27th Friedrich Merz Visiting Professorship Award Symposium

November 22, 2017
Frankfurt am Main

Prof. Aaron D. Gitler
Department of Genetics
Stanford University

MERZ

GOETHE UNIVERSITÄT FRANKFURT AM MAIN

Dear colleagues,

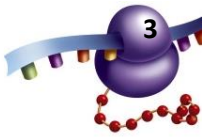
With great pleasure, we welcome you to our Frankfurt symposium on “Motor neuron and cerebellar degeneration: causal preventive treatment soon?”.

We honor the achievements of Prof. Aaron Gitler from Stanford University, with support from the Friedrich Merz Visiting Professorship that is being awarded in 2017 for the 27th time.

Among the neurodegenerative disorders of old age, Alzheimer’s and Parkinson’s disease are more frequent in the population, but exceptional advances in the past years have been made of motor neuron and cerebellar degenerations. We understand the mechanisms much better, and are successful with neuroprotective therapy.

The role of RNA dynamics in health and disease was particularly elucidated by Prof. Aaron Gitler. His discoveries have started with yeast genetics and have reached patient genetics / pharmacology in very few years. It is now probable that routine hospital treatment of ALS / SCA mutation carriers will include intrathecal administration of antisense oligonucleotides in the near future.

Interventional neurology at the prodromal stage has been a dream, and may now become reality. To discuss the opportunities, complexities and dangers of these developments during a full day, international experts now convene in Frankfurt with the generous support of Merz Pharmaceuticals.



We are looking forward to a lively exchange of arguments and hope to create an environment that fosters new ideas, stimulating the next generation of experiments and researchers!

Mit herzlichem Glückwunsch an den Preisträger –

Prof. Dr. Georg Auburger
Goethe University Frankfurt

Dr. Stefan Albrecht
Merz Pharmaceuticals

Symposium Venue:
Building 22, Lecture Hall 2
Goethe University Hospital
Theodor Stern Kai 7
Frankfurt am Main

Symposium Chairs:

Prof. Dr. Helmuth Steinmetz
Chair of Neurology Department
Goethe University Hospital, Frankfurt
Prof. Dr. Ivan Dikic
Chair of Biochemistry Institute II
Speaker of SFB117 on Selective Autophagy
Goethe University Hospital, Frankfurt
Prof. Dr. Harald Schwalbe
Institute for Organic Chemistry and Chemical Biology
Speaker of SFB902 on RNA Regulation
Goethe University, Frankfurt
Prof. Dr. Jochen Roeper
Chair of Neurophysiology Institute
Goethe University Hospital, Frankfurt

Symposium Organization:

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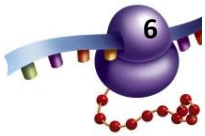
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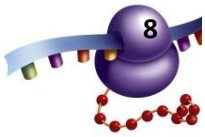
SCIENTIFIC PROGRAM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08:00 – 08:30 Registration

08:30 – 08:45 Welcome Address

08:45 – 09:00 Poster Slam

Session 1: Patient analyses reveal disease and modifier genes

Chair: Helmuth Steinmetz

09:00 – 09:30 Olaf Riess
Dissection of the pathogenesis of SCA3 using animal models

09:30 – 10:00 Ulrich Müller
ALS, a disorder within the spectrum of neurodegenerative diseases

10:00 – 10:30 Brunhilde Wirth
SMA protective modifiers help to unveil the cellular mechanism and to develop combinatorial therapies

10:30 – 11:00 Luis-Enrique Almaguer-Mederos
Genome-wide modifier gene screen in ataxia patients

11:00 – 11:30 Coffee break

Session 2: Disease models and mechanisms

Chair: Ivan Dikic

11:30 – 12:00 Michael Sendtner
Altered axonal actin dynamics in Spinal Muscular Atrophy and Amyotrophic Lateral Sclerosis

12:00 – 12:30 Dieter Edbauer
Early role of dipeptide repeat proteins in C9orf72 ALS

