Translational development of CRMA-1001, an epigenetic silencer for the treatment of chronic hepatitis B

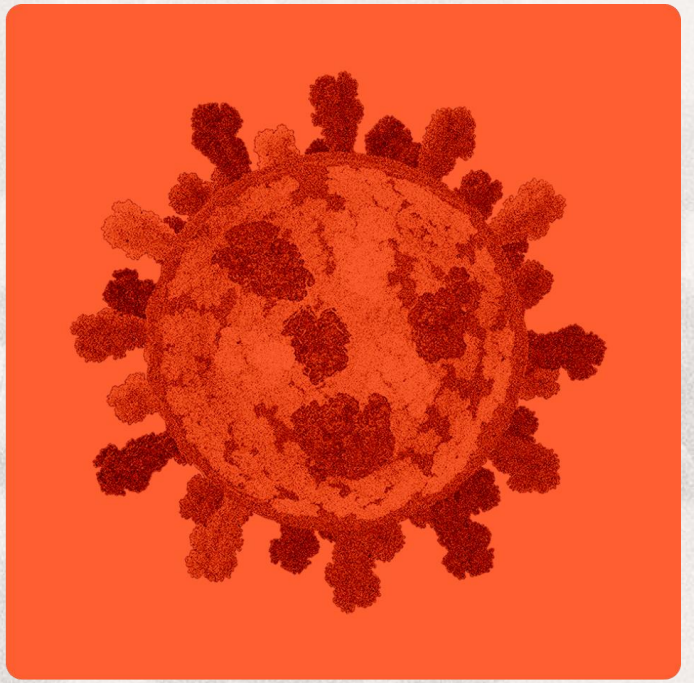
Sarah Voytek, PhD

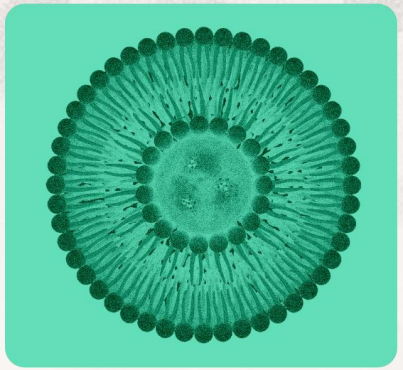
Vice President, Translational Medicine

Global Program Lead

ASGCT

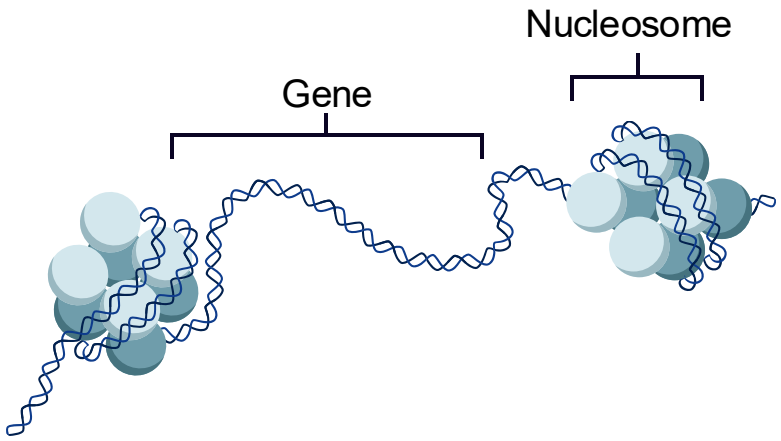
May 12, 2026





Epigenetic silencing leverages endogenous mechanisms to precisely control gene expression

