Efficacy and Safety of TALEN® Mediated Genome Editing of the Hepatitis B Virus cccDNA and Integrated DNA *in vivo*

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Global Hepatitis Summit 2023

Disclosure

Ramon Diaz Trelles is a full-time employee of Arcturus Therapeutics, Inc (NASDAQ: ARCT)

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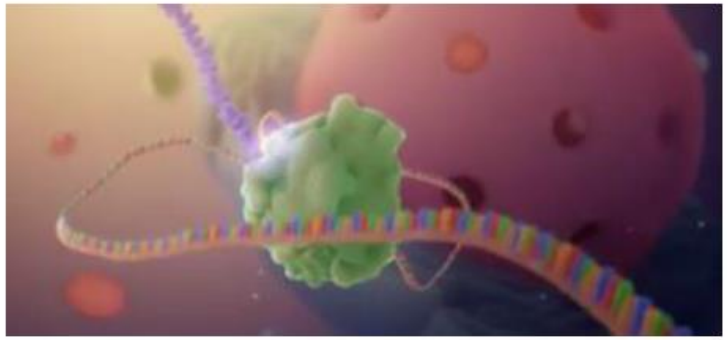
Arcturus Therapeutics



Global Late-Stage Clinical mRNA Medicines Company

Nasdaq: ARCT

Headquarters: San Diego, CA

Employees: 172

Founded: 2013

mRNA Medicine Candidates

LUNAR-OTC *Ornithine Transcarbamylase Deficiency*

LUNAR-CF *Cystic Fibrosis*