12:30 – 13:00 Dorothee Dormann
Molecular Mechanisms of ALS/FTD – from nuclear transport defects to protein aggregation

13:00 – 14:00 Lunch

14:00 – 14:30 Poster Session

Session 3: Emerging role of RNA

Chair: Harald Schwalbe

14:30 – 15:00 Georg Auburger
Ataxin-2 and RNA damage

15:00 – 15:30 Aaron Gitler
New insights and therapeutic targets for motor neuron disease

15:30 – 16:00 Michaela Müller-McNicoll
Nucleo-cytoplasmic shuttling and selective mRNA export activities of SR proteins in health and disease

16.00 – 16:30 Coffee break

Session 4: Towards functional understanding

Chair: Jochen Roeper

16:30 – 17:00 Jochen Weishaupt
The contribution of TBK1 to ALS an FTD

17:00 – 17:30 Simon Alberti
Mechanisms of quality control ensuring RNP granule functionality and dynamics

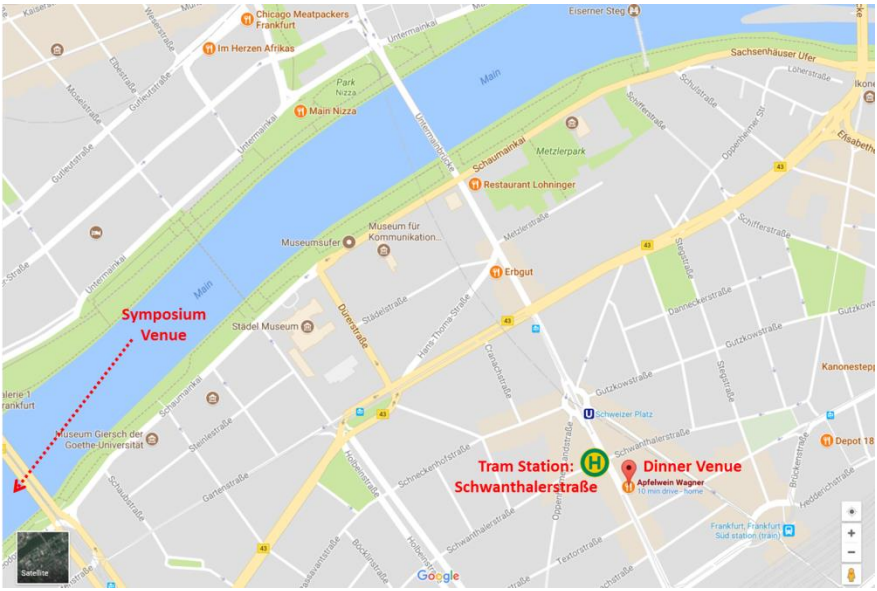
17:30 – 18:00 Adriano Aguzzi
Protein aggregation and pathways of toxicity

18:00 – 18:30 Georg Auburger & Aaron Gitler
Concluding Remarks

19:30 – Dinner – Traditional Frankfurt Cuisine
Apfelweinwirtschaft Adolf Wagner

Apfelweinwirtschaft Adolf Wagner
Schweizer Str. 71, 60594 Frankfurt am Main
http://www.apfelwein-wagner.com/

Take **Tram 15** from Universitätsklinikum to Schwanthalerstraße



SPEAKERS & ABSTRACTS

Deciphering the pathogenesis of SCA3 using animal models

Prof. Dr. Olaf Riess

Department of Medical Genetics, University of Tübingen

Spinocerebellar ataxia type 3 is caused by a CAG repeat expansion in the MJD1 gene leading to an expanded polyglutamine repeat in the encoded protein. Interestingly, whereas the normal protein is predominantly in the cytoplasm of the cell, the aberrant protein is aggregated in the nucleus. Using extensive protein cleavage experiments we could identify that Calpains play a dominant role in ataxin3 cleavage and that prevention of cleavage in vitro and in vivo leads to reduced intranuclear inclusions, reduced cell death and in mouse models to a milder phenotype. In contrast, activation of Calpains increases cleavage, aggregation and cell death. The transport of the cleaved protein is actively supported by nuclear transport proteins like KPN3A. Inhibiting KPN3A leads to reduced aggregation of cleaved atx3 in the nucleus and to milder phenotype in Drosophila and mice. These data indicate that as well cleavage as nuclear transport play a role in the pathogenesis of SCA3 and its inhibition may become interesting targets for treatment strategies.

