BIOGRAPHICAL SKETCH

NAME: **Achsel, Tilmann**, Ph.D.

eRA COMMONS USER NAME:

POSITION TITLE: staff scientist

EDUCATION/TRAINING

INSTITUTION AND LOCATION	DEGREE	Completion Date MM/YYYY	FIELD OF STUDY
University of Würzburg, Germany	M.Sc.	09/1990	Chemistry
University of Würzburg, Germany	Ph.D.	03/1993	Biochemistry
University of Kyoto	Postdoc	12/1994	Mol Biology
University of Marburg, Germany	Postdoc	12/1999	Mol Biology

A. Personal Statement

Numerous genetic defects that cause neurological disorders affect genes with an obvious link to mRNA metabolism, indicating that post-transcriptional gene regulation is disturbed. Yet there are several distinct steps of post-transcriptional control, and in most cases, it is not possible to pinpoint the particular mechanism that is affected in the disease. Starting from the affected genes, we study the influence of the encoded proteins on the three major steps of post-transcriptional gene regulation - alternative splicing, translational control, and regulated mRNA decay. We look at candidate target mRNAs and also use transcriptomic approaches. These studies will not only enhance our understanding of the neuropathologies, but also give invaluable insights into post-transcriptional gene regulation in the mammalian nervous system.

B. Positions and Honors

Academic Appointments:

1999 – 2002 Staff scientist in the laboratory of Prof. R. Lührmann at the Max Planck Institute for Biophysical Chemistry, Göttingen, Germany.
Work on Sm/LSm proteins in mRNA silencing.

2003 – 2007 Group leader at the Department of Experimental Neurosciences, Fondazione Santa Lucia, Roma, Italy.
Work on mRNA metabolism in neurons, with a particular focus on the LSm proteins.

2008 – 2016 Project leader in the laboratory of Molecular Neurobiology,
Department of Molecular and Developmental Genetics, VIB, Leuven, Belgium.
Continuation of the projects started in Rome: LSm- and FMRP-regulated mRNA metabolism in neurons.

Since 2016 Staff scientist at the Department for Fundamental Neurosciences, University of Lausanne. Continuation of the projects: regulation of mRNA metabolism in neurons.

Honors:

- During my undergraduate studies (1985 to 1990), I was a fellow of the "Studienstiftung des Deutschen Volkes".
- My Diploma was awarded the faculty prize 1990-1991.
- The work for my PhD thesis was supported by a fellowship of the "Fonds der Chemischen Industrie".
- My PhD diploma was awarded the faculty prize 1992-1993.
- In 1993, I was awarded a "Studienabschluß-Stipendium" by the "Fonds der Chemischen Industrie"for excellence of my PhD thesis.
- During my stay in Japan, I was fellow of the Japan Society for the Promotion of Science (JSPS).
- From Feb. 1995 to Jan. 1996, I was research fellow of the Deutsche Forschungsgemeinschaft (DFG).

Scientific commitments:

Reviewer for the following journals: Molecular Cellular Biology, Nucleic Acids Research, Nature Neuroscience, PLoS

One, Neuroscience, BMC Cell Biology, Applied Environmental Microbiology. In addition, I reviewed ad hoc for Cell, Neuron, and Proc. Natl. Acad. Sci. USA.

Referee for the following funding agencies: AFM-Telethon (France), Agence Nationale de la Recherche (France).

C. Contribution to Science

Trained as molecular biologist and specialized in mRNA metabolism, I soon became interested in neurobiology because of the many genes that are involved in RNA metabolism and linked to neurological disease.

Fragile X Syndrome and Autism Spectrum Disorders (ASD). The Fragile X Syndrome is the most common hereditary cause of intellectual disability with a very high incidence in ASD. FMRP, the protein lacking in the Fragile X Syndrome, regulates mRNAs encoding key synaptic proteins and thus modulates synaptic morphology and function, as well as brain development. I have substantially contributed to the deciphering the mechanism of target recognition by FMRP (Zalfa et al., J. Biol. Chem. 2005; Lacoux et al., Nucleic Acids Res. 2012). One of the FMRP targets encodes N-cadherin, and its dysregulation in Fragile X mice causes alterations in cortical development that have long-lasting consequences (La Fata et al., Nat. Neurosci. 2007). Of note, lack of FMRP has important consequences specifically on striatal function and behavior (Mercaldo et al., Neuron 2023: see description of selected publications).

