

***A gene editing approach for  
chronic hepatitis B:***

*Elimination of hepatitis B virus in vivo by  
targeting cccDNA and integrated viral genomes  
with a sequence-specific ARCUS nuclease*

June 22, 2023

EASL

Emily B. Harrison, PhD  
HBV Research Lead, Gene Therapy Discovery



# Forward-Looking Statements

This presentation contains forward-looking statements, as may any related presentations, within the meaning of the Private Securities Litigation Reform Act of 1995. The Company intends such forward-looking statements to be covered by the safe harbor provisions for forward-looking statements contained in Section 27A of the Securities Act and Section 21E of the Exchange Act. All statements contained in this herein and in any related presentation that do not relate to matters of historical fact should be considered forward-looking statements, including, without limitation, statements regarding research advancement, expected efficacy and benefit of our platform, programs, and product candidates, the approach and goal of providing a functional cure for genetic diseases, expectations regarding on-target activity and specificity of our gene editing approach, and application of novel HBV episomal in vivo models. In some cases, you can identify forward-looking statements by terms such as “aim,” “anticipate,” “approach,” “believe,” “contemplate,” “could,” “estimate,” “expect,” “goal,” “intend,” “look,” “may,” “mission,” “plan,” “possible,” “potential,” “predict,” “project,” “should,” “target,” “will,” “would,” or the negative thereof and similar words and expressions.

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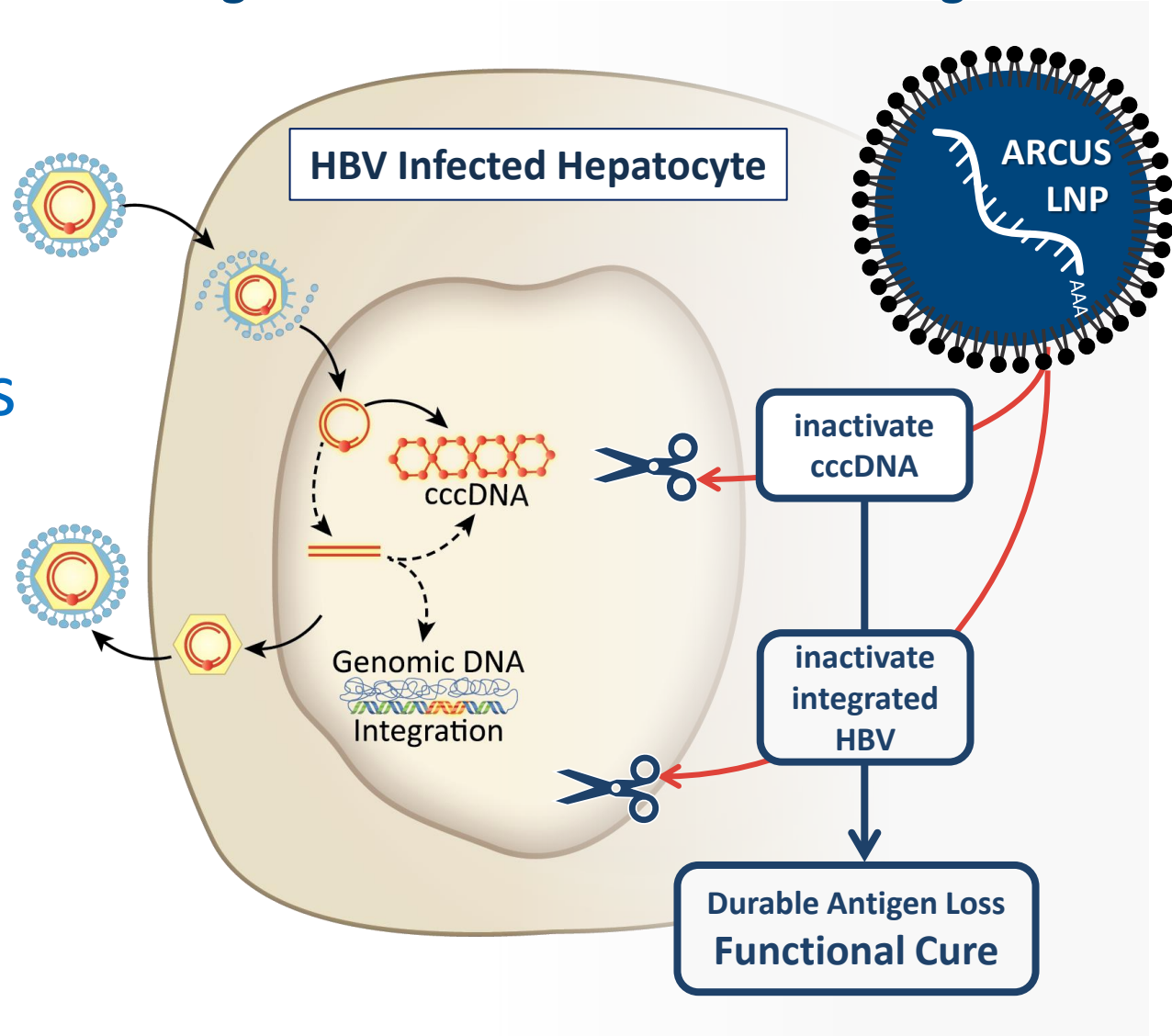
# Disclosures

- I am an employee of Precision BioSciences, Inc. (Nasdaq: DTIL)

# Rationale for a functional cure:

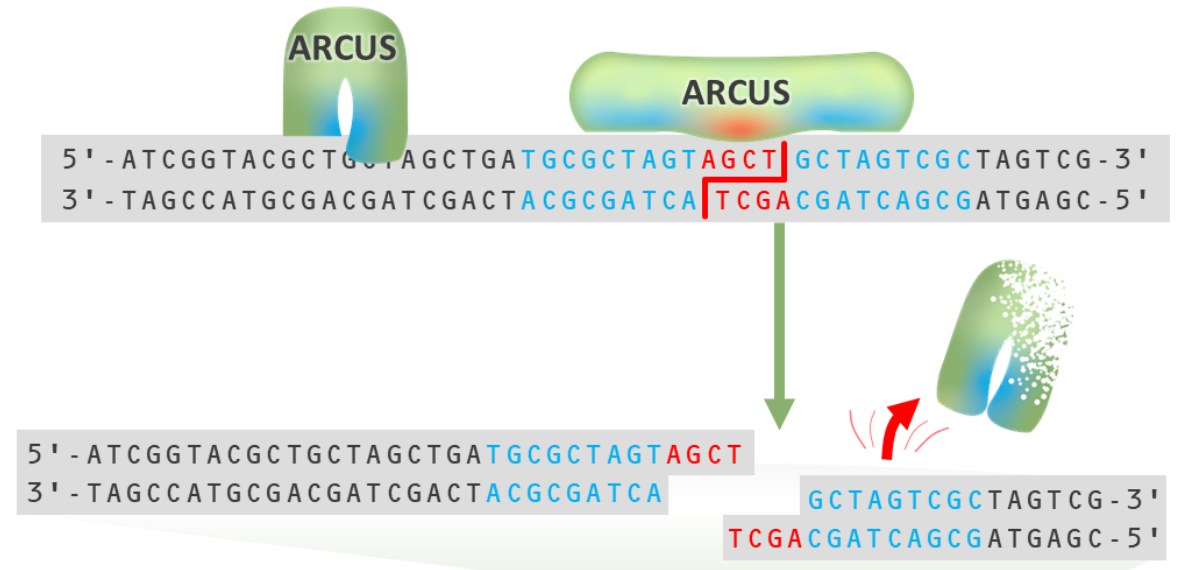
ARCUS gene editing inactivates cccDNA and integrated HBV to drive durable antigen loss

