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1986	Master of Science, KU Leuven
1990	Doctor in Science (PhD), KU Leuven
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Science

Neurodegenerative diseases are a major challenge to biomedical research and a major burden to the social care system. There is no cure for any of these disorders. The lack of therapies is for a large part due to our insufficient understanding of their etiology and pathogenesis.

In the group of neurodegenerative diseases, the motor neuron disorders are a heterogeneous group of conditions. Their pathogenic mechanism remains incompletely understood and the major aim of our research is to get better insights into this by using different *in vitro* and *in vivo* model systems. The motor neuron disorders on which we focus are amyotrophic lateral sclerosis (ALS) and distal hereditary motor neuropathy (distal HMN). The ultimate goal of our research is to use our insights to develop and to test new therapeutic strategies for these diseases.

Excitotoxicity and the selective vulnerability of motor neuron in ALS

ALS is characterized by the progressive and selective death of upper and lower motor neurons. These neurons combine the presence of calcium-permeable AMPA receptors in the plasma membrane with a low calcium-buffering capacity in the cytoplasm. This combination is unique for this type of neurons and is essential for their normal function. However, in pathological condition the extracellular glutamate concentration is increased and this will lead to excitotoxicity due to calcium overload. At the level of the AMPA receptor, we demonstrated that the absence of the GluR2 subunit in this receptor is crucial for the selective motor neuron death. We also found that the GluR2 expression is regulated by factors secreted by astrocytes. At this moment, we are investigating these factors as well as different aspects of the calcium metabolism in astrocytes and motor neurons.

FUS/TLS mutations and ALS

Recently, mutations in the gene encoding 'fused in sarcoma/translocated in liposarcoma' (FUS/TLS) were identified as a new cause of familial ALS (FALS). These FUS/TLS mutations account for approximately 5% of FALS cases. In the Belgian FALS population, we identified an R521H FUS/TLS mutation. It is unclear how FUS mutations lead to motor neuron loss. We created zefrafish and *Drosophila* models for mutant FUS/TLS related ALS in order to investigate the pathogenic mechanism. We investigate the nature of the mutations: 'loss-of-function', 'gain-of-function' or a combination of both. In addition, we investigate which cell types are involved in this pathogenic mechanism. Finally, we aim to identify the molecular mechanism(s) involved in the pathogenic mechanism and we screen for modifying factors and therapeutic strategies that can counteract the negative effects of mutant FUS/TLS.

Mutations in small heat shock proteins as the cause of distal HMN and Charcot-Marie-Tooth disease (CMT)

Distal hereditary motor neuropathies (distal HMN) are a group of axonopathies, most often starting in youth or early adulthood, that are slowly progressive in nature. They have many similarities to Charcot-Marie-Tooth disease (CMT) but have, by definition, no sensory involvement. Patients are clinically characterized by progressive muscle weakness and atrophy, reduced or absent deep tendon reflexes, steppage gait and foot (and hand) deformities including hammertoes and *pes cavus.* The pathogenesis of distal HMN and CMT is poorly understood and no treatments are available.

We identified mutations in the gene encoding HSPB1 (HSP27) that cause dHMN. HSPB1 is a small heat shock protein that has anti-apoptotic and chaperoning activity. We investigated the pathogenesis of the axonopathy induced by HSPB1 mutations by creating transgenic mouse models by selective expression of human wild type or mutant HSPB1s in postnatal neurons. These mutant HSPB1 mice develop progressive muscle weakness and atrophy leading to reduced motor performance and muscle force. These mice accurately recapitulate the key features of human symptoms of distal HMN or CMT. We used these transgenic mice to investigate the pathological mechanism (see below).

Therapeutic effect of inhibitors of histone deacetylase 6 (HDAC6) in animal models of CMT, distal HMN and ALS

In isolated dorsal root ganglion neurons from symptomatic mutant HSPB1 mice, axonal transport of mitochondria was dramatically disturbed and we discovered that the acetylated α-tubulin levels were significantly reduced in the presence of mutant HSPB1. Histone deacetylase 6 (HDAC6) is the major tubulin deacetylating enzyme in peripheral nerves and it plays an important role in the regulation of axonal transport. We observed that treatment with HDAC6 inhibitors restored the axonal transport of mitochondria and we could cure our transgenic mice by treating them with HDAC6 inhibitors. In addition, the therapeutic effect of HDAC6 inhibition was paralleled by a significant increase in the number of fully innervated neuromuscular junctions. We are currently investigating whether a similar therapeutic effect is found in other models of distal HMN or CMT. In addition, we investigate whether HDAC6 inhibitors also have a therapeutic effect in animal models of ALS. Moreover, we are investigating the molecular mechanism of the therapeutic effect of HDAC6 inhibition.

Selected publications

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Van Den Bosch, L., De Smedt, H., Borghgraef, R. (1989). Characteristics of Na^{+}-dependent hexose transport in OK, an established renal epithelial cell line. *Biochimica et Biophysica Acta*, 979, 91-98.

Scientific prizes

1997: Laureate of the Belgian 'Royal Academy of Medicine'
2005: Schamelhout-Koettlitz prize
2008: Monique Brauns prize of the 'Geneeskundige Stichting Koningin Elisabeth'