ALS, a disorder within the spectrum of neurodegenerative diseases

Prof. Dr. Ulrich Müller

Institute of Human Genetics, University of Giessen

Amyotrophic lateral sclerosis was first described by Jean-Martin Charcot in 1869 as a distinct disease entity that is characterized by upper and lower motor neuron degeneration. Symptoms of frontotemporal dementia (FTD) were first recognized by Arnold Pick in 1892 in a patient with progressive cognitive impairment and bouts of aggression and in similarly affected patients thereafter (Pick disease, now bv-FTD). In 1911 Alzheimer recognized distinct spherical argyrophilic inclusions in neurons of the frontal lobes of patients with Pick disease (bv-FTD).

Almost 100 years after these initial discoveries it has been recognized that both disorders overlap by clinical and neuropathological criteria. Clinical overlap was most convincingly shown in familial cases with autosomal dominant transmission. Mutations in identical genes can cause either familial ALS or familial FTD. Furthermore, there are families in whom some members present with symptoms characteristic of ALS, other members of the same family have symptoms of ALS plus behavioral problems and still others present as typical FTD. These findings clearly demonstrate that the same cause, i.e. a mutation in identical genes can cause ALS, FTD and mixed forms. Furthermore, neuropathological findings such as ubiquitin, tau, TDP-34 and SOD1 positive inclusion bodies can be found in both ALS and FTD.

Mutations in more than 22 genes have been identified in familial ALS-FTD. More commonly mutated genes include SOD1 (encoding superoxide dismutase 1, TARDBP (encoding TDP43, transcription

of RNA activating/TAR DNA binding protein), and C9ORF72. The mutations in C9ORF72 are expansions of GGGGCC repeat units (700-2400 fold). Most significantly, C9ORF72 mutations have – in addition to ALS and FTD - also been found in patients with other neurodegenerative syndromes, including Alzheimer´s disease, Parkinson´s disease, corticobasal degeneration, and ataxia.

In the common forms of ALS that have a multifactorial etiology, analyses of genome wide association studies (GWAS) in large cohorts of patients with ALS and FTD also established that both disorders are at the extreme ends of a disease spectrum. As part of a large consortium (Karch et al., in press) we analyzed the shared genetic risk between ALS and other neurodegenerative disorders. Single nucleotide polymorphisms (SNPs) that increase risk in ALS were found to be shared with FTD, FTD-TDP43, progressive supranuclear palsy (PSP) and corticobalsal degeneration (CBD). Five SNPs were jointly associated with increased risk for ALS and FTD (closest genes: C9ORF72 and UNC13A, encoding Protein Unc-13 Homolog A that plays a role in neurotransmitter release at synapses), ALS and FTD-TDP43 (closest gene: C9ORF72), ALS and PSP (closest genes: MOBP encoding Myelin-Associated Oligodendrocyte Basic Protein and NSF encoding N-Ethylmaleimide Sensitive Factor, Vesicle Fusing ATPase). Pathway analysis showed that shared risk genes are enriched for pathways involving neuronal function and development. Finally, the microtubule-associated protein tau, i.e. MAPT H1 haplotype known to increase risk for FTD, PSP, CBD, AD, and PD was also found to increase ALS risk.

In conclusion, clinical, neuropathological, and genetic studies establish that ALS is not a distinct nosologic entity but shares many characteristics with other neurodegenerative disorders.