Chronic Hepatitis B affects  
~250 million people

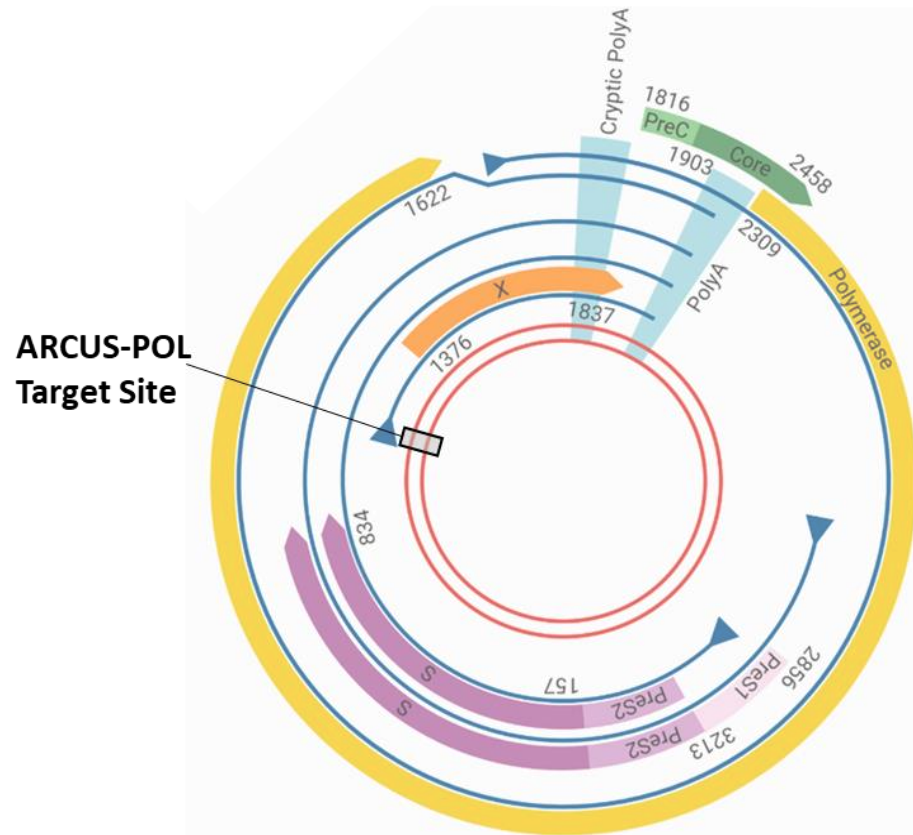


# ARCUS: Engineering Nature's Genome Editing System

- ARCUS is derived from **I-CreI**, a homing endonuclease from algae
  - Protein optimization results in high specificity
  - Sticky ends at cut site allow for:
    - Complex edits, such as gene insertion
    - Sensitive detection of off-target editing

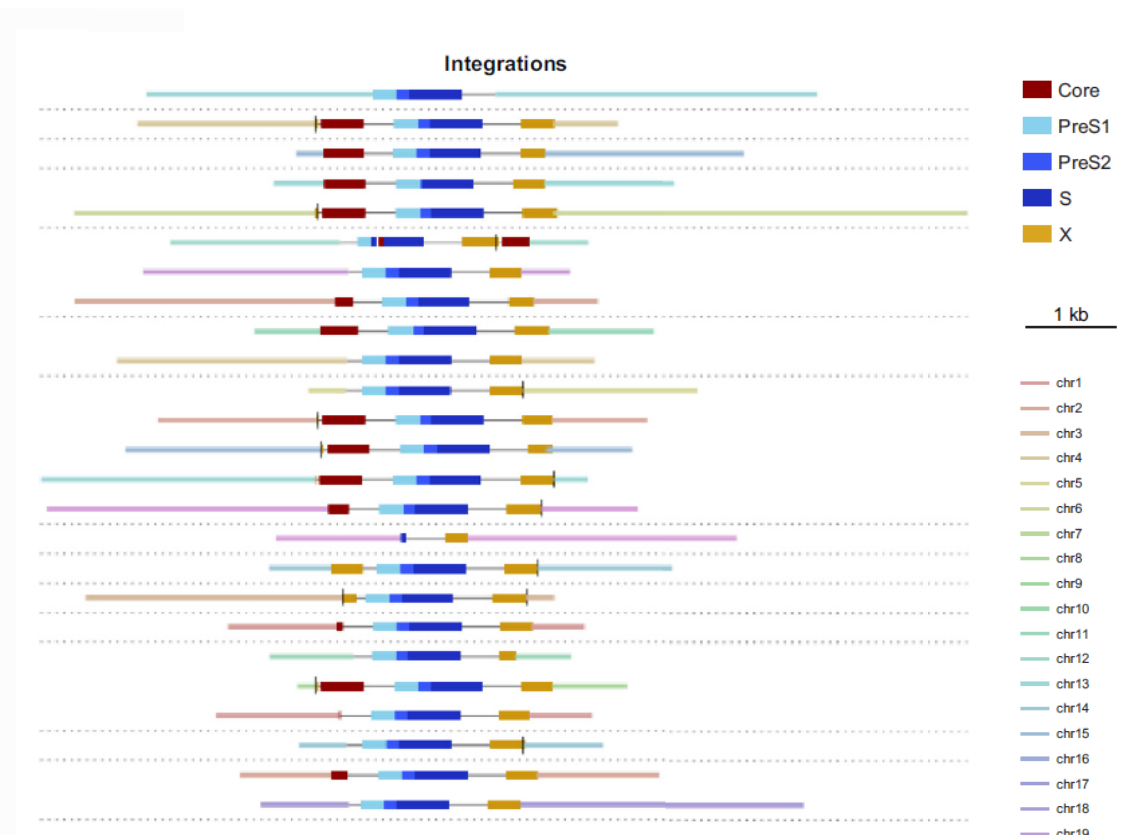


# ARCUS-POL recognizes a highly conserved sequence in HBV-POL gene



ARCUS-POL Target Site

Target site conserved in 92% of isolates across serotypes<sup>1,2</sup>

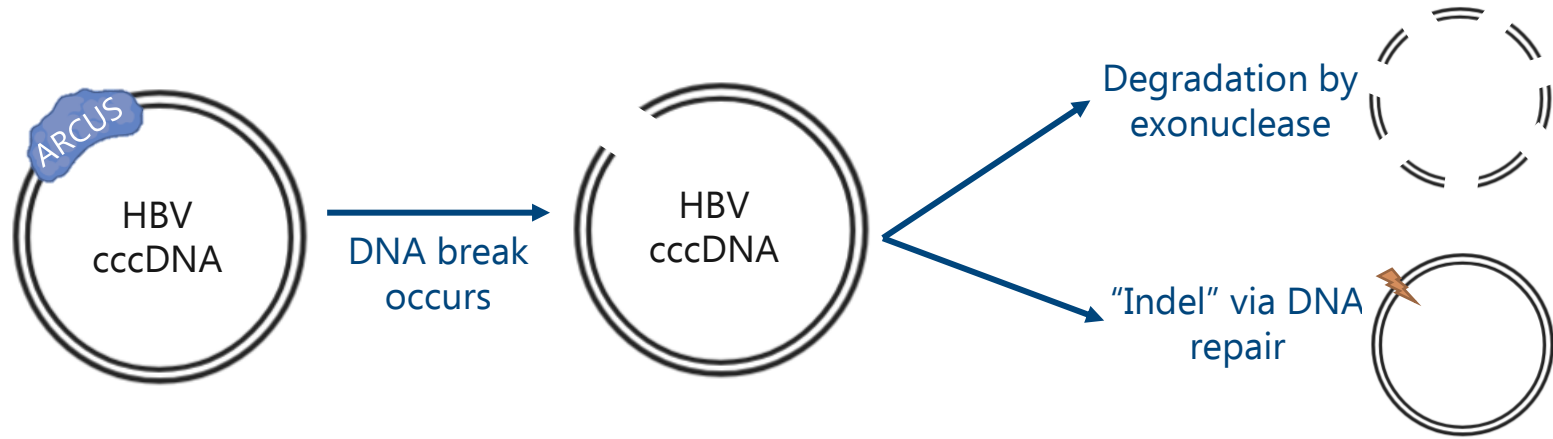


Targeted region is present in the majority of integrations<sup>3</sup>

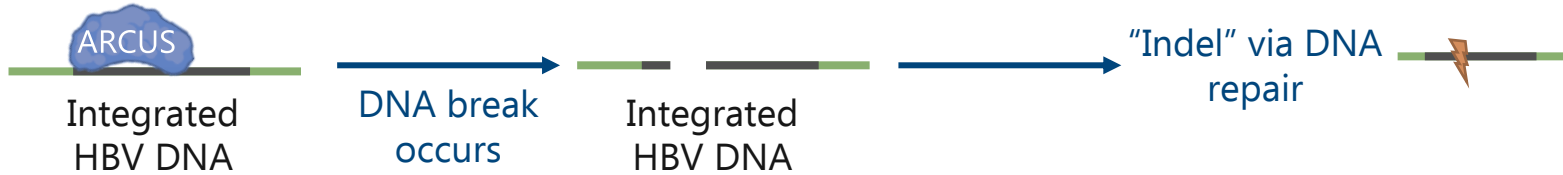
1. Gorsuch CL, et al. *Mol Ther*. 2022;30(suppl 9):2909-2922. 2. Image source adapted from: Tu T, et al. *Viruses*. 2021;13(2):180. Published 2021 Jan 26. doi:10.3390/v13020180 3. van Buuren, N, et al. *JHEP Rep*. 4.4 (2022): 100449. Published 2022 Feb 12. doi:10.1016/j.jhepr.2022.100449