Durable regulation of gene expression without cutting or nicking the DNA

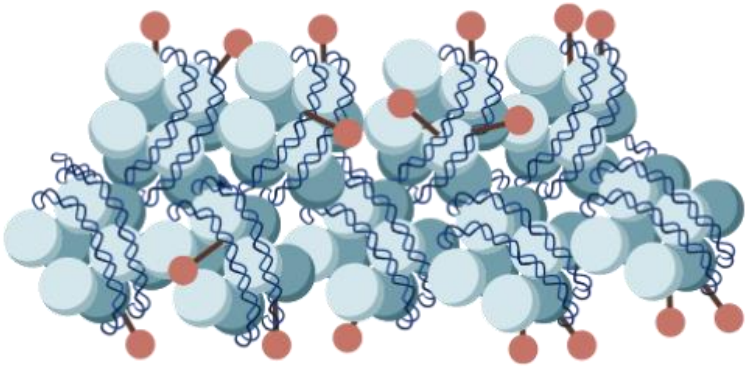


Gene is Active
DNA is Open and Accessible

Epigenetic Silencer
Methylates Targets

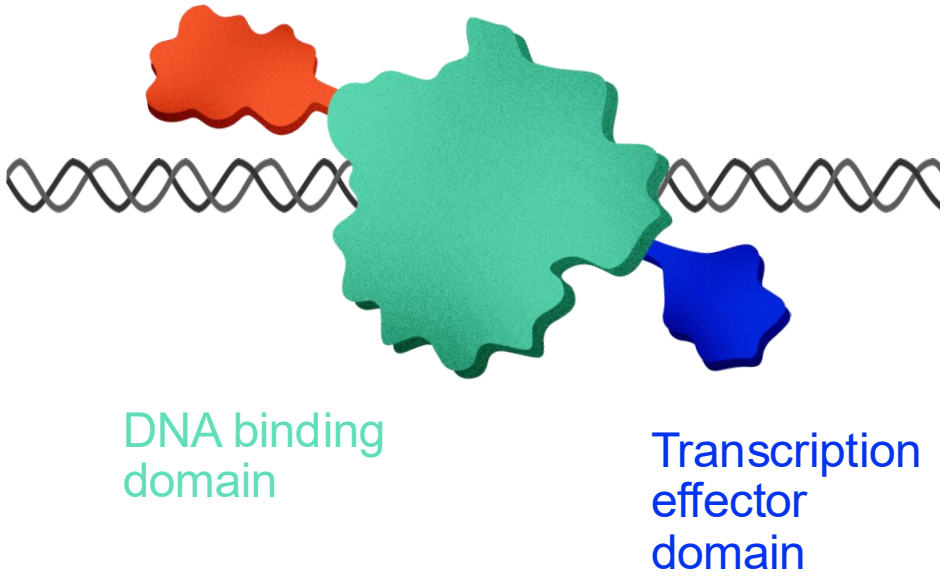
Transient Application

Gene is Inactive
DNA is Closed and Inaccessible



Epigenetic silencers are modular constructs that can be delivered to the liver by LNPs

Epigenetic Silencer Protein

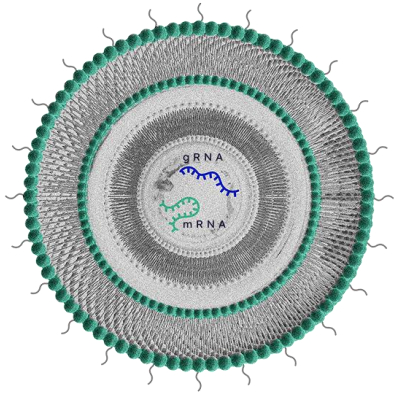


DNA binding domain precisely localizes effector domains to target sequence

Transcription effector domain transiently suppresses the target gene

Methylation effector domain durably represses the target gene

LNP delivery

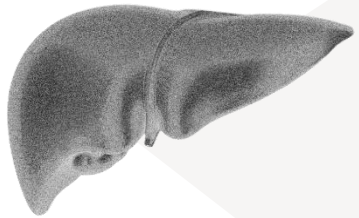


mRNA and gRNA delivered via LNP

Abbreviations: gRNA (guide RNA); LNP (lipid nanoparticle); mRNA (messenger RNA)

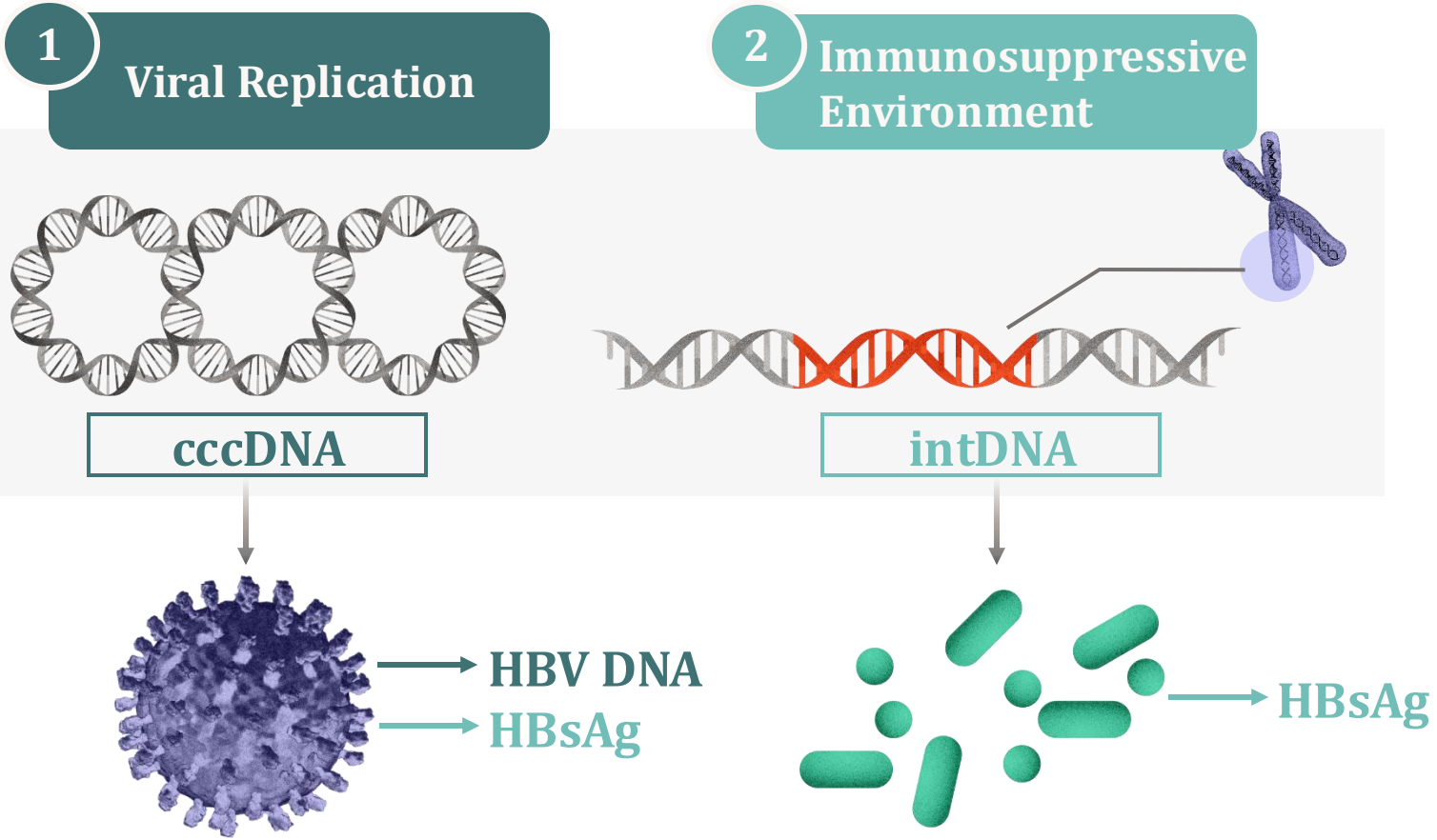
Novel therapies needed for chronic HBV to drive functional cure