Protective modifiers help to unveil the cellular mechanism and to develop combinatorial therapies in spinal muscular atrophy

Prof. Dr. Brunhilde Wirth

Institute of Human Genetics, Center for Molecular Medicine Cologne and Institute for Genetics, University of Cologne

Spinal muscular atrophy (SMA), a devastating neuromuscular disorder, affects around 1:6000 people, every 1:35 is carrier in Europe and it is the most frequent genetic cause of infant death. Recently, the first SMA therapy based on antisense oligonucleotides, namely SPINRAZA, has been FDA- and EMA-approved. SPINRAZA restores the suboptimal full-length SMN2 transcript expression and elevates SMN protein level. SMN is crucial for all cells but particularly for motor neurons and neuromuscular junctions (NMJ). In the most severe type I - accounting for 60% of SMA-affected individuals, who carry only two SMN2 copies - the elevated SMN level may be still insufficient to restore motor neuron function lifelong. We show that genetic SMA modifiers might provide additional functional support at MN and NMJ level.

Here I will talk about two human SMA protective modifier, identified in asymptomatic SMN1-deleted individuals carrying either 3 or 4 SMN2 copies. Plastin 3 (PLS3), an F-actin binding and bundling protein rescues SMA by overexpression and Neurocalcin delta (NCALD), a neuronal calcium sensor protein counteracts SMA by suppression. We found that both, PLS3 overexpression or NCALD suppression protect against SMA across species including zebrafish and mice. Moreover,

both modifiers show a rescuing effect using combinatorial therapies – low dose SMN-ASO and PLS3 overexpression or NCALD suppression - in severely-affected SMA mice. Lastly, both modifiers hinted us towards the main cellular mechanism in SMA, which we believe is impaired endocytosis, and which is restored by both modifiers.

Genome-wide modifier gene screen in ataxia patients

Luis-Enrique Almaguer-Mederos, PhD

Center for Research and Rehabilitation of Hereditary Ataxias, Holguín, Cuba

Experimental Neurology Department, Goethe University Frankfurt

Among the cerebellar degenerative processes with autosomal dominant inheritance, Spinocerebellar Ataxia type 2 (SCA2) is the second most frequent disease world-wide. It is particularly frequent in Cuba, reaching a prevalence of up to 130 patients per 100,000 residents in some districts of Holguín province. The manifestation age varies widely from the neonatal period until senescence, and the disease-triggering unstable expansion of the poly-glutamine domain with the Ataxin-2 (ATXN2) protein explains most of this variance, but not all.

In order to identify the crucial modifier genes that exacerbate or alleviate the disease progression and modulate the manifestation age considerably, our team and its collaborators have collected over 400 SCA2 patients in Cuba plus almost 200 SCA2 patients in Turkey and Germany. As crucial phenotype we ascertain the age at onset, in addition we document clinical ataxia scales, the neurophysiological profile, MRI spectroscopy data and blood biomarkers. In collaboration with the Institute of Neurology in London and the Sanger Center in Cambridge, a genome-wide assessment of single-nucleotide-polymorphisms, their association with expansion instability and with parameters of the clinical course will be

carried out. Promising modifier-effects will be validated in the latest generation of SCA2 mutation carriers in Holguín/Cuba, with follow-up studies over the coming decade.

We hope that the identification of modifier targets and the implementation of pioneer antisense-nucleotide approaches in patients and in presymptomatic mutation carriers will enable us to alleviate or prevent the neurotoxic process within the next few years.

Altered Axonal Actin Dynamics in Spinal Muscular Atrophy and Amyotrophic Lateral Sclerosis

Prof. Dr. Michael Sendtner

Institute of Clinical Neurobiology, University of Wuerzburg

Loss of motor endplates, axonal degeneration and cell death are characteristic pathological features of motor neuron diseases. Gene defects in familial amyotrophic lateral sclerosis (ALS) and spinal muscular atrophy (SMA) point to distinct pathophysiological pathways. These include disturbed RNA metabolism, toxicity from dipeptides generated by RAN translation from the C9ORF72 intronic hexanucleotide repeat expansion, but also loss of function which could be relevant for synaptic and axonal degeneration. A prominent phenotype of motor neurons from a mouse model of SMA is reduced axon elongation in the absence of altered motor neuron survival. In order to study the role of altered axonal RNA transport in Smn deficient motor neurons, we used compartmentalized microfluidic chambers to investigate the axonal mRNA content of cultured motor neurons. Smn depletion produced a large number of transcript alterations. On the axonal side, transcripts associated with axon growth and synaptic activity, including those coding for α-, ß- and γ-actin were downregulated. These alterations correlate with disturbed axonal actin dynamics which could contribute to axon degeneration in spinal muscular atrophy.

