FVIII expression via non-viral vector DNA medicine platform results in efficacious levels of FVIII protein and correction of the bleeding phenotype in hemophilia A mice

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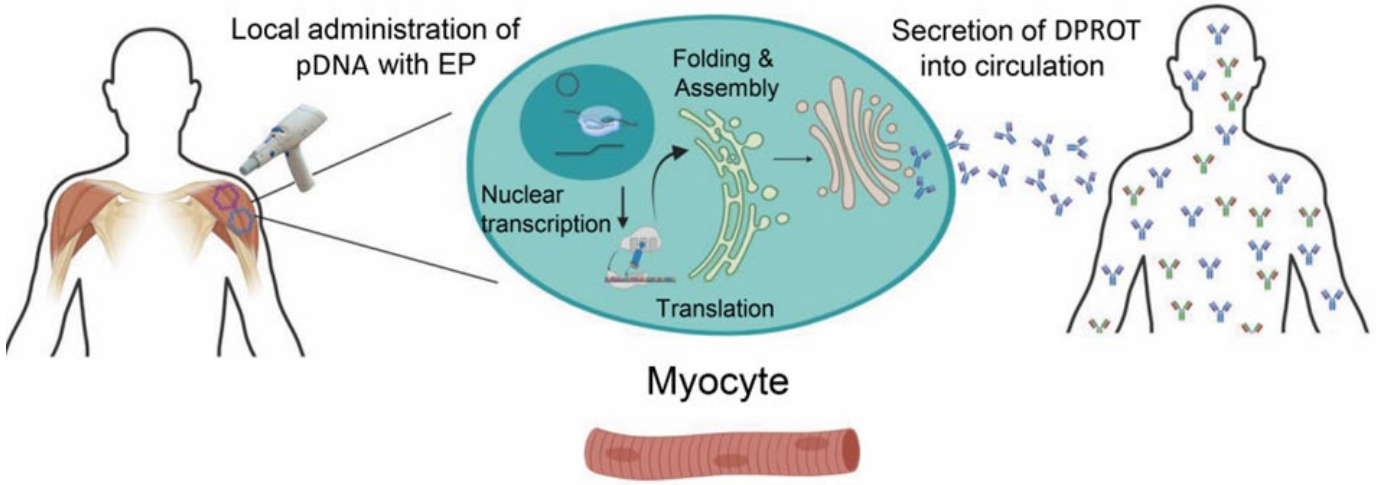
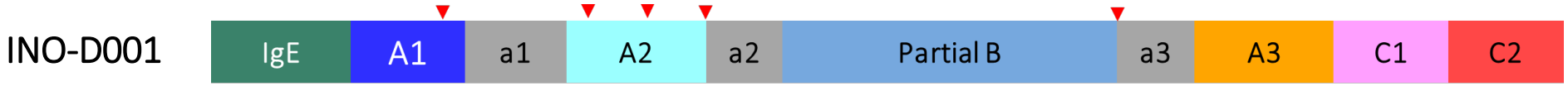
DNA Medicine Technology Platform



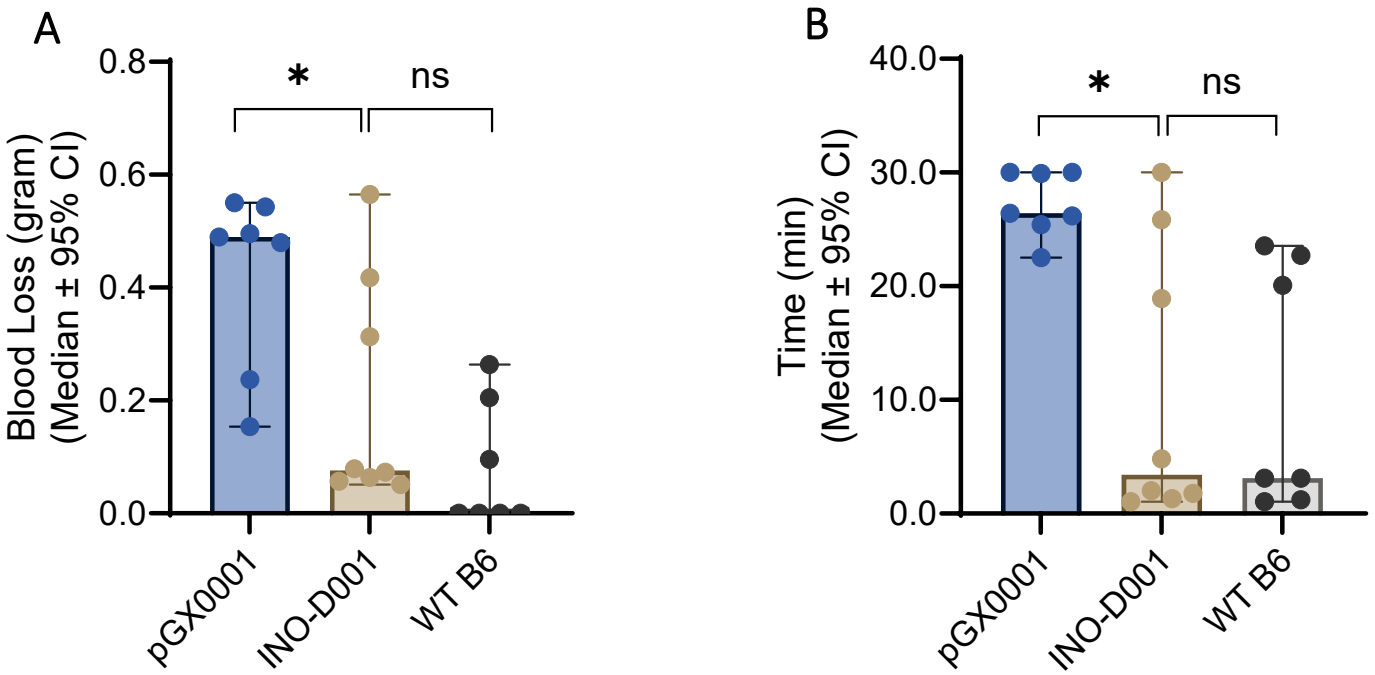
- Synthetic plasmid DNA constructs are administered intramuscularly (IM) followed by *in vivo* electroporation (EP) for the local expression of the transgenes in the deltoid muscle
- DNA-encoded proteins (DPROTs) are expressed in the myocytes and secreted into circulation



