Symposium- Parallel Symposium SMA Physiopathology
• *Suzie Lefebvre (FRANCE)* • *Martine Barkats (FRANCE)* • *B. Kaspar*

Nuclear bodies and therapeutic targets in spinal muscular atrophy pathogenesis
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Mutations in survival motor neuron 1 (SMN1) gene lead to infantile spinal muscular atrophy (SMA). SMA is a genetic neurodegenerative disease characterized by the loss of spinal motor neurones and skeletal muscle atrophy. At present time, there is no cure for this devastating disorder. The SMN1 mutations associated with SMA are loss-of-function mutations, and there is a correlation between the severity of SMA disease and residual levels of SMN protein produced by the copy gene SMN2. The ubiquitously expressed SMN complex localizes in the cytoplasm and nucleus, where it concentrates in two types of nuclear structures called Gemini of Cajal bodies (gems) and Cajal bodies (CBs). Gems are often found to overlap with CBs, the compartments of small nuclear ribonucleoprotein particle (snRNP) maturation. Although the cytoplasmic function of SMN in splicing snRNP biogenesis is established, its role in the nucleus is not completely understood. It is of note that the loss of SMN from nuclear bodies correlates with disease severity in SMA and in some adult motor neuron disorders. These observations raise the possibility that a perturbation in nuclear SMN functions contributes to neurodegenerative diseases. Studying the regulatory mechanisms by which SMN is recruited to nuclear bodies, we found that SMN deficiency in fibroblast cells derived from SMA patients leads to a disrupted composition of CBs that can be modulated by small-molecule compounds. We have been using a combination of cell imaging screens, biochemistry, proteomics and RNA-Seq approaches to understand the complexity of interplay between nuclear processes both in SMA cells and mouse models. Hopefully, these convergent studies will provide new insights into RNA metabolism, pathogenic mechanisms and help design therapeutic strategies against SMA disease.

AAV-based gene therapy and modeling of motor neuron diseases
MG Biféri, A Besse, T. Marais, M. Cohen-Tannoudji, C. Bos, S. Astord, Y. Tanguy and M. Barkats

Previously, we discovered that a single intravenous (IV) scAAV9 injection was able to mediate substantial gene transfer into the central nervous system (CNS), including motor neurons (MNs). Importantly, we demonstrated the great potential of this method for SMA gene therapy with the induction of a dramatic survival increase in a severe mouse model of SMA after IV AAV9-SMN delivery. Clinical translation of these results has been initiated by B. Kaspar and J. Mendel, and a phase I/II trial is currently ongoing at the Nationwide Children hospital of Columbus (AveXis Corporation, US).
Growing data from mouse and human suggest that other tissues than MNs are involved in the severe form of SMA, which reinforces the idea that SMA is a multisystemic disease, and demonstrate the need of targeting all tissues for SMA type I gene therapy. Moreover, and contrary to what is commonly believed, SMN expression might also be crucial for therapy of SMA type II/III (Bogdanik et al., PNAS, 2015). In line with these data, we found that intracerebroventricular (ICV) injection of AAV9-SMN vectors expressing SMN under a ubiquitous PGK promoter mediated SMN expression in both the CNS and peripheral organs and was highly efficient to rescue SMA mice, but that expressing SMN specifically in neurons (using a neuron-specific Synapsin promoter) did not provide significant rescue of ICV injected SMA mice. Moreover, our results suggested a superior effect of IV and ICV co-delivery as compared to IV or ICV alone, particularly in symptomatic mice injected at 8 days of age. Altogether, our results and data from the literature strongly suggest that combined ICV/IV AAV9-SMN delivery would be the optimal option for SMA gene therapy in both SMA type I and SMA type II/III patients.
Our further results showed a superior MN transduction efficiency of GFP-expressing AAVrh10 (AAV10) over AAV9 vectors. Accordingly, we used AAV10 in our next studies focused on amyotrophic lateral sclerosis (ALS) modeling and therapy. In particular we set up the most relevant model of ALS-FTD (frontotemporal dementia) to date, using AAV10-mediated overexpression of mutant UBQLN2^{Pro497His} in wild-type mice.
We finally developed a new and powerful gene therapy strategy for familial SOD1-linked ALS using systemic AAV10-SOD1 silencing in SOD1G93A mice. SOD1 silencing was induced by engineering of U7-Antisense (AS) RNA in AAV10 vectors. The AS targeting of SOD1 pre-mRNA splicing sequences led to « exon skipping » and generation of a truncated mRNA. This approach is the most efficient to date to rescue ALS pathology in a mouse model.

Brian Kaspar
Abstract missing

Symposium- Parallel Symposium Muscle Ageing
• *Marco Sandri (ITALY)* • *Gillian Butler-Browne (FRANCE)* • *Eusebio Perdiguero (SPAIN)*

AGEING SARCOPENIA AND THE MITOCHONDRIAL QUALITY CONTROL
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The mechanisms of age related muscles loss and weakness, named sarcopenia, are still unknown. However, recent findings suggest that protein and organelle quality control systems have a major impact on myofiber function, neuromuscular junction maintenance and force generation. Impairment of these pathways leads to precocious ageing while their activation counteracts the age-related decline of muscle mass and strength. Here, I' ll present data about the role of mitochondrial quality control in sarcopenia and life span. This quality system includes the mitochondrial fusion and fission machinery and