Key Mechanisms Driving HBV Pathophysiology



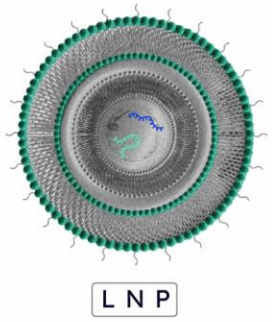
Current Therapies are Limited

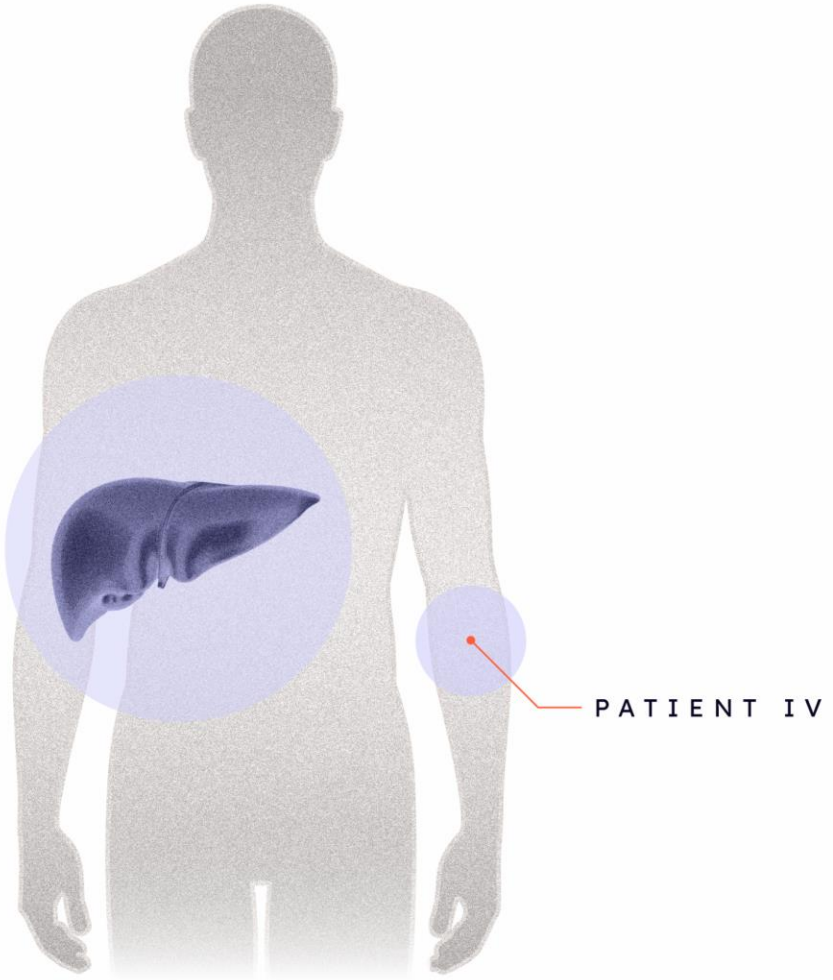
- 254M chronic hepatitis B patients globally
- 1.1M hepatitis B related deaths annually
- Current therapies don't robustly target both mechanisms – very low functional cure rates
- NUC therapies generally require lifelong treatment



Abbreviations: cccDNA (covalently closed circular DNA); HBsAg (hepatitis B surface antigen); HBV (hepatitis B virus); intDNA (integrated HBV DNA); NUCs (nucleos(t)ide analogs)

