chemical shift perturbation experiments using 2D spectra. VHHs sharing the same CDR3 but with various CDR1 and CDR2 recognize strictly the same epitope. Affinity parameters characterizing the interaction were evaluated using SPR. The majority of determined Kd between Tau and the different VHH are within the micromolar range. Optimized VHHs were obtained by yeast double hybrid. We confirmed that optimized VHHs have a lower Kd than the WT counterpart.

These results validate the use of these VHHs for in vitro studies and they will be now tested in cellular and mice models to explore the mechanisms underlying the Tau pathology.

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### Establishing drug discovery models in proteinopathies ? A focus on Tau

Das Does, G., François, A., Ribeiro, N., Machado, P., Pasteau, V., Cistarelli, L., Rollin-Jego, G., Challal, S., Hugot, A., Gandon, M-H., Llopis, K., Touzard, M., Hubbard, J., Schenker, E., Jeggo, R.

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Among the known proteinopathies, Alzheimer's disease is the most prominent neurodegenerative disorder, showing abnormal accumulation of misfolded B-amyloid and Tau proteins. For a disease modifying approach targeting the pathological processes by which Tau drive Alzheimer's disease, different in vitro and in vivo models have been set-up in our laboratory to provide the necessary tools for drug discovery.

In vitro, the neuroblastoma cell line, SH-SY5Y, expressing a doxycycline-inducible human wild-type (hWT) Tau (isoform 2N4R), was used to investigate markers of tau pathology. In parallel, mouse (hWT tau knock-in) primary neuronal cultures were transduced with lentivirus, harboring the mutant 2N4R P301S Tau. Both approaches showed hyperphosphorylation and abnormal folding of tau, as well as oligomer formation.

Furthermore, we are developing zebrafish models for stable expression of hWT or mutated variants of Tau. Plasmids were designed for their overexpression in zebrafish motor neurons (with and without fluorescent reporters) and biochemical, imaging and electrophysiological based approaches are used to characterize the lines.

Finally, in mice, the adeno-associated viral 9 (AAV9) vector was used to obtain rapid expression of hWT and mutated P301S Tau in the hippocampus of 12 months-old animals. Using optimized injection conditions, a rapid, robust, and reproducible model for tau expression was obtained and is under characterization for oligomer formation, aggregation and seeding and potentially associated behavioral deficits.

The different approaches described herein aim at developing a battery of early drug discovery tests, adaptable to the field of proteinopathies and able to provide rapid insight into target engagement and pathway involvements.

# Towards developing therapeutical approaches

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## Resveratrol maternal supplementation: a neuroprotective role in neonatal hypoxia-ischemia brain damages

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Neonatal hypoxia-ischemia (HI) is a major cause of perinatal mortality and chronic disability. Hypothermia is the only therapy but numerous baby do not respond to it. Brain lesions are partly induced by the reduction of O<sub>2</sub> and substrate intakes. Trans-resveratrol (RSV) plays a neuroprotective role in various neurodegenerative pathologies and in CNS energy metabolism (glycolysis). Our aims was to study the effects of different pattern of RSV maternal supplementation on brain lesions after neonatal HI episode in rats.

Methods: 4 groups of pregnant Wistar females were used: CT-Group [drinking water]; rsvGL-Group [water+RSV 0.15mg/kg/day during last wk gestation+first wk lactation]; rsvG-Group [water+RSV during last wk gestation] and rsvL-Group [water+RSV during first wk lactation]. P7 pups underwent an HI lesion (right carotid artery ligation + hypoxia: 8%O<sub>2</sub>, 92%N<sub>2</sub>, 2h). Brain lesions, ADC and FA were evaluated (P7, 9, 30), in vivo, by MRI (4.7T). Behavioural tests were performed (P8toP45).

Results: HI induced cerebral lesions (39.77±2.80% of brain, at P7), motor and cognitive deficits. 48h after HI, a neuroprotective effect of RSV maternal supplementation was measured in pups lesion for rsvGL-Group (lesion size at P9: 18.29±2.71%, 18.96±2.93%, 16.24±3.63% Vs 8.51±2.15% of brain, for Ct-Group, rsvG-Group, rsvL-Group Vs rsvGL-Group, respectively). At P30, rsv-GL and rsv-L presented the smallest lesion sizes when compared to the other groups. They also had the best behavioral score.

