**Project Title: Identification and regulation of toxic elements secreted by ALS vesicles**

**Background to the project:**

Studies in animal models and ALS patients show that motor neuron degeneration starts at the neuromuscular junction and that post-synaptic muscle changes may play an active role[1,2]. Work in our lab[3–5] and others have shown that skeletal muscle has a functional secretory activity. The muscle secretome contains exosomes - vesicles that carry out intercellular transport of functional proteins, mRNA, and miRNA[5–7]. The exosomes may act in an autocrine/paracrine manner on muscle cells or other types of cells and contribute to muscle growth and regeneration, body-wide metabolism, and other functions[3].

Pathological aggregations of misfolded proteins, such as SOD1, TDP-43 or FUS in affected neurons and also neighbouring glia are now considered as hallmarks of ALS[8–10]. Several recent studies have shown that these intracellular proteins can be released through vesicle-mediated exocytosis, and then phagocytosed by neighbouring cells allowing a self-perpetuating transmission to adjacent motor neurons (see[10] for review). In addition, in familial ALS, mutations of genes involved in autophagy pathways and in vesicles biogenesis (ALSIN, VAPB, CHMP2B, VCP) have been identified. Together these published data strongly suggest a disruption of the endosome and lysosome pathways in sporadic and familial ALS patients - both of these pathways are involved in exosome genesis.

We have already confirmed that ALS muscle cells release 2-fold more exosomes than healthy controls – exosomes that are toxic once added to the culture medium of healthy muscle cells or motor neurons.

Working with an established collaborative network - C Raoul (INSERM, Montpellier, France) and C Martinat (iSTEM, Evry, France) - the student will pursue the following aims: (1) determining whether a specific exosome sub-population has toxic constituents; (2) regulating the secretion of the toxic elements either by targeting specifically their expression (knock-down), or by controlling their secretion through the exosome pathway. The latter should open new therapeutic strategies for ALS.

**Skills required of applicant** The project requires good skills in cell culture, immunostaining, as well as rigorous and methodical approach to lab work. Experience in PCR, RT-PCR, and western blot, as well as knowledge of statistical analysis would be beneficial, but can be learned during the project. Good written/oral communication skills are encouraged as well as attention to detail.

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