# ARCUS-POL gene editing inactivates cccDNA and integrated HBV to drive durable antigen loss

1



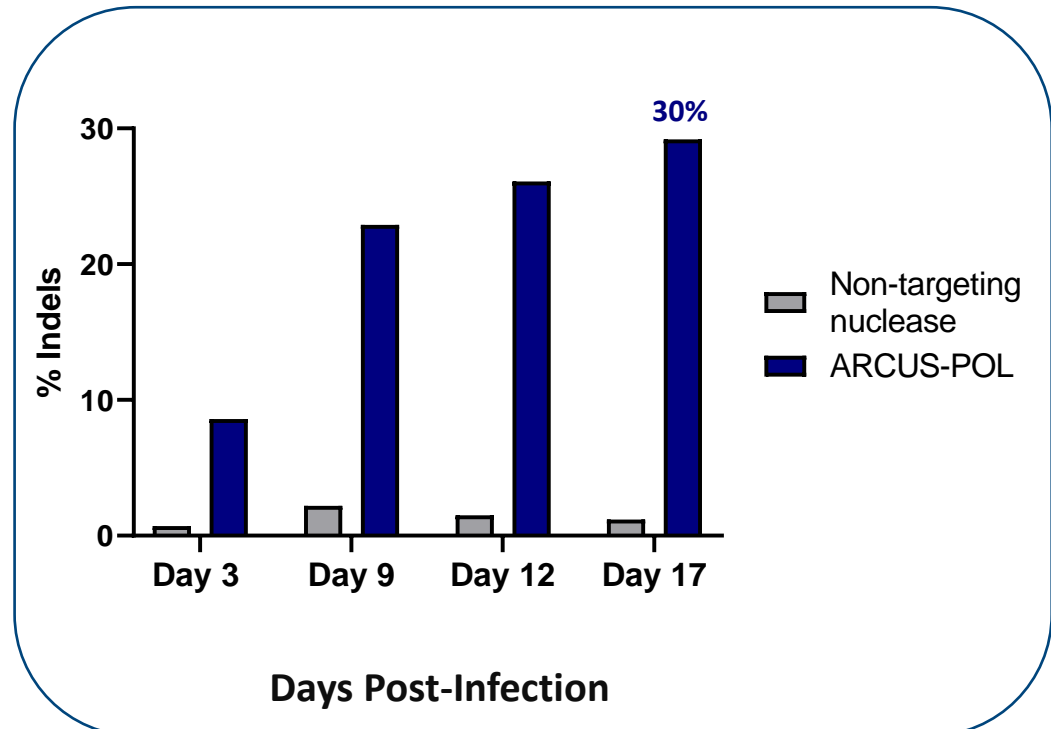
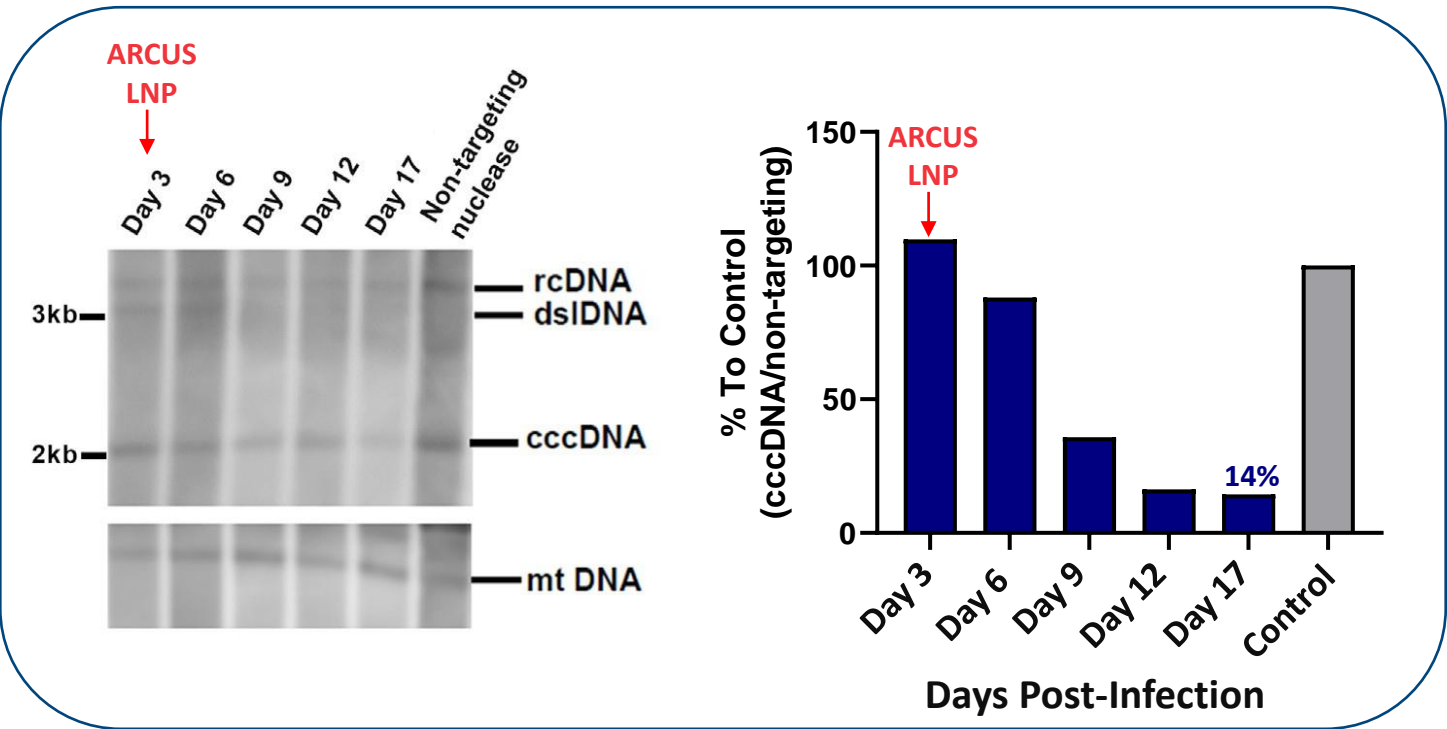
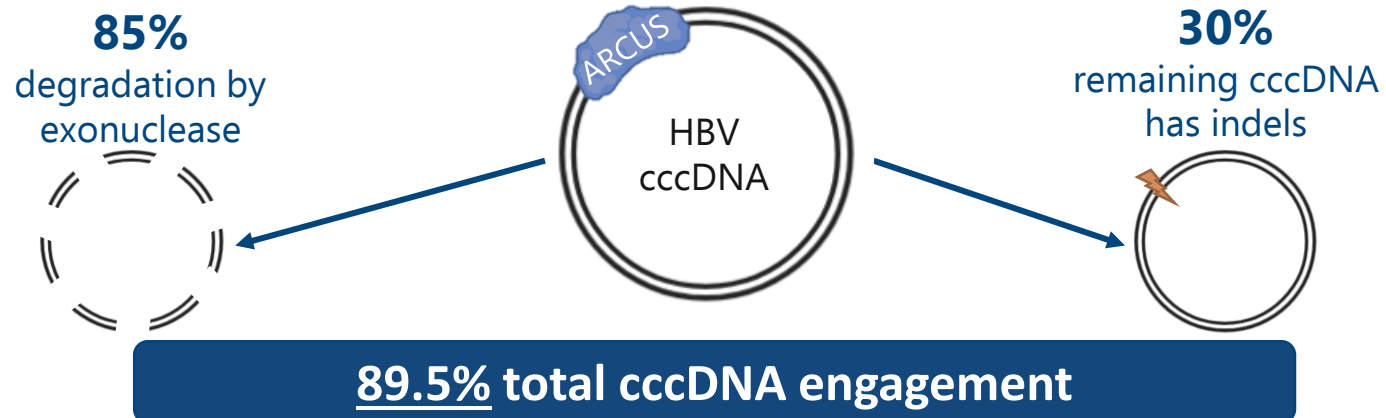
2