Additional Earlier Stage Programs

Multiple Strategic Partners

CSL™

ultragenyx pharmaceutical

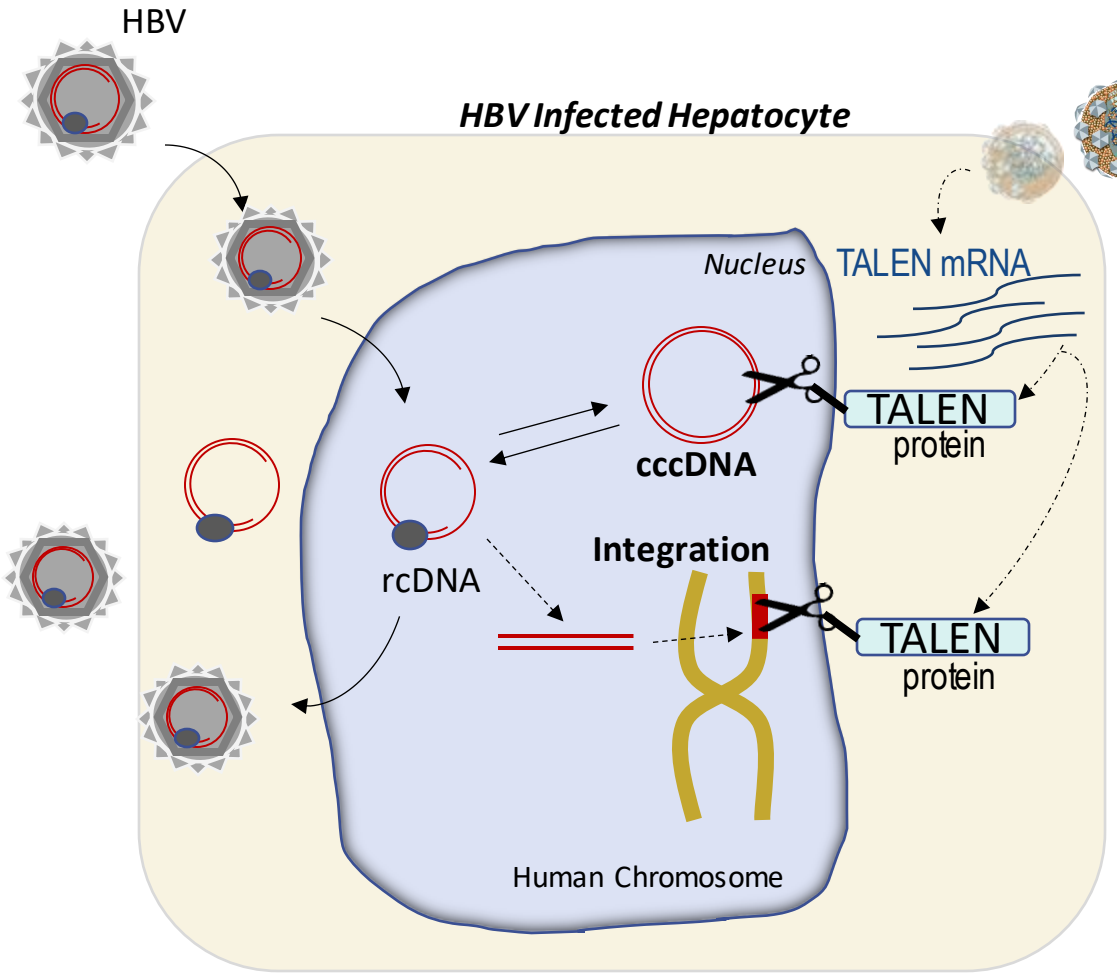
CYSTIC FIBROSIS FOUNDATION®

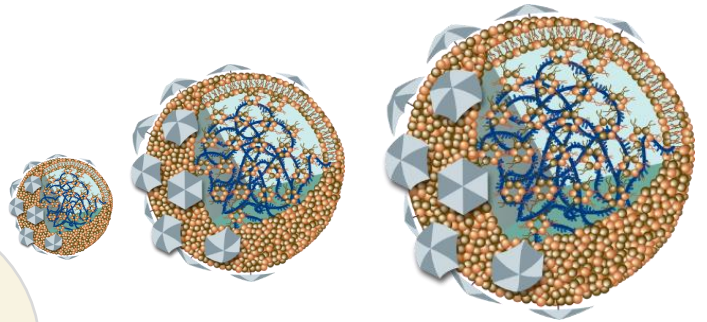
BARDA

mRNA Vaccines (COVID, FLU)

mRNA Vaccine (FLU)

LNP-mRNA Technology is Optimal for the Delivery of TALEN as a Genome Editing Therapy for HBV





LUNAR LNP with TALEN mRNA

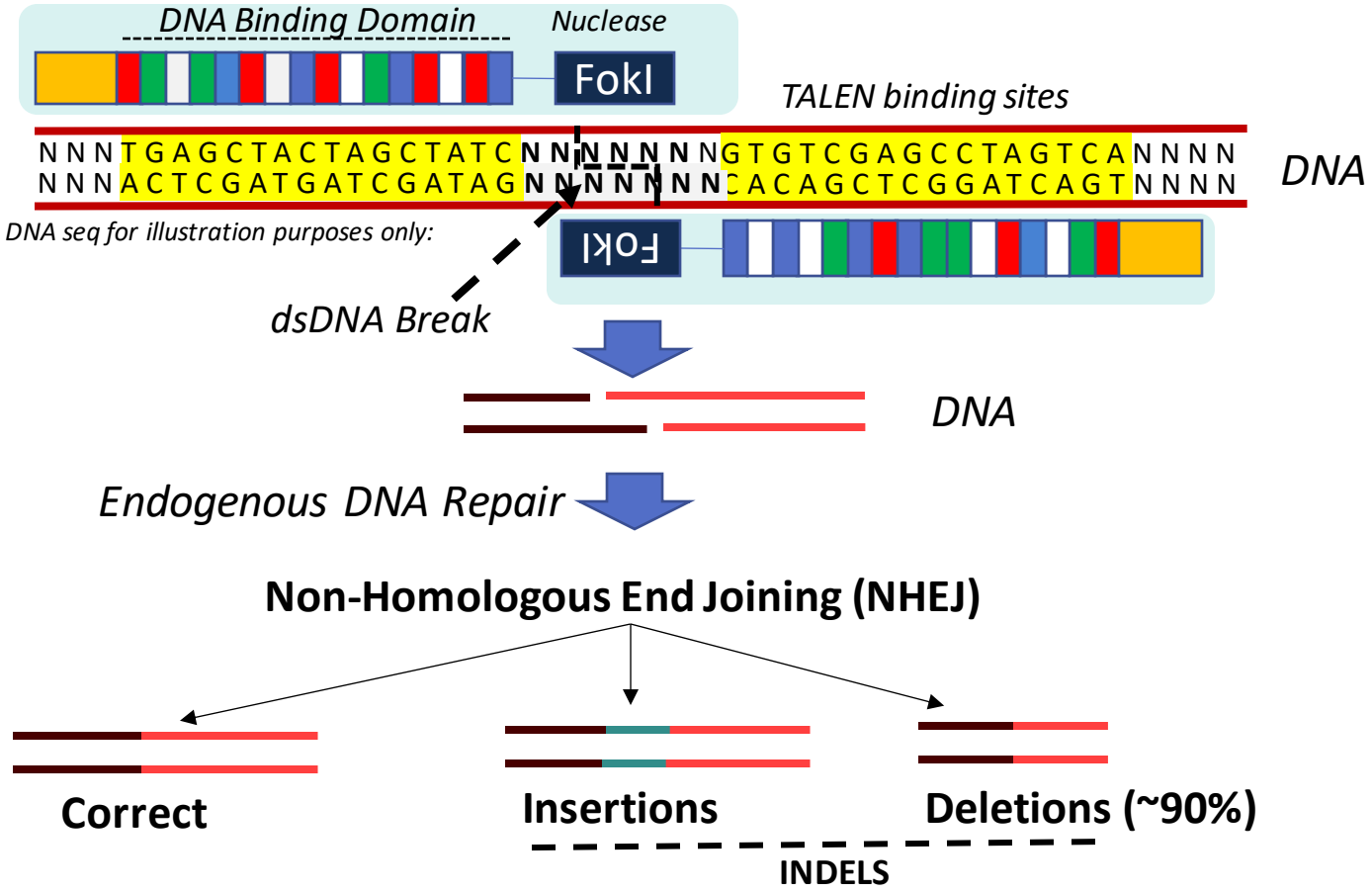
- **LUNAR® Lipid Nano-Particle:**
  - Biodegradable, Low Immunogenicity, Liver Specificity
- **TALEN mRNA:**
  - Transient, No-Integration, Dose Dependent Activity
- **TALEN® Proteins:**
  - Transient, High Specificity, Targetable