Conclusion: RSV maternal supplementation during lactation or gestation/lactation but not during gestation alone would be neuroprotective in neonatal HI context. The curative effect of RSV maternal supplementation has to be evaluated.

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## Serotonin 5-HT7 receptor: identification of new potent ligands with original pharmacological properties

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Serotonin receptors are highly heterogeneous and are classified in seven classes of receptors (5-HT<sub>1</sub>-5-HT<sub>7</sub>) that comprise at least 15 subtypes. With the exception of the 5-HT<sub>3</sub> receptor which is a ligand-gated ion channel, all others are G-protein coupled receptors (GPCRs) with each family sharing structural, pharmacological and transductional characteristics. 5-HT receptors are known to be implicated in the regulation of several psychiatric and neurological disorders. Furthermore, recent data support the idea that 5-HT<sub>7</sub> receptors agonists might have also potential therapeutic interest for the treatment of chronic pain. However, most available 5-HT<sub>7</sub> agonists have a low selectivity and/or an insufficient bioavailability. Our goal is to design selective and potent 5-HT<sub>7</sub> agonists and to characterize their pharmacological profile in *in vitro* assays. Pharmacomodulation studies performed at ICOA in Orleans, associated with pharmacological studies conducted at the institute of Pharmacology in Krakow, allow us to select new potent 5-HT<sub>7</sub> compounds. To understand the molecular bases of their effects, we evaluated their intrinsic activities in various functional assays. We defined their agonist, inverse agonist or antagonist activity by measurement of cAMP levels using BRET or TR-FRET methods in HEK cells stably expressing 5-HT<sub>7</sub> receptor. We also investigated their ability to activate others 5-HT<sub>7</sub> receptor signaling pathways (ERK activation, calcium mobilization, recruitment of arrestins...). Our results demonstrate that some molecules can engage different transducer-effector systems. These results can be related to preliminary results showing their anti-nociceptive effect *in vivo* in mice. These mechanisms may underlie their benefic effect on pain state.

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## ROLE OF THE TAIL OF THE VENTRAL TEGMENTAL AREA ON SYMPTOMS OF PARKINSON'S DISEASE

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In the past decade, a new mesopontine structure was described in the rat brain: the tail of the ventral tegmental area (tVTA) or rostromedial tegmental nucleus (RMTg). This new brain region attracted a lot of attention as it



densely innervates the VTA and substantia nigra (SNc), providing the most potent inhibitory GABA control of dopamine systems. It has also been showed by our team that a lesion of the tVTA can compensate the rotation bias induced by amphetamine injections observed with a unilateral lesion of the SNc. My project, conducted in the rat, explores the impact of such tVTA lesion in a model of Parkinson's disease. In rats with bilateral 6-hydroxydopamine lesion in the SNc, we tested the influence of a tVTA lesion on motor coordination deficits and on non-motor symptoms (anhedonia and mechanical hyperalgesia). Our results show that SNc-lesioned animals exhibits motor and non-motor deficits that can be compensated by the co-lesion of the tVTA.

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## **ER-stress regulation and effect of Guanabenz in primary cortical neurons injured with A $\beta$ 1-42 peptide, an in vitro model of Alzheimer's disease.**

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Alzheimer disease (AD) affects mainly people over the age of 65, suffering from progressive decline in memory, thinking, language, and learning capacity. Increasing evidence points to soluble oligomeric A $\beta$  (A $\beta$ O) aggregates/protofibrils as putative toxic species in AD pathogenesis, through a deficiency in protein homeostasis. Endoplasmic reticulum (ER) stress is involved in many neurodegenerative disorders and is caused by misfolded proteins and protein aggregates. ER stress activates an unfolded protein response (UPR) through PERK, ATF6 and/or IRE1 $\alpha$  proteins.

Here, we aimed to study the ER signalling pathways in primary cortical neurons injured with A $\beta$ 1-42 peptide (an in vitro model of AD). UPR pathways (with CHOP, PERK, eIF2 $\alpha$ , ATF6 and IRE1 $\alpha$ ) were carefully studied after 4h, 8h, 16h or 24h exposition to the amyloid peptide. In addition, the neuronal survival, the integrity of the neurite network, as well as the accumulation of hyperphosphorylated Tau, were investigated in absence and in presence of Guanabenz (5 $\mu$ M), a well-known inhibitor of eIF2 $\alpha$  dephosphorylation.

