Modifying workflow on mouse hydrodynamic gene delivery platform to improve animal welfare and reduce animal use

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Background:
Hydrodynamic gene delivery (HGD) is a non-viral gene therapy method for fast and safe expression of genes of interest (GOIs) in animals. The HGD method is to fast bolus inject large volume DNA solution into a mouse through tail vein, resulting in hydrodynamic pressure mediated uptake of plasmid DNA primarily into hepatocytes. The gene products will then be expressed by hepatocytes, and secreted into circulation, such that the pharmacological function of novel GOIs can be directly evaluated in the mice (1). HGD platform at NNRCC currently supports discovery of new biological entities for NN therapeutic areas such as diabetes and obesity.

Description of initiative:
Efficacy evaluation of novel GOI by HGD is performed in disease model animals such as diabetic db/db mouse for blood glucose lowering, or diet induced obese (DIO) mouse for weight loss. And these studies usually contain animals of relatively big group size (8 mice / group), and are of relatively long duration (2-4 weeks). The GOI forms for HGD injection are rationally designed based on literature information, aiming at getting the functional GOI form and achieving optimal and sustainable plasma protein levels for in vivo efficacy studies. Even though, there is still a chance that one novel GOI form turns out to produce low / no plasma proteins after HGD, causing the efficacy evaluation of this GOI form to be inconclusive.

In order to minimize this, we modified the workflow of HGD platform. We perform a short duration screening study with a small group (3 mice / group) of healthy animals to confirm if a novel GOI form will produce good plasma protein levels, before we use it in a long duration efficacy study with a big group (8 mice / group) of diabetic/obese animals. Novel GOI forms with very low / no plasma protein levels in screening studies will not be used in efficacy studies.

Results:
With the modified workflow of HGD platform, we have tested 105 novel GOI forms in “gate control” studies, and decided not to move forward 52 GOI forms into efficacy studies due to their low plasma protein levels. In one year, this has avoided the unnecessary use of ~400 disease animals.

Conclusion:
With the modified workflow at HGD platform, reduce animal use, and deliver more conclusive studies.

Impact of initiative: Based on estimated annual test of ~100 GOI forms in screening studies, and prioritizing only ~50 forms in efficacy studies (n=8 disease mice / GOI form), we can save ~400 diabetic/obese mice per year.

Perspectives:
Any departments within or outside Novo Nordisk who works with hydrodynamic gene delivery, can also use this workflow to improve animal welfare.

References: