mRNA delivery of potently and broadly neutralizing antibodies against HIV

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Background:
The most effective antibodies against HIV are potently and broadly neutralizing antibodies targeting conserved epitopes hidden behind the extensive glycan shield on the envelope protein. The human response to HIV very rarely generates such antibodies. On the other hand, we discovered that cows vaccinated with stabilised HIV envelope trimers, generate a B cell response characterised by extremely potent and broadly neutralizing antibodies that engage a superlong complementary determining region of the third heavy chain (CDRH3) to penetrate the HIV envelope glycan shield and target the conserved CD4 receptor binding site.

Methods:
We have engineered one of these patented antibodies (MEL-1872) (IC_{50} = 0.009 ug/mL, breadth 66%) onto human IgG and IgA backbones and developed an mRNA platform for in vivo delivery of both IgG and IgA derived forms.

Results:
LNP formulated IgG and IgA mRNA were infused into mice and the levels of isotype and HIV Env specific antibodies assayed in serum 48 hrs later. Surprisingly, the level of isotype specific IgG or IgA was significantly higher than that of HIV Env specific antibody. Co-formulation with a murine TLR7 antagonist boosted both isotype and HIV Env specific antibody levels equivalently.

Conclusion:

We are characterising these antibodies further by mass spectrometry to understand in vivo tolerance to mRNA delivery of antibodies. These outcomes will be compared to those from a humanised mouse model to optimise mRNA delivery of these potent broadly neutralizing HIV antibodies for therapeutic effect.

Disclosure of Interest Statement:
Nothing to disclose