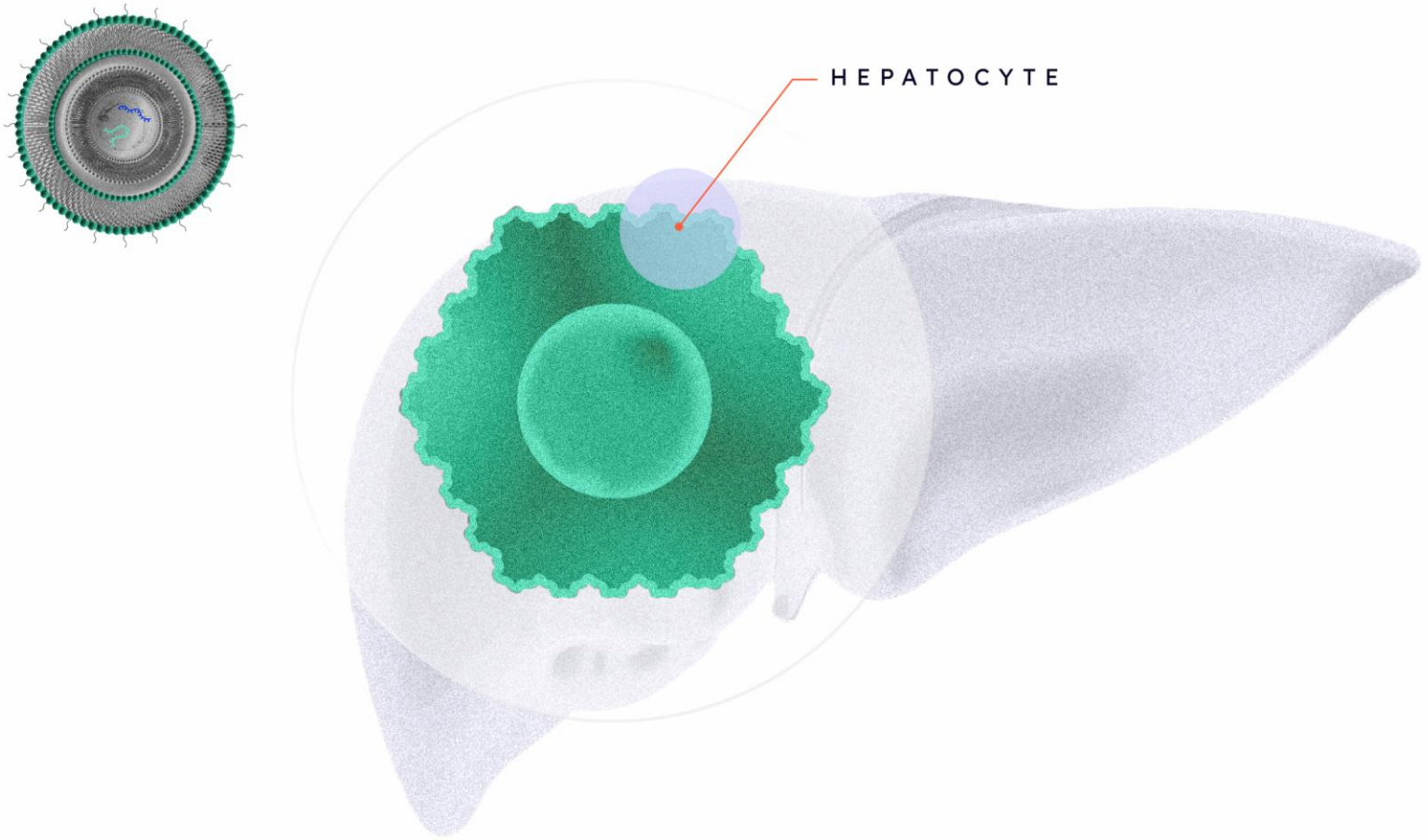
CRMA-1001 silences both HBV integrated and cccDNA