## Outcomes

DNA	HBsAg
Loss of cccDNA	Transcript and protein loss
Edited cccDNA	Transcript and protein loss
Edited Integrated HBV DNA	Transcript and protein loss

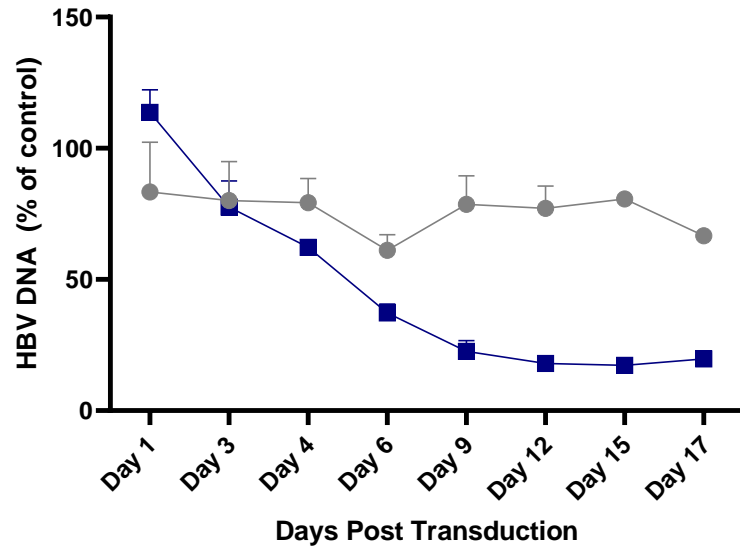
# ARCUS-POL inactivates cccDNA in HBV-infected primary human hepatocytes