TALEN mediated inactivation of cccDNA and integrated HBV could lead to HBV cure

HBV TALEN Pair Designed to Target Specific HBV DNA Sequence

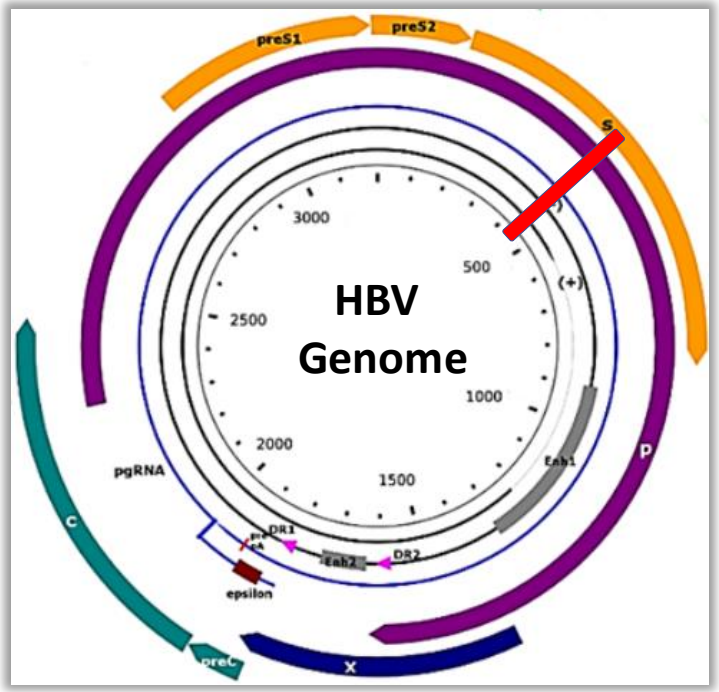
TALEN Code:

NG = T NI = A NN = G/A HD = C



HBV TALEN-Target Sequence:

- Long target sequence (~38 bp), High Specificity
- Target HBV S Antigen and Polymerase Coding Sequence
- Highly Conserved Sequence Across All HBV Genotypes