Similar axonal defects were also observed in motor neurons with reduced expression of C9ORF72. In order to characterize alterations in axon elongation in C9ORF72 depleted motor

neurons in more detail, we determined the interactome of C9ORF72 in motor neurons and found that C9ORF72 is part of a complex with cofilin and other actin binding proteins. Phosphorylation of cofilin was enhanced in C9ORF72-depleted motor neurons, in patient-derived lymphoblastoid cells, iPS cell–derived motor neurons and post-mortem brain samples from ALS patients. C9ORF72 modulates the activity of the small GTPases Arf6 and Rac1, resulting in enhanced activity of LIM-kinases 1 and 2 (LIMK1/2). This correlates with reduced axonal actin dynamics in C9ORF72-depleted motor neurons. Dominant negative Arf6 rescues this defect, suggesting that C9ORF72 acts as a modulator of small GTPases in a pathway that regulates actin filament dynamics.

Early role of dipeptide repeat proteins in C9orf72 ALS/FTD

Prof. Dr. Dieter Edbauer

Cell Biology of Neurodegeneration, German Center for Neurodegenerative Diseases (DZNE), Munich

Expansion of the (GGGGCC)n repeat in C9orf72 is the most common cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). The repeat RNA is translated in all reading frames into five dipeptide repeat (DPR) proteins by an unconventional mechanism. It is still unclear how toxicity of the repeat RNA and the DPR proteins are driving neurodegeneration in patients. To elucidate the role of DPR proteins in ALS/FTD, we generated cellular and animal models expressing the DPR proteins individually. Poly-GA, the most abundant DPR species in patient brains, is neurotoxic in vitro and in mouse models. Structural studies provide new insights into DPR toxicity. Immunoassays detect DPR proteins in the CSF of presymptomatic mutation carriers many years prior to disease onset. Together the data indicate that early DPR expression contributes to the prodromal symptoms and disease progression of C9orf72 patients.

Molecular mechanisms of ALS/FTD- from nuclear transport defects to protein aggregation

Dr. Dorothee Dormann

Department of Anatomy-Cell Biology, Ludwig-Maximilians-Universität München

Pathological protein aggregates are a central hallmark of all neurodegenerative diseases. In the related disorders ALS and FTD, the pathological aggregates consist mostly of the ubiquitous RNA-binding proteins TDP-43 or FUS. Both proteins are usually located in the nucleus, whereas in neurons and glial cells of ALS/FTD patients, they are partially lost from the nucleus and accumulate in large cytoplasmic inclusions. Which molecular defects cause TDP-43 or FUS mislocalization and aggregation in ALS/FTD patients and how we can possibly prevent or revert them are central questions that we try to address in my lab.

For FUS, we have successfully used cellular and in vitro models combined with neuropathological analysis of human post-mortem brains to identify key pathomechanisms that cause FUS mislocalization and aggregation in ALS and FTD patients: In ALS-FUS, genetic mutations in the nuclear localization signal (NLS) of FUS cause impaired binding to the nuclear import receptor Transportin. This impairs nuclear import of FUS and, upon cellular stress, favors recruitment of FUS into stress granules, where FUS aggregation may be promoted due to high local FUS concentrations. In FTD-FUS

patients, Transportin is aggregated and a post-translational modification of FUS, arginine methylation, is lost. Our unpublished data show that both Transportin and arginine methylation help to keep FUS soluble in the cytoplasm and prevent aberrant liquid-to-solid state transition and accumulation of FUS in stress granules. Our work suggests that certain binding proteins and post-translational modifications can modulate aberrant solidification of ALS/FTD-linked proteins and hence could potentially be targeted in new therapeutic approaches.