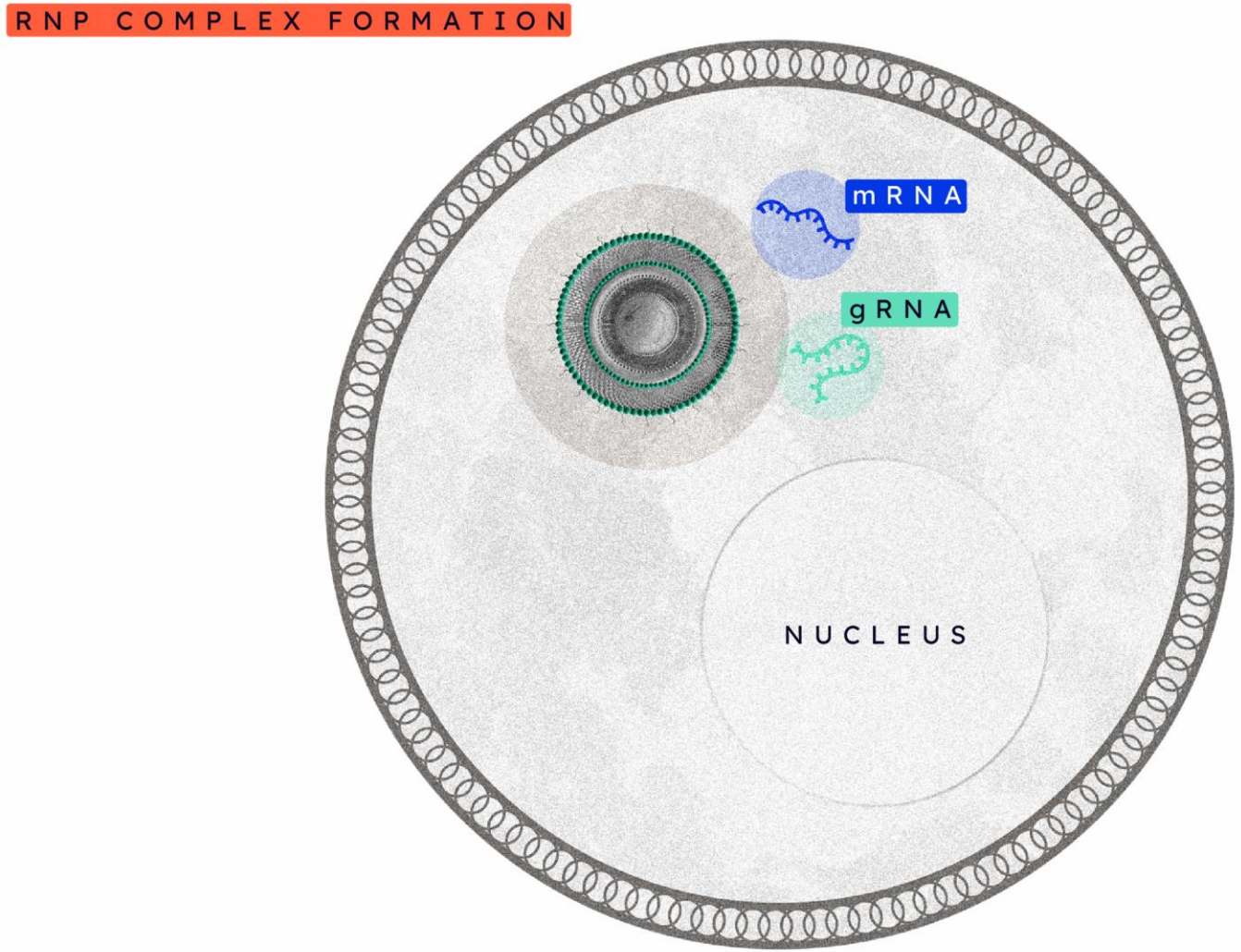
Abbreviations: cccDNA (covalently closed circular DNA); HBV (hepatitis B virus); IV (intravenous), LNP (lipid nanoparticle); RNP (ribonucleoprotein)