HBV TALEN introduces insertions and deletions in the S/Pol region of HBV DNA

Summary of LUNAR TALEN Evaluation

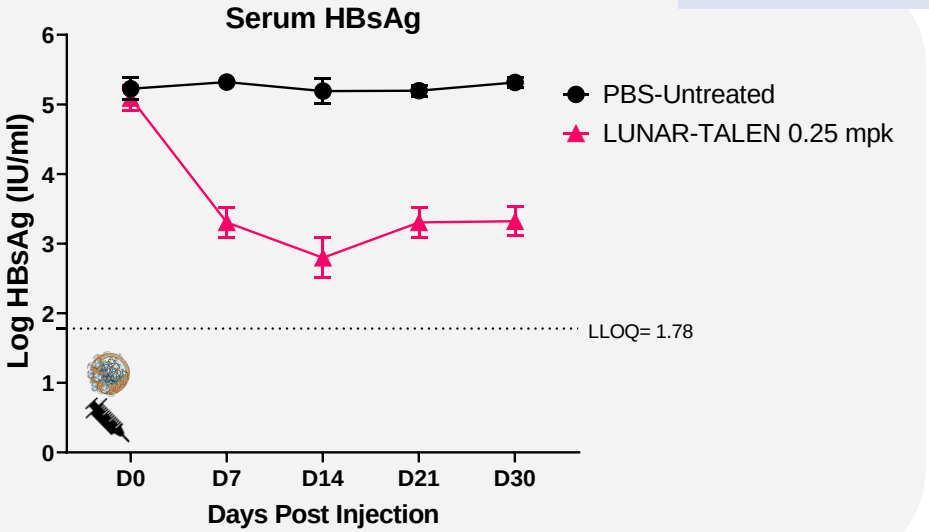
- LUNAR TALEN **targets**, inactivates and eliminates **episomal HBV DNA** in the mouse liver *in vivo*
- LUNAR TALEN **targets** and inactivates **integrated HBV DNA** in the mouse liver *in vivo*
- Low risk of **off-target** activity in cell lines *in vitro*

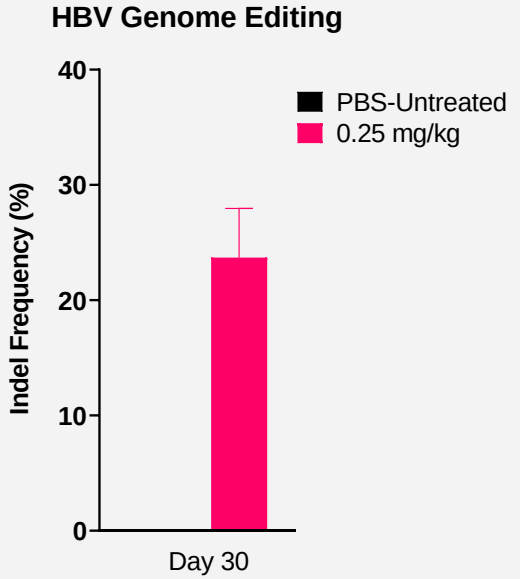
Irreversible Reduction of Serum HBsAg After LUNAR TALEN Dosing in AAV HBV mice

AAV-HBV mouse model:

- HBV replication
- Chronic HBV infection model
- No re-infection of mouse hepatocytes

Single Dose





= LUNAR TALEN Dose

➢ HBV DNA Editing Outcome is Irreversible

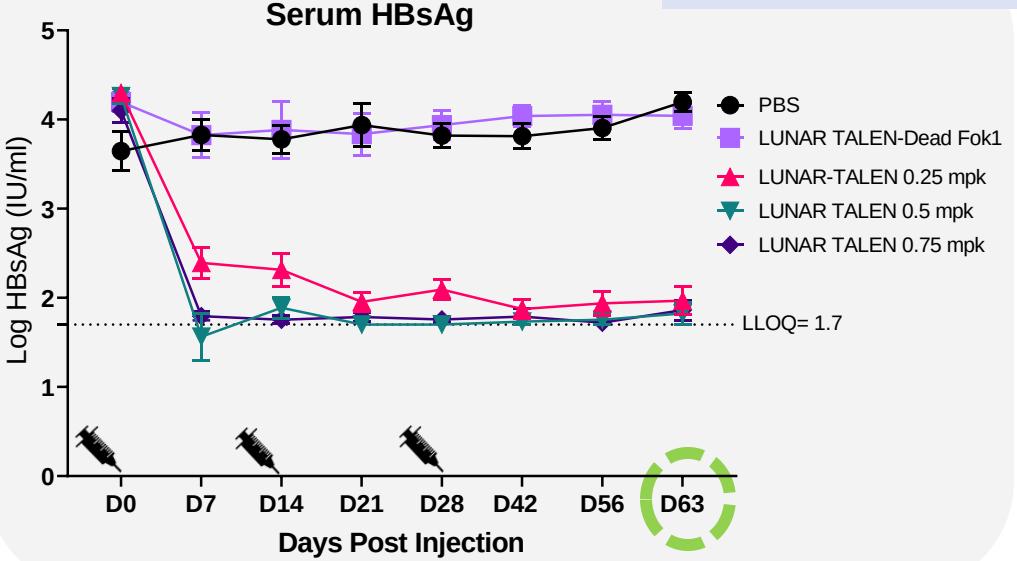
Mouse image from © The Jackson Laboratory

LUNAR-TALEN Targets and Edits Episomal HBV DNA and reduces serum HBsAg, HBV DNA levels in vivo