Ataxin-2 and RNA damage

Prof. Dr. Georg Auburger

Experimental Neurology Department, Goethe University Frankfurt

Ataxin-2 (ATXN2) depletion ensures nutrient storage, while its overactivity drives cell atrophy. Thus, unstable expansions of its polyglutamine domain with consequent accumulation of ATXN2 enhance the risk for motoneuron degeneration, cerebellar ataxia and Levodopa-responsive Parkinson's disease, while its deficiency is associated with obesity, insulin resistance and metabolic excess syndrome.

ATXN2 binds directly to RNA molecules occurs via its Lsm domain, and to poly(A) binding protein via its PAM2 motif. Periods of cell stress trigger its transcriptional induction and its relocalization from the ribosomal translation apparatus to cytosolic stress granules, where RNA folding undergoes a quality control.

We are currently studying the effects of ATXN2 dysfunction on other RNA-binding proteins (like TDP-43 from the nucleus, AHNAK, or PCBP2 during the formation of toxic aggregates) and on nutrient metabolism (like the myelin-neurite crosstalk and the leucine control of mTOR signaling). In addition, the position of ATXN2 within phosphorylation cascades from AMPK to PINK1 signaling is a primary interest. Finally, the rescue of diverse neuron populations from degenerative processes via depletion of ATXN2 and perhaps of ATXN2-like is crucial for preventive therapy of several age-associated brain atrophies.

New insights and therapeutic targets for motor neuron disease

Prof. Dr. Aaron Gitler

Department of Genetics, Stanford University

My goal is to discover the cellular and molecular mechanisms by which protein aggregates contribute to neurodegeneration and to harness these mechanisms to devise novel therapeutic strategies. We use the baker's yeast, Saccharomyces cerevisiae, as a simple, yet powerful, model system to study the cell biology underpinning protein-misfolding diseases, which include Alzheimer's disease, Parkinson's disease, and amyotrophic lateral sclerosis (ALS). We are focusing on the ALS disease proteins TDP-43 and FUS/TLS and have generated yeast models to define mechanisms by which these proteins cause ALS. Because these proteins aggregate and are toxic in yeast, we have used these yeast models to perform high-throughput genome-wide modifier screens to discover suppressors and enhancers of toxicity. Launching from the studies in yeast, we have extended our findings into animal models and even recently into human patients. For example, we discovered mutations in one of the human homologs of a hit from our yeast TDP-43 modifier screen in ALS patients. Mutations in this gene are relatively common (~5% of cases) making it one of the most common genetic risk factors for ALS discovered to date. These screens are also providing new and completely unexpected potential drug targets, underscoring the power of such simple model systems to help reveal novel insight into human disease.

Nucleo-cytoplasmic shuttling and selective mRNA export activities of SR proteins in health and disease

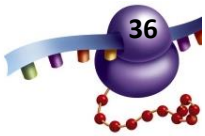
Jun. Prof. Dr. Michaela Müller-McNicoll

Institute of Cell Biology and Neuroscience, Goethe University Frankfurt

SR proteins are essential RNA binding proteins (RBPs) that shuttle continuously between the nucleus and cytoplasm and function in nuclear pre-mRNA processing, mRNA export and translation in the cytoplasm. Recently, it was shown that SRSF1, a prototypic member of the SR protein family, selectively binds and exports expanded repeat RNAs of the C9orf72 transcript to the cytoplasm where they are translated into toxic peptides. Blocking SRSF1-dependent nuclear export reduced cytoplasmic levels of expanded repeat RNAs and protected motor neurons in models of C9orf72 ALS (Hautbergue, 2017).

To investigate the shuttling and selective RNA export activities of SR proteins we developed a quantitative shuttling assay, which detects differences in nucleo-cytoplasmic shuttling among RBPs and their mutants (Botti, 2017). Moreover, to study changes in bound RNA targets across subcellular compartments, we developed fractionation iCLIP (Fr-iCLIP), in which chromatin, nucleoplasmic, cytoplasmic and polysomal fractions are prepared from UV-crosslinked cells and then subjected to iCLIP and deep sequencing (Brugiolo, 2017; Botti, 2017; Müller-McNicoll, 2016). We discovered that their shuttling capacities differ in pluripotent and differentiated cells,

identified amino acid residues that are required for shuttling and post-translational modifications of SR proteins that regulate their RNA binding and export activities. Our findings may help to better understand the molecular mechanisms underlying cytoplasmic RNA toxicity in ALS.