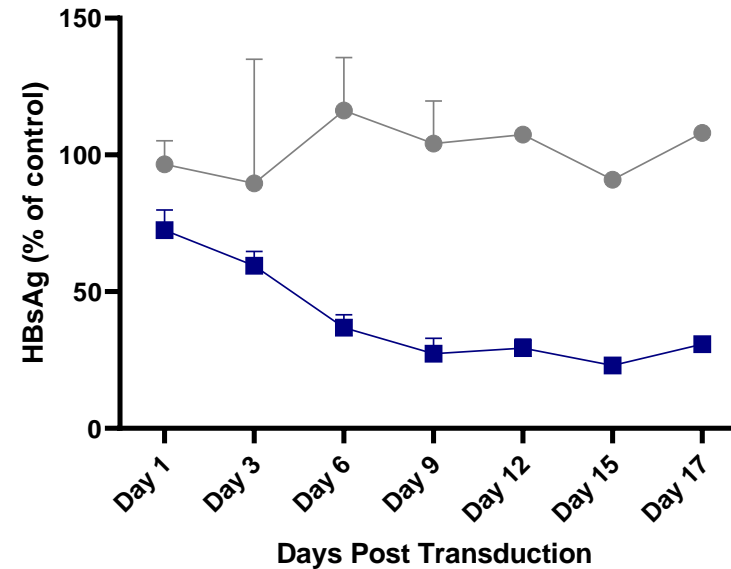


# ARCUS-POL reduces extracellular HBV DNA and HBsAg in primary human hepatocytes

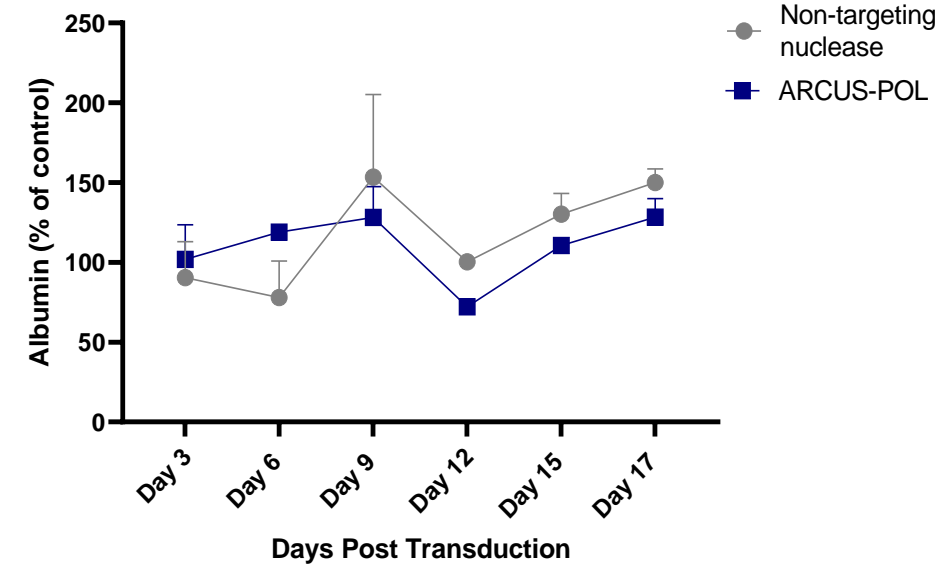
80% reduction in extracellular HBV DNA



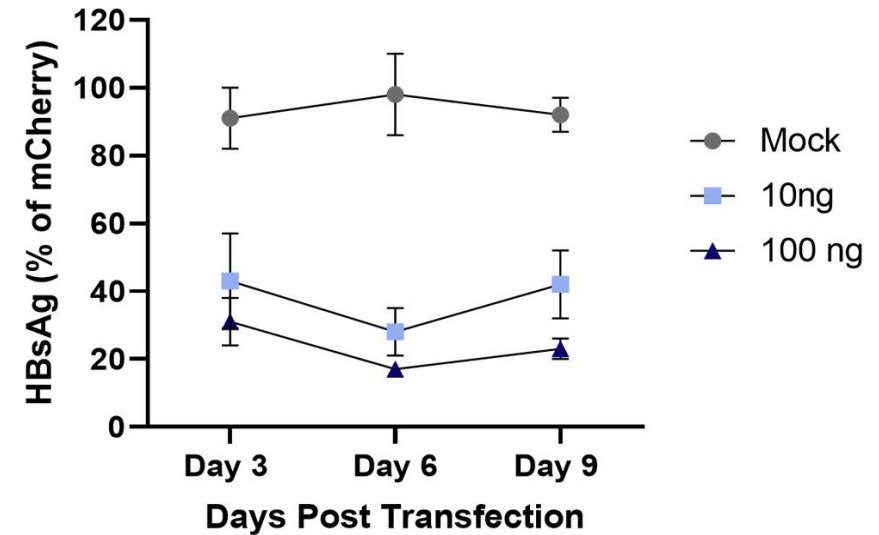
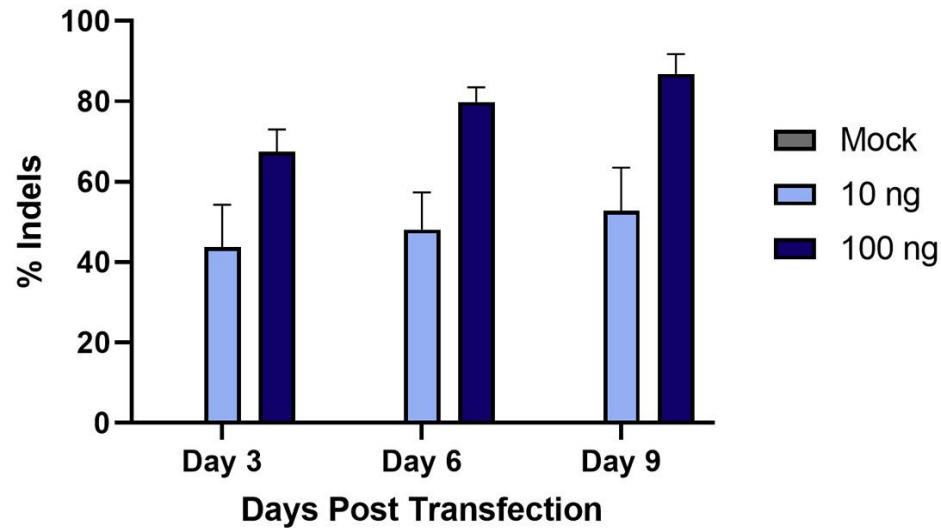
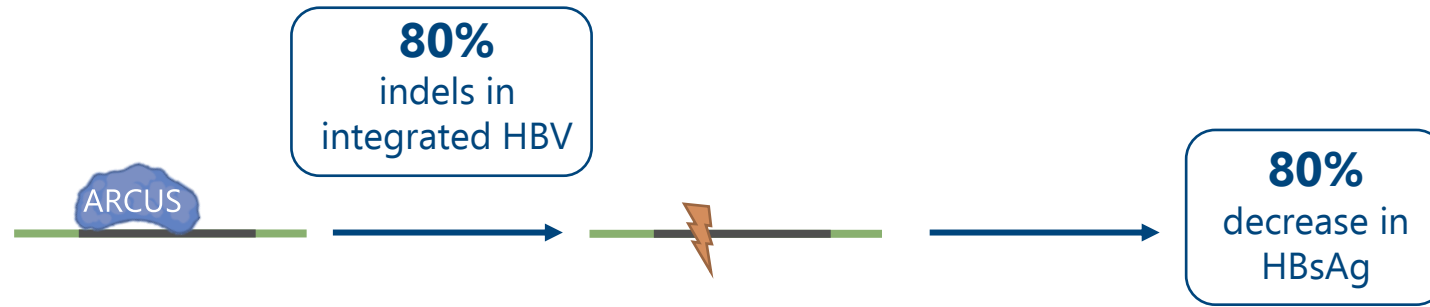
77% reduction in extracellular HBsAg