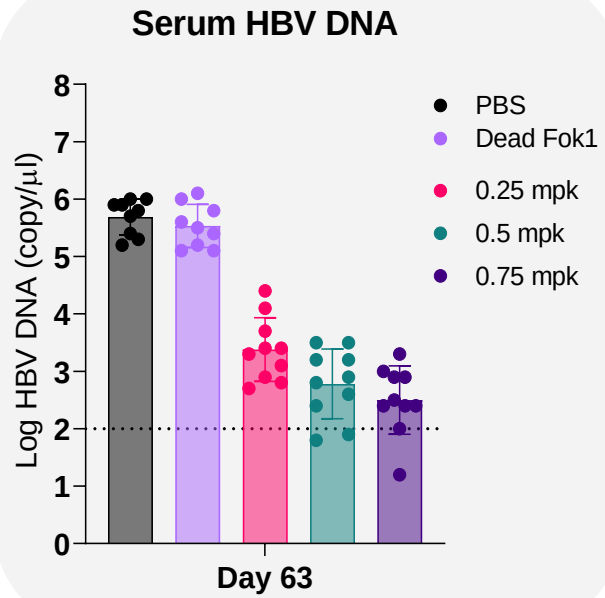
AAV-HBV mouse model:

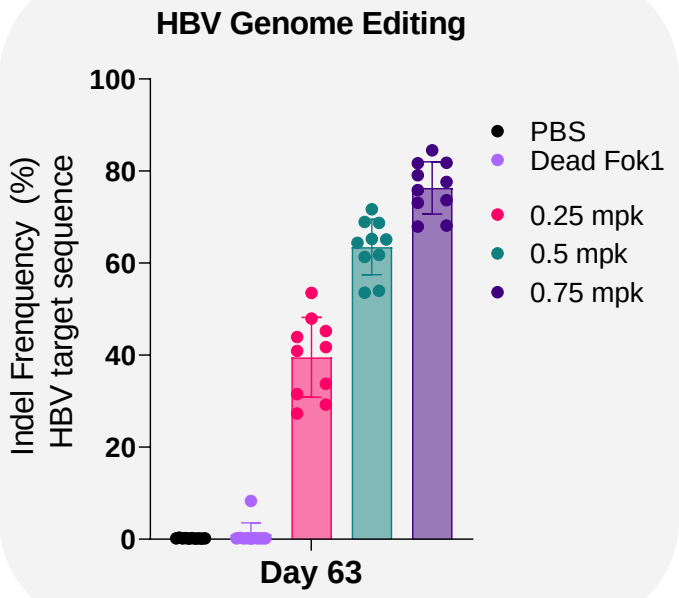
- HBV replication
- Chronic HBV infection model
- No re-infection of mouse hepatocytes

Repeated Dosing



= LUNAR TALEN Dose





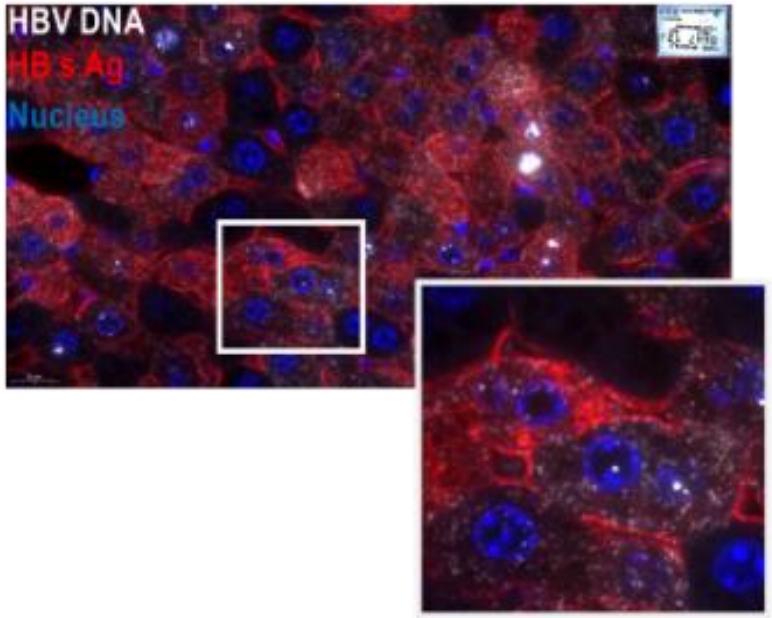
- LUNAR TALEN Efficacy is dose dependent
- HBV DNA editing effect is irreversible