An important partner of FMRP is the Cytoplasmic FMRP-interacting protein CYFIP1, which is strongly linked to social disorders - ASD and schizophrenia. I made important contributions towards the molecular understanding of translation regulation by the FMRP/CYFIP1 protein complex, suggesting that CYFIP1 acts as a eIF4E-binding protein (Napoli et al., Cell 2008). CYFIP1 has a second role in actin polymerization, and we identified a conformational switch in the CYFIP1 protein that orchestrates the two functions to mediate spine plasticity (De Rubeis et al., Neuron 2013). Of note, Drosophila CYFIP1 regulates the expression of proteins involved in mitochondrial energy metabolism, with an important effect on GABAergic transmission (Kanellopoulos et al., Cell 2020: see selected publications).

Proximal Spinal Muscular Atrophy (SMA) is the selective degeneration of the alpha motor neurons in the ventral horn of the spinal cord. The disease is caused by insufficient supply of the SMN protein. At the molecular level, SMN catalyses the assembly of the seven Sm proteins onto the spliceosomal snRNAs. The Sm-snRNA complex is necessary for the stability, nuclear localisation and function of the snRNAs, and thus for pre-mRNA splicing. Alterations of pre-mRNA splicing patterns, however, cannot explain the disease. I had previously identified the closely related Like-Sm (LSm) proteins (Achsel et al., EMBO J. 1999, Ingelfinger et al., Nucleic Acids Res. 2002), which we showed to regulate the length of the poly(A) tail, thereby modulating mRNA translation and stability (Totaro et al., Nucleic Acids Res. 2011: see selected publications). Of note, the LSm proteins have a role in mRNA localization to the synapses (Di Penta et al., J. Cell Biol. 2009: see selected publications).

Another motorneuron disease with links to mRNA metabolism is the ***amyotrophic lateral sclerosis (ALS)***. The RNA-binding protein FUS is mutated in a significant subpopulation of patients with familial ALS. Interestingly, FUS-related proteins bind to spliceosomal snRNAs. We have shown that FUS binds to Sm-snRNA complexes, and this function is not compromised by the mutations. Instead, the mutations trap part of the spliceosomal Sm-snRNA complexes in the cytoplasm, which reduces their effective concentration in the nucleus and thus affects alternative splicing (Gerbino et al., Neurobiol. Dis. 2013). Overexpression of G4C2 repeat RNA is another, even more frequent, cause of ALS, but the pathological mechanism is disputed. We have implicated nuclear mRNA export (Rossi et al., J. Cell Sci. 2015), a finding that has been since replicated with major impact (Jovičić et al., Nat. Neurosci 2015; Zhang et al., Nature 2015; Freibaum et al., Nature 2016).

5 SELECTED PUBLICATIONS

(out of 60: https://www.ncbi.nlm.nih.gov/pubmed/?term=Achsel+T)

1. Mercaldo, V., B. Vidimova, D. Gastaldo, E. Fernández, A.C. Lo, G. Cencelli, G. Pedini, S. De Rubeis, F. Longo, E. Klann, A.B. Smit, S.G.N. Grant, **T. Achsel***, and C. Bagni*. 2023. Altered striatal actin dynamics drives behavioral inflexibility in a mouse model of fragile X syndrome. ***Neuron*** 111:1760-1775. *** Joint corresponding authors.**

   Characterization of the proteome associated with the glutamatergic synapses in Fragile X mice indicated a deficit in the attachment of the postsynaptic field to the actin cytoskeleton, specifically in the striatum. Further investigation showed a deficit in actin dynamics causing striatal inflexibilty.

2. Kanellopoulos, A.K., V. Mariano, M. Spinazzi, Y.J. Woo, McLean C., U. Pech, K.W. Li, J.D. Armstrong, A. Giangrande, P. Callaerts, A.B. Smit, B.S. Abrahams, A. Fiala, **T. Achsel**, and C. Bagni. 2020. Aralar Sequesters GABA into Hyperactive Mitochondria, Causing Social Behavior Deficits. ***Cell*** 180: 1178-1197.

   Mitochondrial activity in the neurons modulates GABA release; mitochondrial hyperactivity, which is often found associated with intellectual disability, thus creates an imbalance in the excitation/inhibition (E/I) ratio.