No change in extracellular albumin

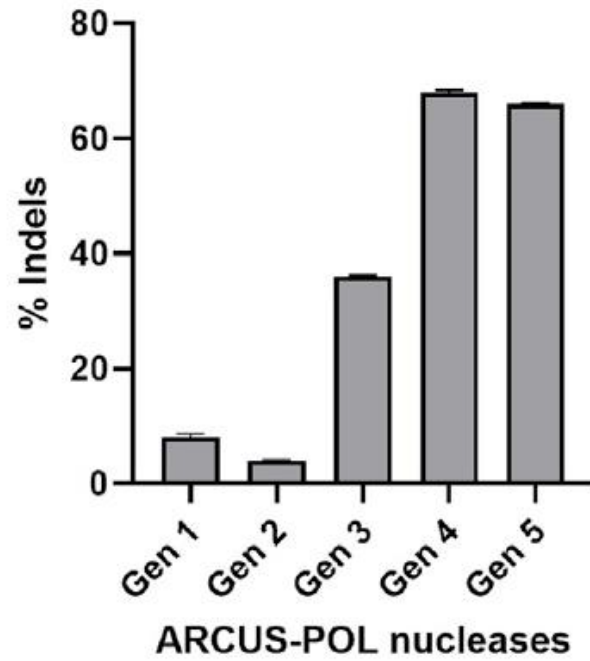


# ARCUS-POL inactivates integrated HBV DNA and decreases HBsAg in liver cells with integrated HBV DNA

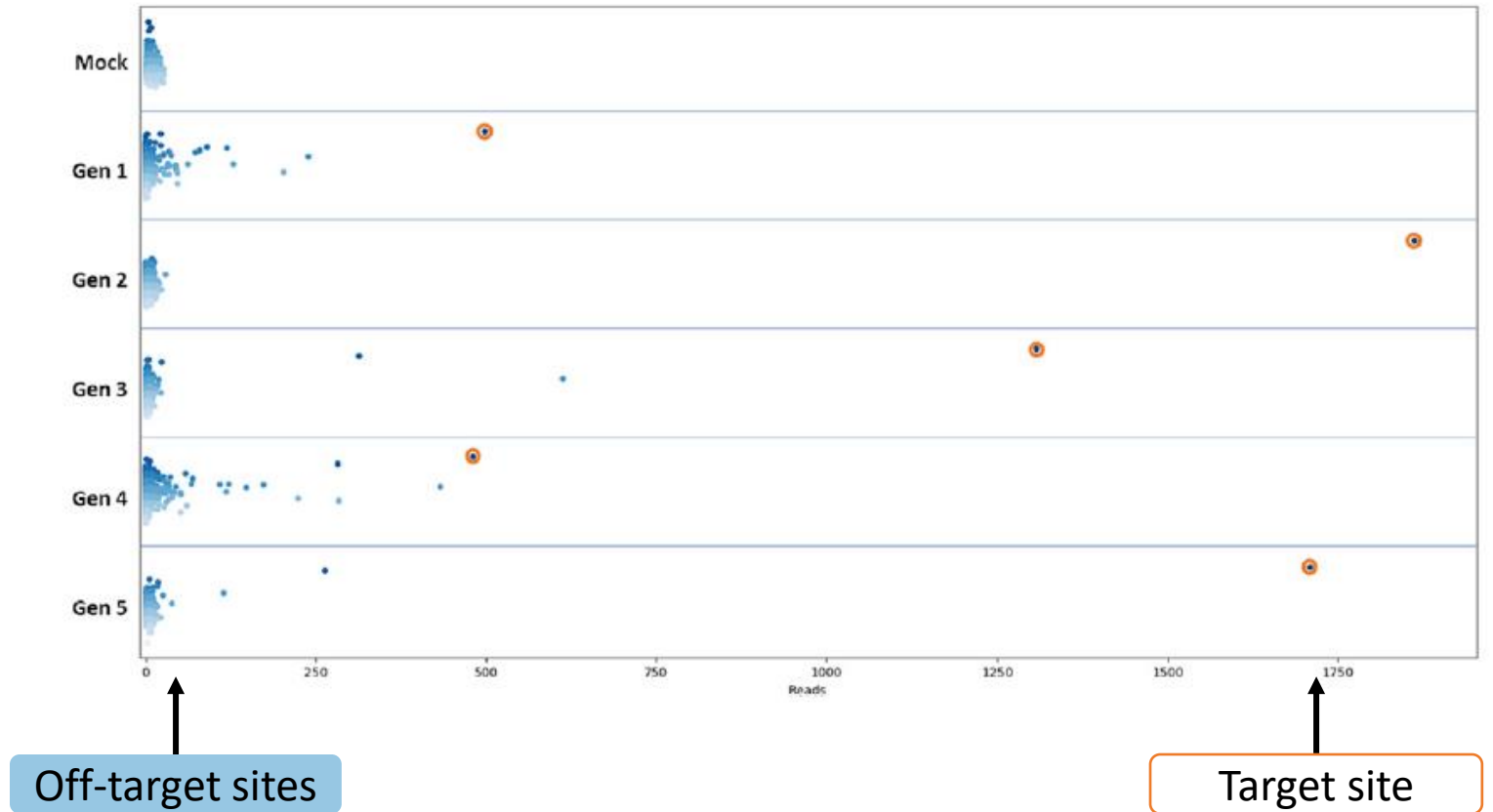


# Optimization of ARCUS-POL increases activity and specificity in liver cells with integrated HBV DNA

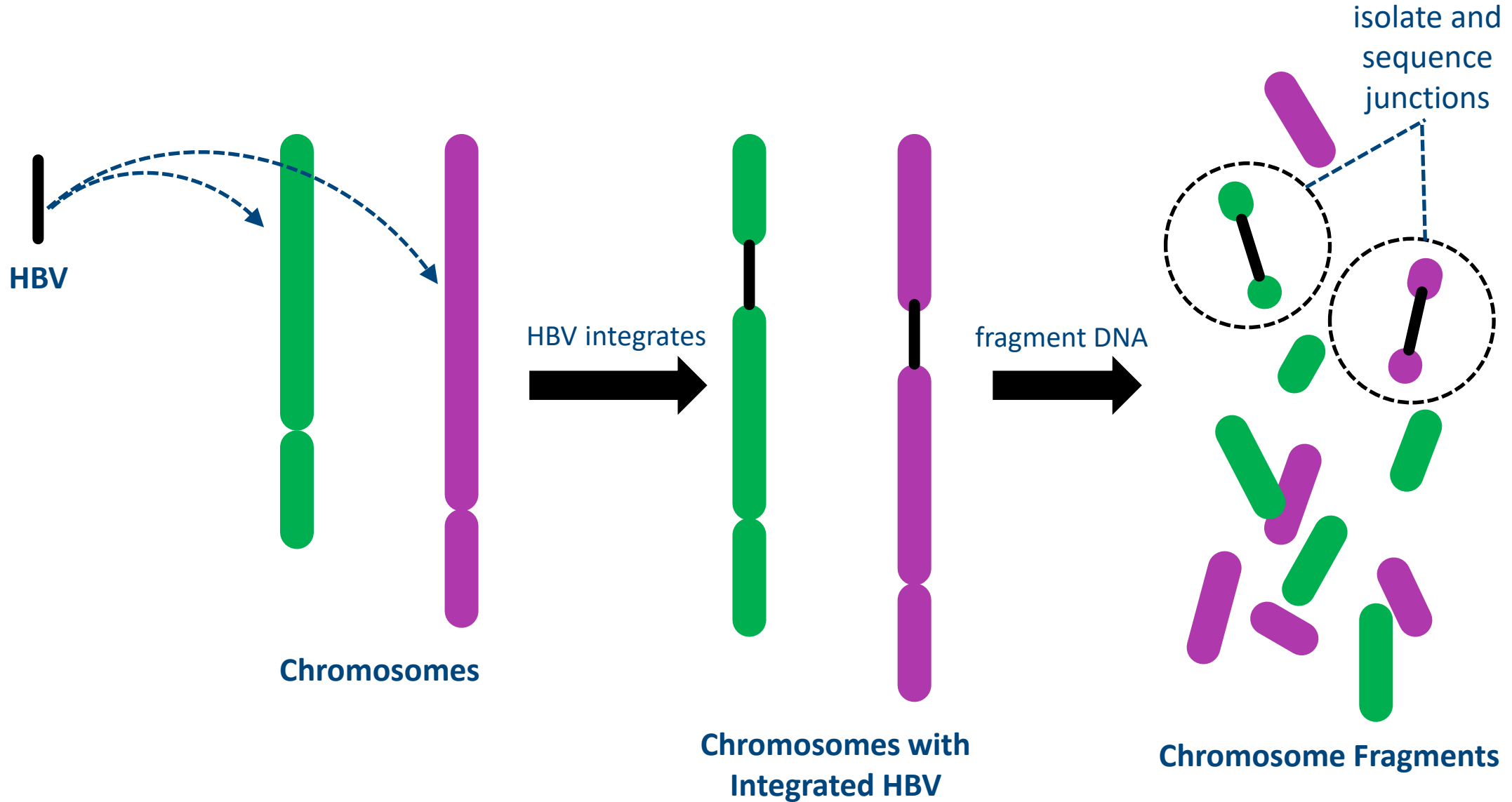