INO-D001 is comprised of a DNA plasmid encoding human FVIII with an IgE leader sequence, a partial B domain, and modifications to boost expression and activity of FVIII protein

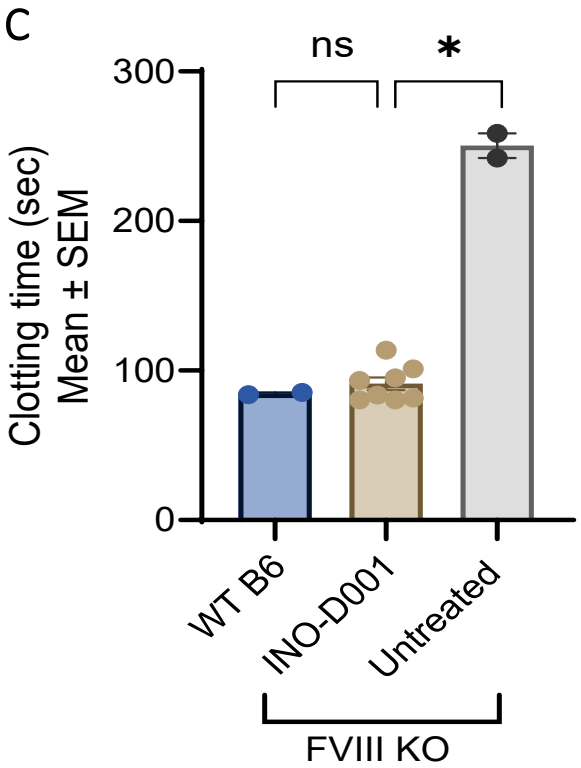
Bleeding Phenotype Correction in Hemophilia A Mice Following *in vivo* FVIII Gene Transfer by EP in Skeletal Muscle Cells

Efficacy assessment by tail bleeding model



FVIII knockout (KO) mice treated with INO-D001 displayed significantly reduced blood loss (A) and bleeding time (B) compared to control (pGX0001) treated mice and displayed a comparable bleeding phenotype as WT B6 mice with a mean FVIII activity level of 20% as measured by two-stage chromogenic assay

Functional FVIII activity measurements by Activated Partial Thromboplastin Time (APTT) clotting assay



The plasma of INO-D001-treated FVIII KO mice showed activity (clotting time) comparable to WT mice indicating complete correction of the bleeding phenotype

Conclusions

- Preclinical proof-of-concept for a novel human FVIII replacement therapeutic modality, demonstrating *in vivo* production of functional FVIII and correction of the bleeding phenotype in FVIII KO HA mice
- Plasma from INO-D001-treated HA mice showed clotting activity comparable to WT mice measured by the one-stage APTT assay, consistent with gain of function mutation
- Data support continued development of INO-D001 as a next generation hemophilia A therapeutic
- Inovio's technology may provide an alternative to viral-based delivery for long-term in vivo protein expression to overcome existing treatment hurdles
  - Pre-existing immunity against viral-based vectors
  - Generation of anti-viral vector immunity after in vivo delivery preventing re-dosing
  - Waning protein expression over time which requires re-dosing
  - Safety and tolerability