Symposium- Parallel Symposium Laminopathies
• *Edgar Gomes (PORTUGAL)* • *Gisèle Bonne (FRANCE)* • *Nicolas Levy (FRANCE)*

Zipping nuclei to the periphery of myofibers
Edgar Gomes (PORTUGAL)

Nuclear position within cells is fundamental for multiple cellular functions. Nuclear positioning in skeletal muscle myofibers is particularly unique since myofibers use a wide array of mechanisms and proteins to drive this process. In their final stage of their journey, nuclei migrate from the center of the myofiber to the periphery by an unknown mechanism. We previously showed that movement of the nucleus from the center to the periphery of muscle fibers is N-WASP and actin-dependent. We now demonstrate that γ-actin but not β-actin, is the actin isoform required for peripheral nuclear movement. In order to investigate the segregated role of actin isoforms, we tackled the missing molecular player bridging N-WASP and γ-actin, namely the Arp2/3 complex. Arp2/3 is a seven subunit actin nucleator of which two subunits (Arpc1 and Arpc5) exist in two isoforms. Knockdown studies of each of these isoforms reveal that Arpc5L, but not Arpc5 is required for peripheral nuclear positioning. We also demonstrate that the γ-actin isoform specifically interacts with Arp2/3 populations containing the Arpc5L subunit but not those containing subunit Arpc5. Moreover, γ-actin only co-localizes with Arpc5L longitudinally in between myofibrils. In order to determine how Arp2/3 and γ-actin exert their effect on peripheral nuclear positioning, we performed 3D live imaging over time in myofibrils. Remarkably we observe the longitudinal zipping up of the myofibrils next to the nucleus resulting in the expelling of the nucleus to the periphery of the myofiber. The nucleus dramatically changes its shape suggesting the zipping of the myofibrils squeeze the nucleus to the periphery of the myofiber. Modeling of the tension created by myofibrils on the nucleus supports this novel mechanism for nuclear positioning. Overall, we show that specific actin isoforms are regulated by a subset population of Arp2/3 complexes to drive nuclear positioning to the periphery of the myofiber by a novel mechanism.

New insights in the pathophysiology of striated muscle Laminopathies.
Gisèle Bonne, PhD
Sorbonne Universités, UPMC Univ Paris 06, INSERM UMRS_974, CNRS FRE3617, Center of Research in Myology, F-75013, Paris, France. g.bonne@institut-myologie.org

Laminopathies are due to mutations in the *LMNA* gene encoding Lamin A and C and comprise highly heterogeneous human disorders including a wide range of cardiac and muscular dystrophies. Lamins A/C are constituents of the nuclear lamina, a meshwork of proteins underneath the nuclear envelope. Since the discovery of the first *LMNA* mutation in the Emery-Dreifuss muscular dystrophy (EDMD), more than 450 different *LMNA* mutations were reported (www.umd.be/LMNA/). In order to dissect the pathomechanisms of *LMNA* mutations in striated muscle, we created knock-in mouse models that reproduced *LMNA* mutation identified in patients presenting with cardiac and muscular dystrophies. We demonstrated an aberrant increase in MAP kinases in hearts from *Lmna* H222P knock-in mice, providing proof of principle for MAP kinase inhibition as a therapeutic option to prevent or delay the onset of the contractile dysfunction and cardiomyopathy in striated muscle laminopathies. Recent insights of the pathophysiological mechanisms of *LMNA* mutations leading to skeletal and/or cardiac dysfunction in these mouse models will be presented.

Nicolas Levy
Abstract missing

Symposium- Parrallel Symposium CMT / Neuropathies
• *Vincent Timmerman (BELGIUM)* • *Jean-Marc Leger (FRANCE)* • *Shahram ATTARIAN (FRANCE)*

Hereditary peripheral neuropathies with focussing on pathogenic mechanisms of small heat shock protein mutations
Vincent Timmerman, PhD

AFFILIATIONS: Peripheral Neuropathy Group, Molecular Genetics Department, VIB and University of Antwerp, Belgium
Charcot-Marie-Tooth (CMT) neuropathies comprise a group of monogenic disorders affecting the peripheral nervous system. CMT is characterized by a clinically and genetically heterogeneous group of neuropathies, involving all types of Mendelian inheritance patterns. Over 1,000 different mutations have been discovered in 80 disease-associated genes. Genetic research of CMT has pioneered the discovery of genomic disorders and aided in understanding the effects of copy number variation and the mechanisms of genomic rearrangements. Clinical, molecular genetic and functional studies suggest for common pathomechanisms and gene networks for peripheral nerve degeneration. The most remarkable group of genes are those coding for small heat shock proteins (HSPBs). Although regulated by stress, they are constitutively expressed and responsible for quality control and protein folding. The HSPBs are not only molecular chaperones but also involved in many essential cellular processes such as apoptosis, autophagy, splicing, cytoskeleton dynamics and neuronal survival. We reported that tubulin differentially interacts with mutant HSPB1. This anomalous binding leads to the stabilization of the microtubule network. We also found that mutations in HSPB1 disrupt the neurofilament network and cause their aggregation.