Mouse image from © The Jackson Laboratory

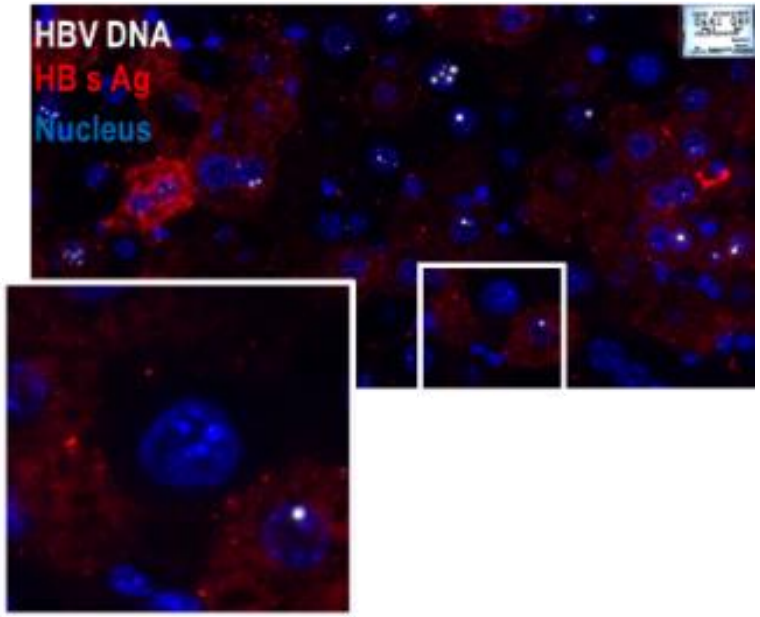
LUNAR TALEN Reduces the Levels of rcDNA and Nuclear HBV DNA in Mouse Hepatocytes

Samples from Day 63 after 3 x dose treatment

PBS

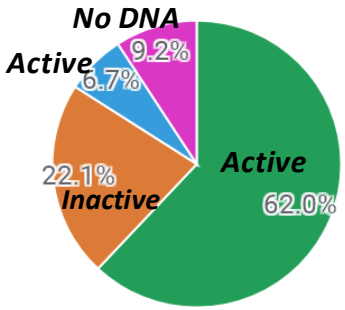


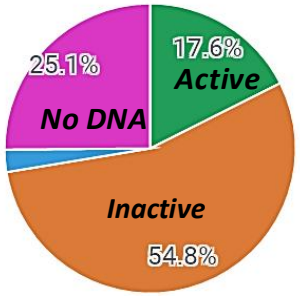
LUNAR TALEN



HBV DNA quantification by location:

- Nuclear and Cytoplasm
- Only Nuclear
- Only Cytoplasm
- Without Foci



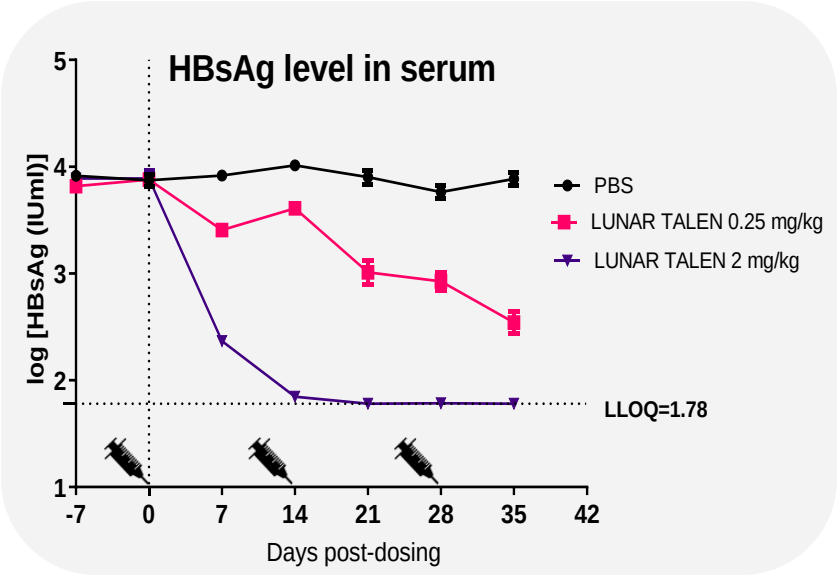


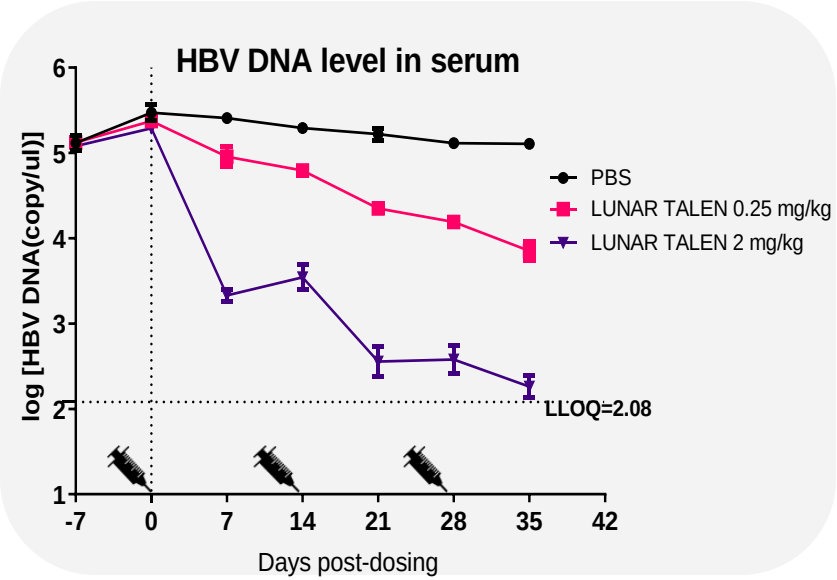
➢ LUNAR TALEN treatment reduces HBV DNA content in hepatocytes

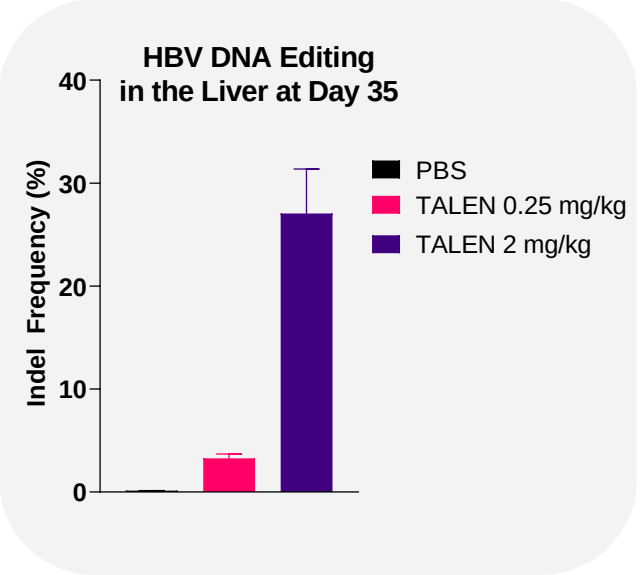
LUNAR-TALEN Targets and Edits *Integrated* HBV DNA and Reduces Serum HBsAg, HBV DNA Levels *in vivo*

HBV transgenic mouse model
(*WUXI*)

- HBV replication from Integrated HBV transgene
- No cccDNA
- No HBV reinfection







- LUNAR TALEN efficacy is dose dependent
- Repeated Dosing Increases LUNAR TALEN efficacy in the HBV transgenic mouse model
- TALEN proteins can access and edit integrated HBV DNA in the mouse genome

