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## **LES SÉMINAIRES DE L'INMG**

*Human pluripotent stem cells for the study and treatment of neuromuscular diseases : myth or reality ?*

Par

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**11 heures**

**Salle des Conférences  
Médiathèque Paul Zech  
Faculté de Médecine Lyon Est  
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## **Abstract :**

Neuromuscular diseases correspond to a vast group of diseases that perturbs the function of the skeletal muscles by affecting motoneurons, muscles and/or NMJs. To date, no efficient curative treatments have been identified for NMD. Progresses towards identification of new treatment have been hampered by the incomprehension of disease pathogenesis, particularly in early phases, as well as the availability of relevant screening tools. Disease-specific human pluripotent stem cells, from embryonic origin or derived from reprogramming somatic cells, offer the unique opportunity to have access to a large spectrum of disease-specific cell models. Due to their ability of self-renewal and differentiation into various tissues affected in each pathological condition, the development of these human disease-specific pluripotent stem cells provide new insights in pathological mechanisms implicated in human diseases for which, accessing homogenous affected tissues is often challenging. Validating this concept, we previously demonstrated that human pluripotent stem cells and derivatives which, express the causal mutation implicated in the Myotonic Dystrophy type 1 (DM1), offer pertinent disease-cell models, applicable for a wide systemic analysis ranging from mechanistic studies to therapeutic screening. Thus, we identified, through a genome-wide analysis, two early developmental molecular involved both in myogenesis as well as in neurite formation and establishment of neuromuscular connections. These neuropathological mechanisms may bear clinical significance as related to the functional alteration of neuromuscular connections associated with DM1. In parallel to these functional pathological studies, we also demonstrated the pertinence of this new disease-specific cell model to identify new therapeutic strategies. Thus, our results identified the possibility to repurposing metformin, the most commonly prescribed drug for type 2 diabetes, for DM1 leading to a phase 2 clinical trial that is actually ongoing.

We are now extending our approach to another incurable neuromuscular disease, spinal muscular atrophy (SMA). This disease, considered as the leading genetic cause of infant death, is due to mutations or deletions in the "Survival of Motor Neuron" gene, SMN1, which results in low levels of the expressed SMN protein. Despite this ubiquitous SMN expression, the pathology is characterized by degeneration of spinal Motor neurons whereas other neuronal types are relatively preserved suggesting that spinal motor neurons specific features control this differential sensitivity. Based on our recent development allowing the efficient and robust conversion of human pluripotent stem cells into affected spinal motor neurons and non- affected cranial motor neurons, our objective is to deepen the mechanisms involved in the specific degeneration of spinal motor neurons in SMA as well as the miscommunication of these neurons with their muscular target.