Establishing PRINT™-mediated protein expression in the retinal pigment epithelium for treatment of ocular diseases

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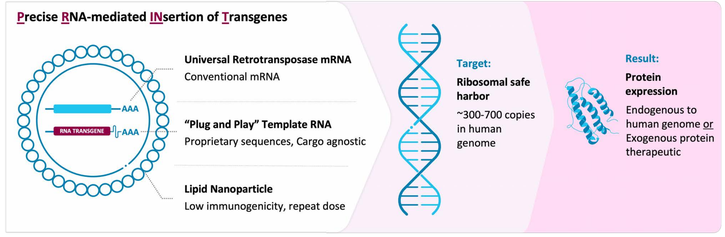
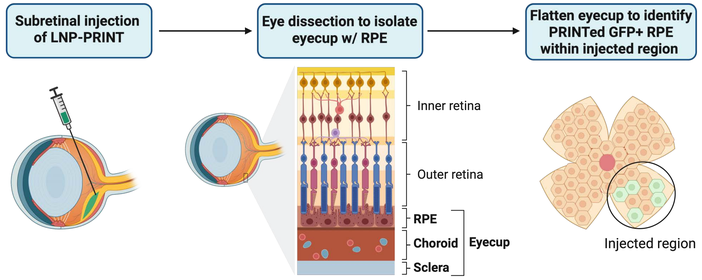
INTRODUCTION

PRINT (Precise RNA-mediated INsertion of Transgenes) is an all-RNA, targeted-transgene insertion approach based on R2-mediated target-primed reverse transcription. PRINT inserts transgenes into the rDNA array, a safe-harbor site in the human genome. The eye's immune privilege, accessibility, and compartmentalized anatomy make it a compelling tissue for the application of genetic medicines. Here, we establish PRINT in the retinal pigment epithelium (RPE) *in vitro* and *in vivo* across species and demonstrate functional expression of a therapeutically relevant payload.



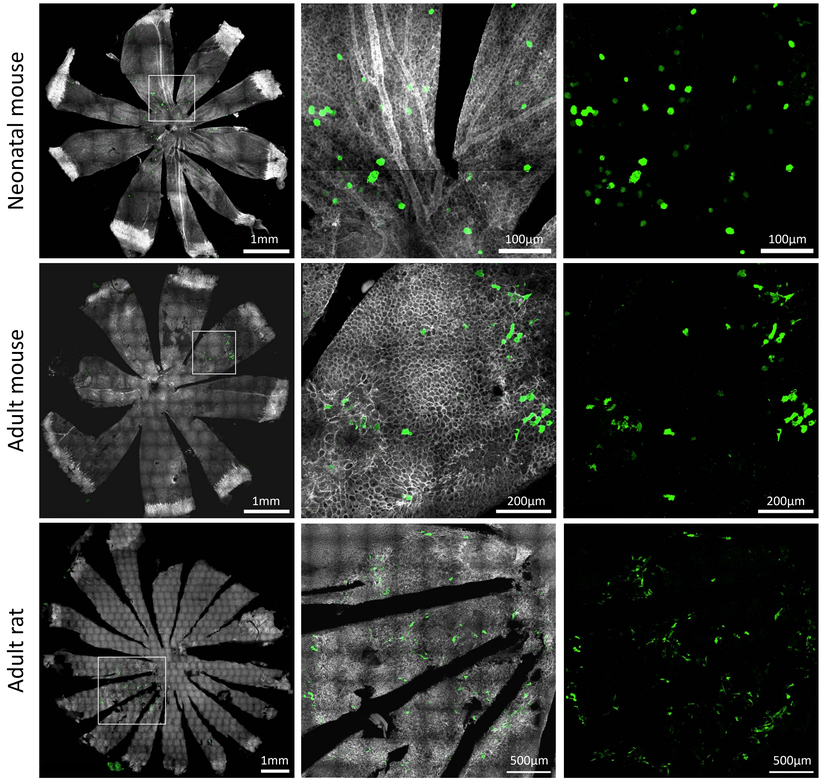
METHODS

- RNA payloads (eGFP template RNA and R2 mRNA) were formulated into LNPs.
- The formulated material was subretinally injected into BALB/c mice and Sprague Dawley rats. Eyes were enucleated and dissected to obtain RPE eyecup flat-mounts for fluorescence imaging of GFP-positive PRINTed cells.
- In rats, optical coherence tomography imaging was performed to assess retinal morphology and tolerability.
- ddPCR analysis of the 3' transgene:rDNA junction was performed on eyecups.
- hTERT RPE-1 cells were transfected with PRINT constructs encoding two anti-VEGF biologics; expression and function were assessed via antigen ELISA.

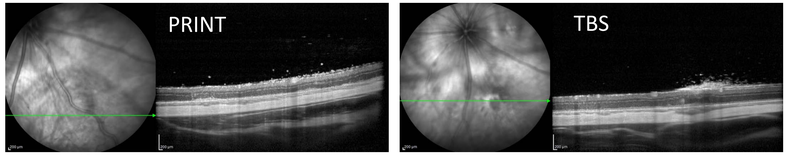


RESULTS

1. PRINT of the RPE *in vivo* across multiple species and ages

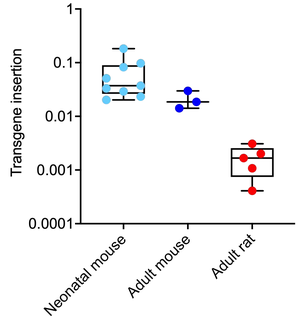


2. PRINT results in minimal acute retinal morphological changes in rats compared to sham injections



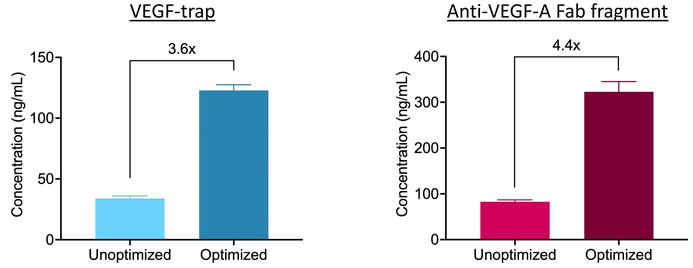
RESULTS

3. Detection of PRINT transgene insertion into the rDNA locus by ddPCR



- ddPCR analysis was performed on the whole eyecup (including the RPE, choroid, and sclera).
- It is not possible to determine the percentage of cells PRINTed from these data as only a small minority of RPE cells in the eyecup were exposed to the LNP.

4. *In vitro* PRINT of therapeutic payloads with target-binding activity in RPE cells



- Anti-VEGFs are efficacious for neovascular AMD but rely on frequent intravitreal injections.
- PRINT's steady, localized protein production could avoid the need for frequent dosing and the resulting compliance challenges associated with current therapies.

CONCLUSIONS & FUTURE DIRECTONS

1. *In vivo*, PRINTed RPE cells were observed within the injected region of the eyes of both adult mice and rats with minimal morphological changes.
2. Transgene insertion was detected *in vivo* by ddPCR.
3. *In vitro,* two distinct anti-VEGF biologics were successfully PRINTed in RPE cells and demonstrated functional expression.

Addition Therapeutics is seeking a strategic partner with expertise in ocular delivery to advance PRINT for ophthalmic indications