Our results show that ER stress and the UPR are upregulated in cortical neurons after A $\beta$ 1-42 application and that Guanabenz, via the activation of PERK pathway, was able to prevent neuronal loss.

Altogether, these results strongly suggest that ER stress and UPR have a key role in the physiopathology of Alzheimer's disease.

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## **Striatal regulation of cholesterol metabolism by CYP46A1 is associated with multiple benefits in Huntington's disease knock-in mice**

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Huntington's disease (HD) is an autosomal dominant neurodegenerative disease caused by abnormal polyglutamine expansion in huntingtin protein. Recently, altered brain cholesterol homeostasis has been implicated in HD pathogenesis. Our team made the original observation that expression level of CYP46A1, the rate-limiting enzyme for the degradation of cholesterol in the brain, is decreased in putamen extracts of post-mortem patients and in the striatum of an HD knock-in (KI) mouse model, the zQ175 mice. We restored CYP46A1 expression into the striatum of zQ175 mice, at a pre-symptomatic stage, using an AAV-mediated approach. A battery of behavioral and neuropathological tests was performed, showing an improvement in locomotor activity and in histological landmarks. Indeed, immunohistochemical studies showed a decrease in aggregates number and an increase of striatal projection neurons soma size. Cholesterol homeostasis was restored with an increase of 24S-OHC, the product of cholesterol degradation associated to a regulation of cholesterol synthesis. Complementary studies (RNAseq, spine density) showed that CYP46A1 improves the synaptic connectivity and the glutamatergic transmission. Additionally, we showed that CYP46A1 increases BDNF vesicle axonal transport and TrkB receptor endosome trafficking in HD cortico-striatal connections reconstituted in microfluidic devices. Finally, we report that CYP46A1-regulated sterols increased the clearance of mHTT aggregates through proteasome and autophagy machineries. In the present project, we showed that CYP46A1 restoration alleviates the pathological phenotype of zQ175 mice. Our results provide a comprehensive model for the mechanisms by which CYP46A1 striatal restoration may promote brain

# Towards developing therapeutical approaches

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homeostasis, opening a novel therapeutic avenue based on promoting compensation of HD phenotype.

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## Molecular bases of Fragile X syndrome: function of FMRP and test of a new therapeutic target in the Fmr1-KO murine model

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The Fragile X syndrome (FXS) is the most common inherited cause of intellectual disability and autism. FXS is caused by an expansion of CGG repeats in 5' UTR region of the FMR1 gene that leads to its transcriptional silencing and the absence of the RNA-binding protein FMRP. The loss of FMRP results in an excessive neuronal protein translation with abnormal synaptic plasticity. Understanding how the lack of FMRP leads to synaptic alterations is a major issue to better define the molecular basis of FXS and identify a treatment.

We recently showed that FMRP is mainly associated with one unique mRNA in cortical neurons: diacylglycerol kinase kappa (Dgkk), a master regulator controlling the balance between the signaling lipids diacylglycerol (DAG) and phosphatidic acid (PA). In absence of FMRP, the translation of Dgkk is impaired in neurons, leading to an excess of DAG and a lack of PA. Dgkk silencing in a WT mouse is sufficient to recapitulate FXS phenotypes and Dgkk overexpression corrects abnormal dendritic spines in Fmr1-KO neurons. Based on these data, we tested the targeting of DGK by pharmaceutical and gene-therapy approach as potential therapeutic mean. In cells, PPAR-gamma agonist pioglitazone corrects excessive eIF4E phosphorylation and protein translation. In Fmr1-KO mice, pioglitazone rescues memory defect, stereotypies, social interactions and macroorchidism. Altogether our data suggest that DGK activity is a promising therapeutic target for FXS. The ability of adeno-associated (AAV) viruses expressing a truncated FMRP-independent-Dgkk transgene to rescue FXS phenotypes is also being tested in vitro and in vivo.

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## Pain secrets: new 5-HT7 receptor ligands with anti-nociceptive properties.