Low Risk of Potential TALEN HBV Activity in the Human Genome

Discovery Phase

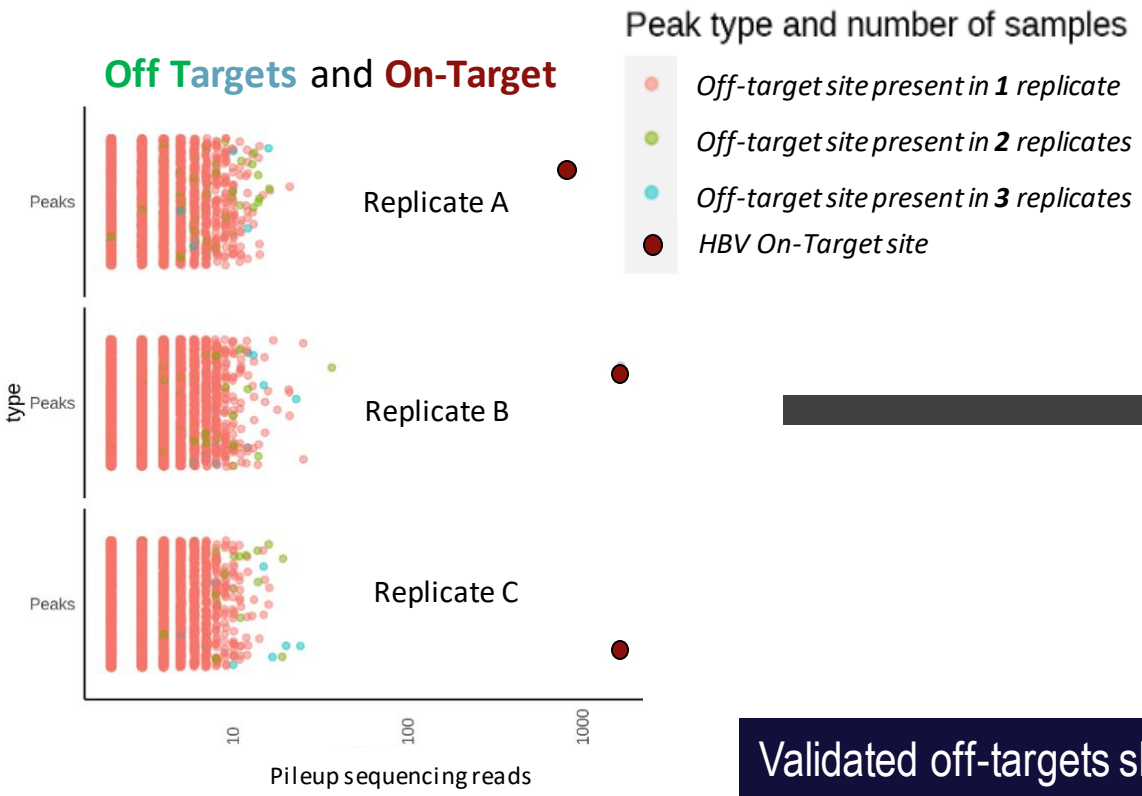
- Bioinformatic Predictions
- Cell-based assays (GUIDE seq)

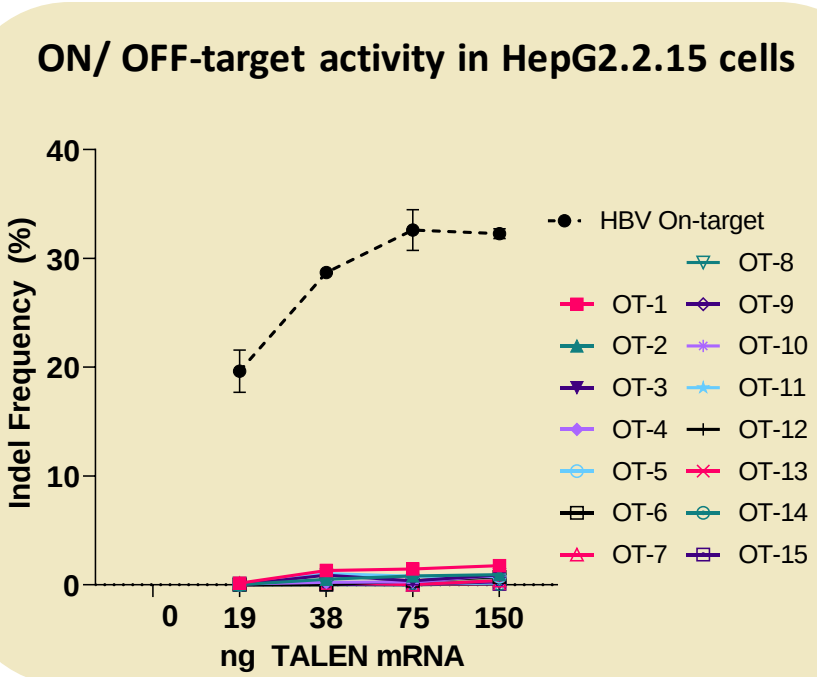
Selection of potential off-target sites in the human genome

Validation Phase

- Targeted NGS-multiplex PCR (rhAMP-seq)
- Dose–Response TALEN mRNA *in vitro*

Confirmation of Editing Activity in the human genome selected sites (~1000)





Validated off-targets show at least a 10-fold safety margin; located at non-coding regions and not reproducible across cell lines

Summary Highlights of LUNAR TALEN HBV therapeutic:

- **LUNAR TALEN HBV targets and edits cccDNA and integrated HBV DNA *in vivo***
- **LUNAR TALEN HBV reduces HBV DNA levels on infected hepatocytes *in vivo***
- **TALEN HBV mRNA shows low potential off-target target activity in the human cell lines**

Data available but not shown

- Broad **Genotype Coverage**: TALEN is active across all HBV genotypes
- **Biodistribution**: TALEN activity detected only in the liver *in vivo*
- TALEN protein **Immunogenicity:**
  - **Low risk** of pre-existing in humans
  - **No antibodies** anti-TALEN detected in mice

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