The contribution of TBK1 to ALS an FTD

Prof. Dr. Jochen Weishaupt

Neurology Department, Ulm University

Haploinsufficiency of the autophagy regulatory gene TBK1 has recently described as a cause for both ALS and FTD. Moreover, the genes coding for optineurin (OPTN) and p62 (SQSTM1), which are both substrates of TBK1, have also been shown to cause ALS/FTD when mutated. Additional ALS/FTD genes, for instance VCP and CHMP2B, are involved in vesicle trafficking and autophagy. Intact autophagic activity may thus control the level of aggregation-prone proteins, which aggregate and exert their toxicity and in a concentration-dependent manner. Similarly, mitophagy protects neuronal cells from defective mitochondria that represent a major oxidative threat to neuronal function. However, autophagy decreases with age, which could result in a dysbalance of protein and organelle homoeostasis late in life. Such conceptual or hypothesis-generating insights into ALS have been driven by the identification of TBK1, OPTN, C9ORF72 or SQSTM1 as ALS disease genes, discoveries that were already highly relevant regarding clinical genetic diagnostic and counseling. However, only the knowledge about the mechanistic role of these genes in the same pathway lead to novel concepts. Yet, although a network of functionally and genetically linked genes points to disturbed selective autophagy as an important biochemical and cell biological contributor to ALS/FTD pathogenesis, the knowledge regarding causative downstream sequelae of

TBK1, optineurin or p62 dysfunction is still very scarce. For example, besides its impact on autophagy, TBK1 is also a central regulator of inflammatory pathways, immune cells and possibly neuroinflammation. In this presentation, we exemplarily outline the current understanding of ALS-associated TBK1 mutations and consequent insights into ALS pathogenesis.

RNP granules: how they form, age and cause disease

Dr. Simon Alberti

Max Planck Institute of Molecular Cell Biology and Genetics, Dresden

My research group aims to elucidate the molecular principles underlying the spatiotemporal organization of the cytoplasm. We are particularly interested in understanding how the cytoplasm changes upon environmental perturbations and stress. Stressed cells undergo controlled changes on many levels to alter their physiology and metabolism. Many of these changes may directly result from alterations in the structure and organization of the cytoplasm. Indeed, our recent work shows that stressed cells form many membrane-less compartments such as RNP granules in the cytoplasm via a biophysical process known as phase separation. However, the initially beneficial ability to form compartments becomes detrimental with increasing age, because compartment-forming have a tendency to misfold and aggregate and thus are closely tied to aging and the pathogenesis associated with age-related diseases such as amyotrophic lateral sclerosis. Thus, recent efforts in the lab are focused on understanding the molecular links between membrane-less compartments such as RNP granules and age-related diseases.

Protein aggregation and pathways of toxicity

Prof. Dr. Adriano Aguzzi

Institute of Neuropathology, University Hospital of Zürich

Transmissible spongiform encephalopathies (TSEs) are neurodegenerative diseases of humans and many animal species caused by prions. The main constituent of prions is PrPSc, an aggregated moiety of the host-derived membrane glycolipoprotein PrPC. Prions were found to encipher many phenotypic, genetically stable TSE variants. The latter is very surprising, since PrPC is encoded by the host genome and all prion strains share the same amino acid sequence. Here I will review what is known about the infectivity, the neurotoxicity, and the neuroinvasiveness of prions. Also, I will explain why I regard the prion strain question as a fascinating challenge – with implications that go well beyond prion science. Finally, I will report some recent results obtained in my laboratory, which is attempting to address the strain question and some other basic issues of prion biology with a “systems” approach that utilizes organic chemistry, photophysics, proteomics, and mouse transgenesis.

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