Optimization increases activity



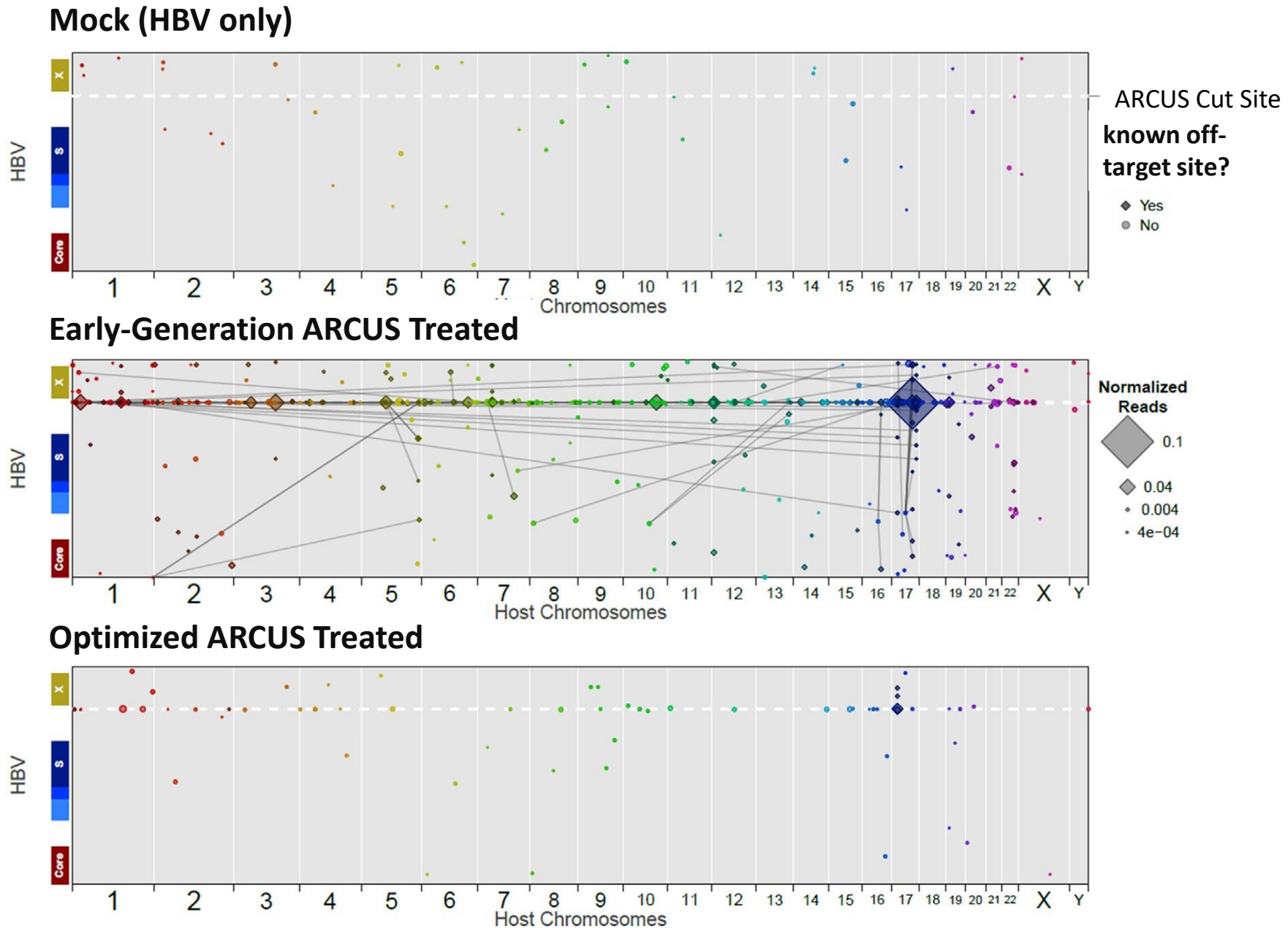
Optimization increases specificity



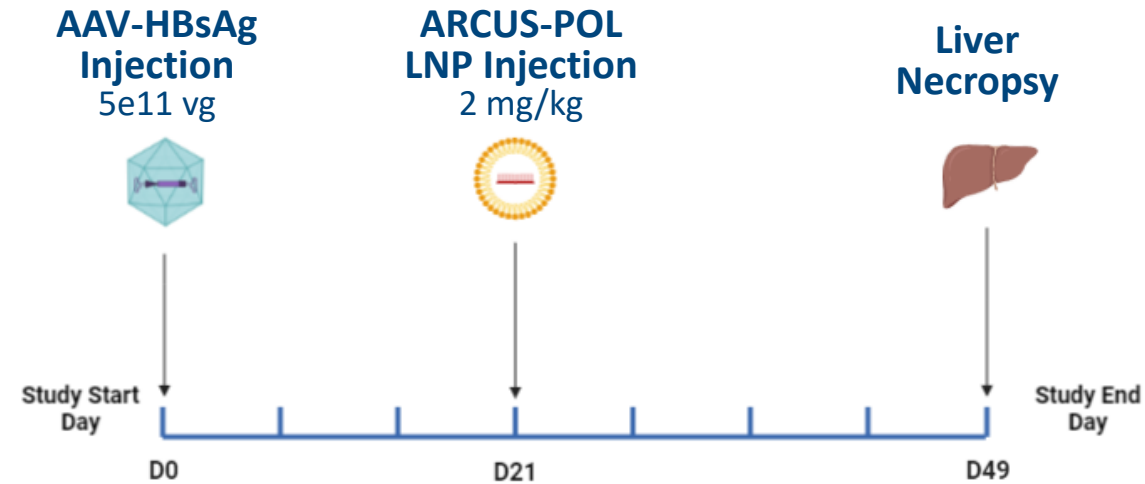
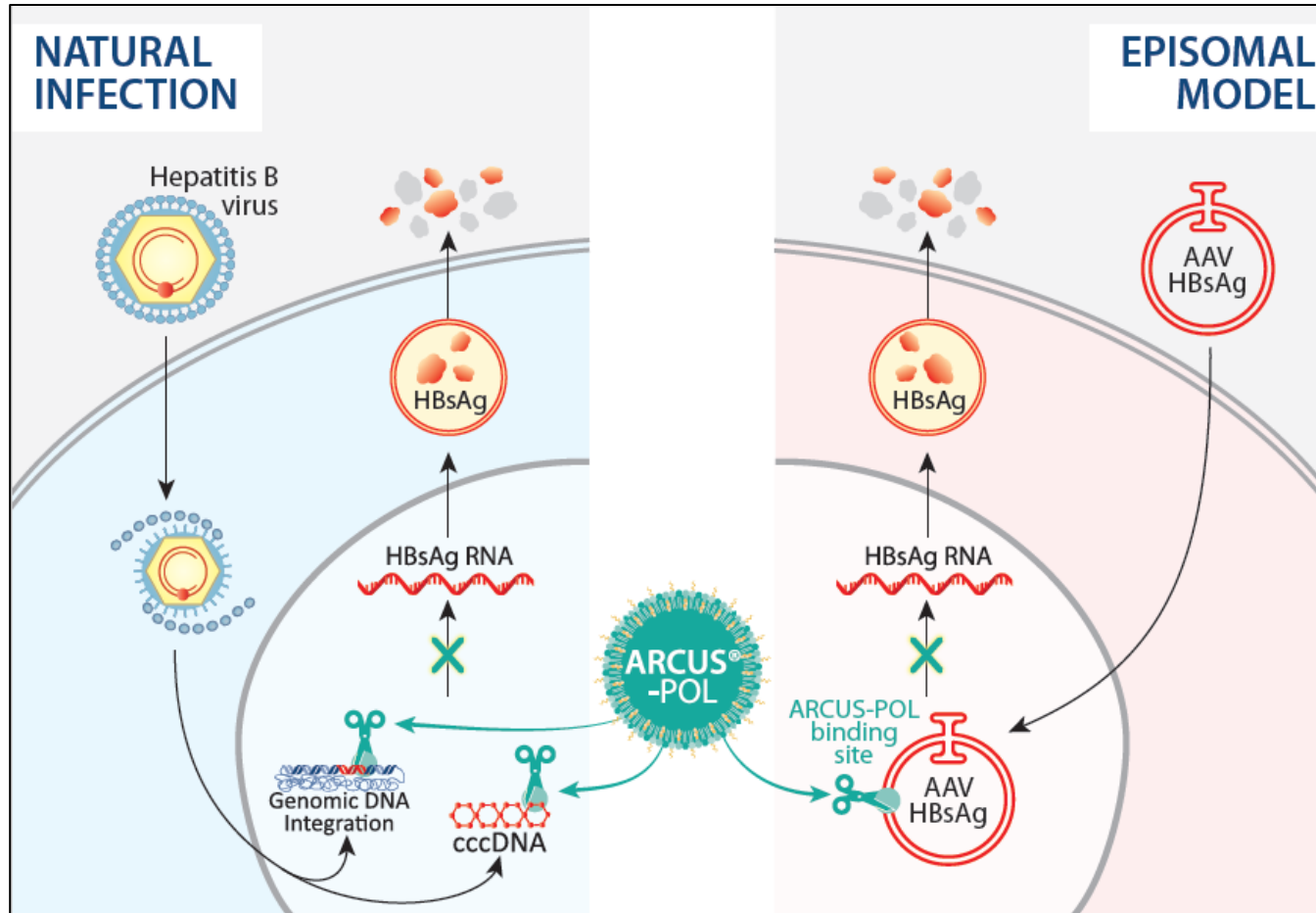
# Measuring HBV DNA integration into the genome of HBV infected primary human hepatocytes