3. Rossi S., A. Serrano, V. Gerbino, A. Giorgi, L. Di Francesco, M. Nencini, F. Bozzo, M.E. Schininà, C. Bagni, G. Cestra, M.T. Carrì, **T. Achsel***, and M. Cozzolino*. 2015. Nuclear accumulation of mRNAs underlies G4C2 repeat-induced translational repression in a cellular model of C9orf72 ALS. ***J. Cell Sci.*** 128: 1787-1799. *** Joint corresponding authors.**

   Motorneuron diseases have strong genetic links to mRNA metabolism, but the precise step – processing, translation, or decay of the mRNAs – that is disturbed in the diseases is not known. Expansion of the G4C2 repeats in C9ORF72 is the major cause of ALS, and it is assumed that the G4C2-containing RNAs exert a toxic effect. Here, we show that expression of G4C2 repeat RNAs inhibits nuclear export of endogenous mRNAs, which has obvious implications on the expression of genetic programs.

4. Totaro, A., F. Renzi, G. La Fata, C. Mattioli, M. Raabe, H. Urlaub, and **T. Achsel.** 2011. The human Pat1b protein: a novel mRNA deadenylation factor identified by a new immunoprecipitation technique. ***Nucleic Acids Res.***, 39: 635-647.

   Because of the possible link of the LSm proteins to spinal muscular atrophy (SMA, see next publication), we were interested in studying how these proteins silence translation of their target mRNAs. We identified a new factor that associates with LSm proteins and targeted mRNAs and induces shortening of the poly(A) tail of the mRNAs, which reduces translation efficiency and can also mark the mRNAs for decay.

5. Di Penta, A., V. Mercaldo, F. Florenzano, S. Munck, M.T. Ciotti, F. Zalfa, D. Mercanti, M. Molinari, C. Bagni, and **T. Achsel**. 2009. Dendritic LSm1/CBP80-mRNPs mark the early steps of transport commitment and translational control. ***J. Cell Biol.*** 184: 423-435.

   Proximal spinal muscular atrophy (SMA) is caused by depletion of a factor, SMN, which is required for maturation of the spliceosomal snRNPs, as it assembles the seven Sm proteins onto the snRNAs. Depletion of SMN therefore lowers the concentration of the snRNPs but the resulting changes in (alternative) splicing have never been conclusively demonstrated to cause the disease. In addition to the Sm proteins, SMN binds the like-Sm (LSm) proteins. We were therefore interested if the LSm proteins have a role that is relevant for neuronal function. We show that binding of the LSm proteins in the nucleus selects mRNAs for transport into the dendrites; only upon synaptic stimulation, the LSm proteins dissociate from their targets, allowing translation.

D. Research Support

Research Support (2010-2018)

(listed is the funding that I received, and the duration):

- 2012. SMA Europe operating grant for the project “mRNA transport in SMA pathogenesis”. EUR 142.100 over two years.
- 2009. IWT project “Specific study of the molecular mechanisms of Spinal Muscular Atrophy and axonal mRNA transport”. One PhD position for four years.
- 2007. Partner of the renewed project “Aberrant mRNA processing – a common mechanism in the pathology of motor neuron diseases”, granted by the CARIPLO foundation; EUR 40.000 in two years.
- 2007. Partner of the network “Danno cellulare e recupero funzionale nel sistema nervoso centrale: Implicazioni per la neuroriabilitazione”, granted by the Italian Ministry of Health; EUR 50.000 in two years.
- 2006. Partner of the network “Molecular mechanism of synaptic plasticity and brain development” granted by the Italian Ministry of University; EUR 60.000 in three years.
- 2004. Partner of the project “Aberrant mRNA processing – a common mechanism in the pathology of motor neuron diseases”, granted by the CARIPLO foundation; EUR 50.000 in two years.
- 2003. “Eziologia della atrofia muscolare spinale”, granted by the Italian Ministry of Health; EUR. 50.000 in two years.
- 2003. “Studio delle variazioni del pattern di espressione dei geni associati alla atrofia spino-muscolare (SMA) (SMN and SIP1) in altre malattie del motoneurone”, granted by the Italian Ministry of Health; EUR 50.000 in two years.
- 2002. "Structure of the LSm complexes and their differential localisation in the cell", as part of the Sonderforschungsbereich 523 grant network. A PhD position was granted for two years.
- 2002. Partner of the project "Time- and space-resolved multi-parameter fluorescence detection", granted by the German Ministry for Science and Technology. EUR 310.000 in three years.