INTRODUCTION

Duchenne muscular dystrophy (DMD) is a degenerative muscle disease caused by mutations in the DMD gene resulting in a lack of dystrophin protein.

OBJECTIVE: Assess immune suppression regimens for their ability to allow AAV redosing in vivo

• Immunosuppression (IS) can dampen the immune response to AAV and has been shown to allow redosing in preclinical models and one clinical trial with local AAV administration [5-6].

• Here we tested different combinations of IS drugs for their ability to allow redosing of systemic injections of AAV9-GFP followed by AAV9-mCherry.

• We removed individual IS drugs to assess the effect on redosing to determine which are essential. We also performed single cell RNA sequencing on PBMCs to understand the immune response.

PRELIMINARY DATA

AAV9-MyoDys45-55 restores dystrophin in a humanized DMD mouse model

RESULTS

CONCLUSIONS AND ONGOING WORK

• Systematic assessment of the required IS drugs for redosing highlights the importance of targeting certain aspects of the immune system.

• There is a clear difference in the immune response as assessed by single cell RNA-seq with and without effective redosing.

• Although mice have not been considered to be a good model for the immune response, they are able to function as a basic model of AAV rejection/neutralization, however further work comparing to large animal models and humans is required.

• Ongoing work is testing novel IS targets for AAV redosing in mice.

• Ongoing studies are assessing dystrophin after redosed AAV-MyoDys45-55.

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