Faculté de pharmacie

Université de Montréal

GRUM
Groupe de recherche universitaire sur le médicament

Séminaire de l'axe « Formulation et analyse du médicament » **en collaboration avec le GRUM**

« Fishing for therapeutics for neurological diseases »

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À l'invitation de la professeure Gaëlle Roullin

Amyotrophic lateral sclerosis (ALS) is a rapidly progressing and fatal disorder with no effective treatment to meaningfully prolong survival and no biomarker. In order to discover new therapeutics, we used simple genetic model organisms to screen phenotypically for compounds that could be used to slow or stop ALS. We screened libraries of 3,850 compounds, mostly approved by the FDA, in *C. elegans* model of ALS, validated hits in zebrafish and tested the most potent molecule in mice and in a small clinical trial with ALS patients. We identified a class of 13 neuroleptics that restored motility in *C. elegans* and in zebrafish ALS models. The most potent was pimozide, prevented the reduction in neuromuscular transmission in zebrafish ALS model and enhanced transmission in a mouse model of ALS. Finally, a short randomized controlled trial of 25 human ALS subjects demonstrated safety and tolerability of 4 mg/day of pimozide and evidence of target engagement at the neuromuscular junction through protection against worsening of abnormal decremental responses of the muscle that influences the movement of the right thumb. The small size and baseline group imbalances necessitate further study in humans. In conclusion, we show that simple genetic models are thus useful in identifying promising compounds for the treatment of ALS, which may be a useful therapeutic approach to stabilize neuromuscular transmission and prolong survival in this disease. Given our success in translating compounds from simple animal models to human trials with ALS, we are currently assessing the feasible of such a screen for other neurological diseases such autism spectrum disorders and spinal muscular atrophy.