# Optimization of ARCUS-POL reduces integrations and translocations resulting from gene editing



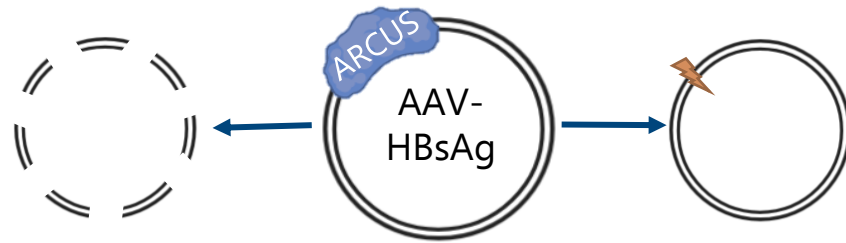
# HBV Episomal *In Vivo* Model



## Readouts:

- Inactivation of AAV-HBsAg (cccDNA surrogate)
- HBsAg loss in serum and liver

# ARCUS-POL inactivates viral DNA and durably reduces HBsAg in an episomal mouse model

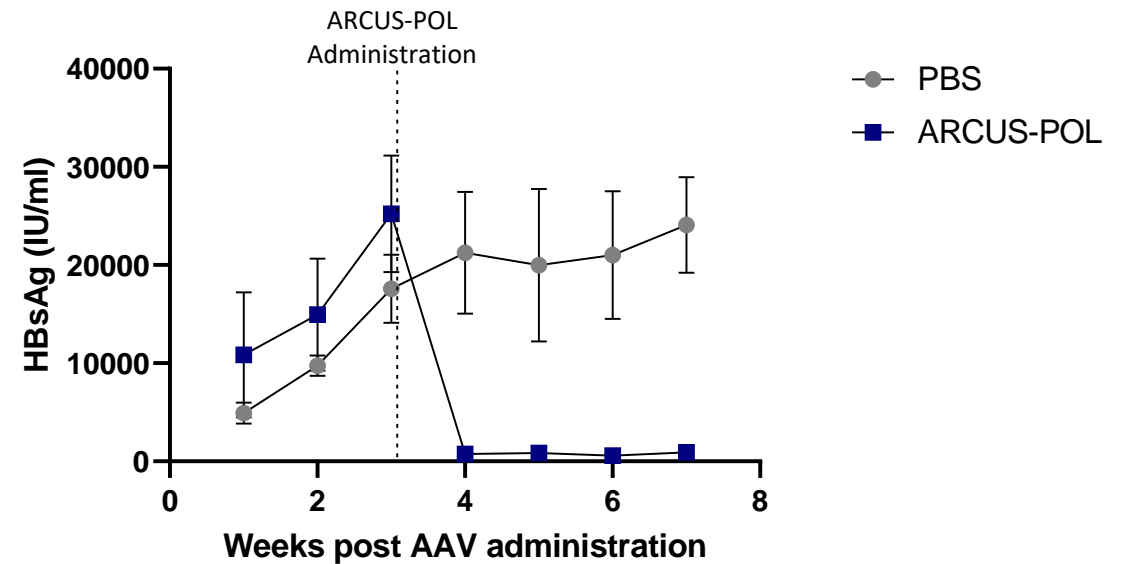
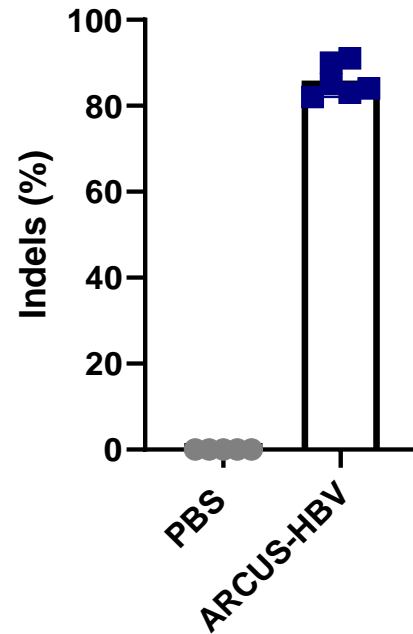
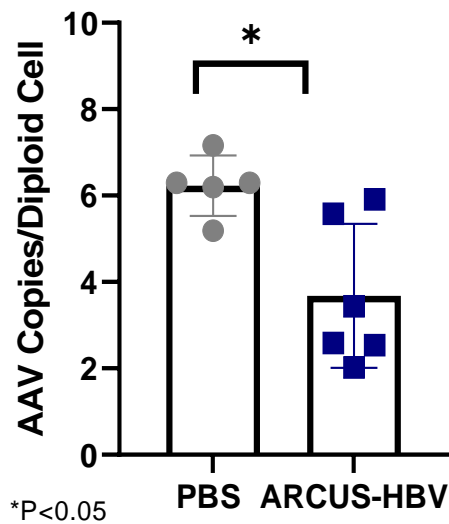


40% reduction in AAV copy number

86% indels in remaining AAV

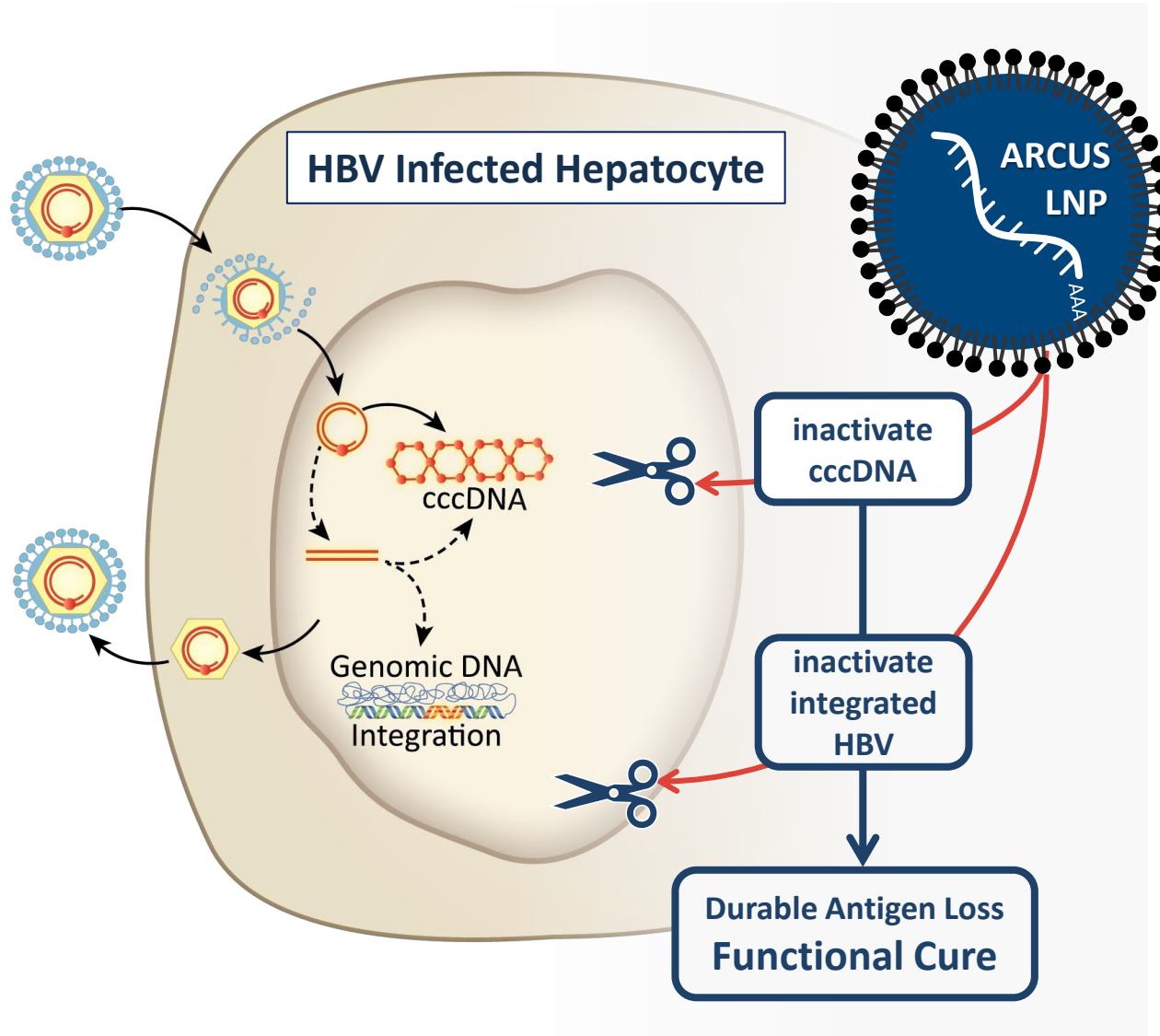
>90% total viral DNA engagement

96% reduction in secreted HBsAg



# Rationale for a functional cure:

## ARCUS gene editing inactivates cccDNA and integrated HBV to drive durable antigen loss





# Acknowledgements

## **Precision BioSciences, Inc.**

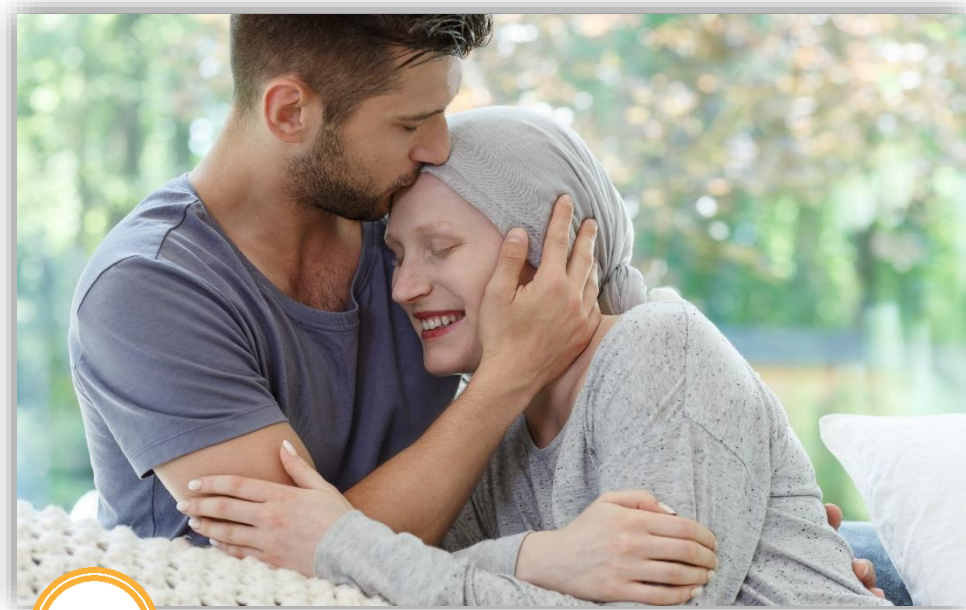
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- Simin Xu
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- Bill Delaney
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- Becket Feierbach

## **Acuitas Therapeutics**

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