Merial Veterinary Scholars Program – France

Vet school : Ecole Nationale Vétérinaire d'Alfort

Pharmacological therapy in a preclinical canine model of Duchenne muscular dystrophy: from ex vivo to in vivo assessment of an NHE-1 inhibitor.

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Scientific background

Duchenne muscular dystrophy (DMD) is a rare genetic muscle disease affecting 1 boy out of 3500 to 5000, and due to the absence of the dystrophin protein at the subsarcolemma of myofibers. The absence of this protein leads to many consequences including membrane fragility, and severely disturbed ionic homeostasis. Several therapeutic strategies are envisioned to cure DMD though this disease still remains incurable. Among these strategies, the replacement of the dystrophin protein, one of the biggest known proteins, in the whole musculature, is a challenge that innovating gene or cell therapy try to rise. In parallel, drugs targeting the consequences of dystrophin deficiency on the biology of the muscle fiber are studied, assuming that treating these consequences may alleviate the condition of the patients suffering from DMD. In the future, a combination of pharmacological and cell/gene therapy could be the key of a cure for DMD. Since a decade numerous clinical trials are proposed to DMD boys, but very few of them lead to convincing improvement of the phenotype. Therefore robust preclinical trials are mandatory in order to reliably assess the functional effect of the tested therapeutic strategy, and to help to well-design the clinical studies. In this context, dogs affected with GRMD (Golden Retriever muscular dystrophy) are a precious model: with the same size as a young child, they carry a spontaneous mutation in the dystrophin gene, and faithfully reproduce the human pathological condition, from the histological lesions to the severe disease phenotype.

The present laboratory has a long-lasting experience of canine models of neuromuscular diseases, including GRMD dogs. The team of this research unit is composed of veterinarians and biologists and aims to use the GRMD model both to perform preclinical therapeutic trials and to contribute to the understanding of the DMD pathogeny. A pharmacological trial is currently ongoing in this laboratory, aiming to test the effects of an NHE-1 (Na+/H+ exchanger) inhibitor on the disease phenotype of GRMD dogs. The inhibition of such an exchanger will hopefully regulate the intracellular pH, and decrease calcium intracellular concentration that is abnormally high in dystrophin-deficient myofibers leading to cell necrosis. It is hypothesized that this will lead to a phenotype improvement. The tested drug has obtained a European orphan drug designation and the results of this preclinical study will be a go –no go for the initiation of the phase II clinical trial. The candidates will be involved in this program and will participate to in vivo functional evaluation performed on dogs under treatment and to data processing and analysis. The functional evaluation panel includes gait analysis, respiratory function evaluation, echocardiographic measurements, holter electrocardiograms, muscle echography, muscle force measurements, and muscle and cardiac NMR studies. In parallel the candidates will participate to the ex vivo challenging of dystrophic canine muscles with this drug, in order to better understand its effects in a simplified drug screening model. The effect of this molecule will be

compared with the one of other drugs with close targets. The candidates will thus have the opportunity to contribute to the comprehensive characterization of the effects of a drug that will hopefully be translated from the bench of our laboratory to the bed of DMD patients.

Examples of references from the laboratory

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