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Pain control is mediating by the serotonin receptor family, among them the 5-HT7 receptor is of special interest being expressed within the spinal dorsal horn. Recent data support the idea that 5-HT7 receptor agonists might have potential therapeutic interest for the treatment of chronic pain. Nevertheless, mechanisms involved by 5-HT7 receptor activation in the peripheral versus central nervous system remain poorly understood. Our goal is to design selective and potent 5-HT7 agonists and to characterize their pharmacological profile both in vivo and in vitro.

Pharmacomodulation studies (team of Pr Guillaumet and Suzenet ICOA, Orléans) associated with pharmacological studies (team of Pr Bojarski PANS, Poland) allow us to select new potent and selective 5-HT7 compounds. Considering the 5-HT7 receptor implication in pain, we investigated the anti-nociceptive properties of these compounds in pain behavioral test. We showed that systemic administration of the new 5-HT7 ligands decreased pain behavior. Interestingly, in the formalin pain model, whereas 5-CT, a reference agonist, decreased nociceptive behavior for both early and the late phases after injection of formalin, a new compound decreased pain only in the second phase, suggesting selective roles of this 5-HT7 compound in spinal levels. To understand this selective implication in pain control, we are performing in vitro and ex vivo approaches to determine cellular and molecular mechanisms involved through the 5-HT7 receptor stimulation. These new ligands, should allow us to further characterize the dual action of 5-HT7 receptor at the periphery versus the central nervous system in pain condition.

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## Lactate: a new hope in therapy for neonatal hypoxia-ischemia.

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Neonatal hypoxia-ischemia (HI) is a major cause of perinatal mortality and chronic disability. Hypothermia is the only therapy but numerous baby do not respond to it. Brain lesions are partly induced by the reduction of O<sub>2</sub> and substrate intakes. Glucose is the preferential

# Towards developing therapeutical approaches

substrate for brain but glucose injection after HI could not decrease the brain damages. Based on the astrocyte-neuron lactate shuttle hypothesis, our aim was to study the effect of lactate administration on brain lesion in the context of perinatal HI in rat.

**Methods:** P7 pups underwent an HI lesion (right carotid artery ligation+hypoxia: 8%O<sub>2</sub>, 92%N<sub>2</sub>, 2h). Six groups were studied: Ct-Group, HIL-Group (lactate injection before hypoxia), HIL-Group (lactate injection after HI), HI3L-Group (3 lactate injections: 3h, 24h and 48h post-HI), HILO-Group (lactate+oxamate injection, LDH inhibitor), and HI3P-Group (3 pyruvate injections). Brain lesions, ADC and FA were evaluated (P7, P9, and P30), in vivo, by MRI (4.7T). Behavioral tests were performed. **Results:** HI induced cerebral lesions (39.77±2.80% of brain, at P7), motor and cognitive deficits. Brain damages were not diminished by pyruvate or lactate+oxamate injections (lesion size at P7: 43.23±4.60 and 46.04±2.40% for HI3P-Group and HILO-Group, respectively). After one lactate administration, a significant curative neuroprotection was measured compared to the other groups (lesion size at P7: 31.64±2.83 vs 28.27±2.10% for HIL and HIL-Group, respectively). A daily injection of lactate was even more neuroprotective (lesion size at P9: 10.38±3.85 vs 1.15±0.52% for HIL and HI3L, respectively).

**Conclusion:** Lactate represents a new therapeutic hope against brain damages in neonatal HI.

our efforts to design, optimize and implement antisense oligonucleotides (ASOs) - short synthetic single stranded nucleic acids - as therapeutic agents against genetically defined neurodegenerative diseases such as C9ORF72 related ALS-FTD.

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### **Nucleic Acid Therapeutics for Genetically Defined Neurodegenerative Diseases**

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Nucleic acids as therapeutic agents are emerging as a new class of drug discovery platform for pharmacologically “undruggable” target. They are also of particular interest when modulation of expression of one specific gene is thought to be therapeutically desirable.

Expansion of intronic G4C2 repeats in the C9ORF72 gene is the most common genetic cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD), two devastating adult-onset neurodegenerative disorders. Disease mechanisms include a toxic gain of function of the repeat containing RNA and the production of aberrant dipeptide repeats (DPR) proteins, advising that the G4C2 repeats might represent a valid target for nucleic acid-based therapy.

In the present study, using C9-ALS/FTD patient derived cells and C9ORF72 BAC transgenic mice, we report









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