CRMA-1001 silences both HBV integrated and cccDNA



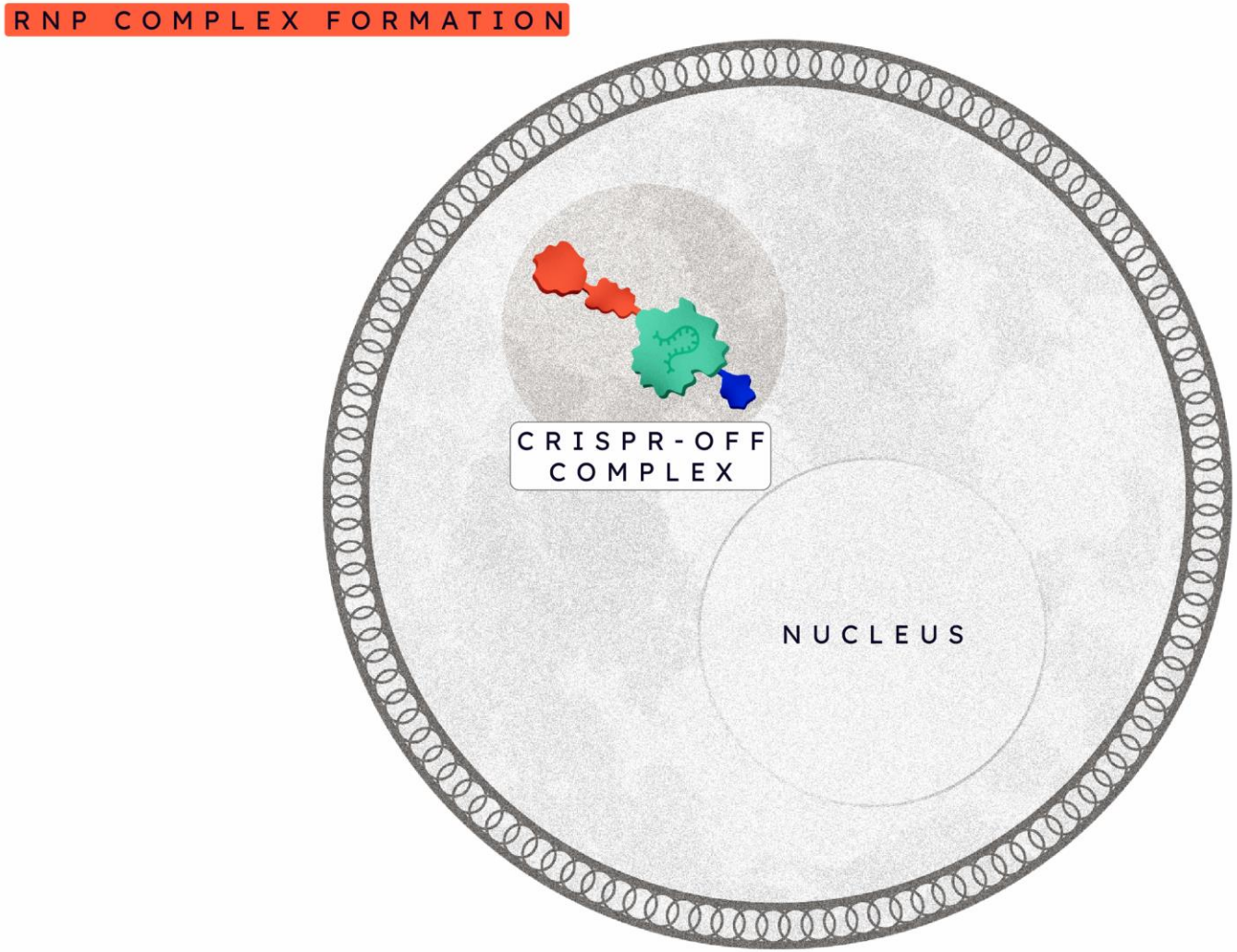
Abbreviations: cccDNA (covalently closed circular DNA); HBV (hepatitis B virus); IV (intravenous), LNP (lipid nanoparticle); RNP (ribonucleoprotein)

CRMA-1001 silences both HBV integrated and cccDNA



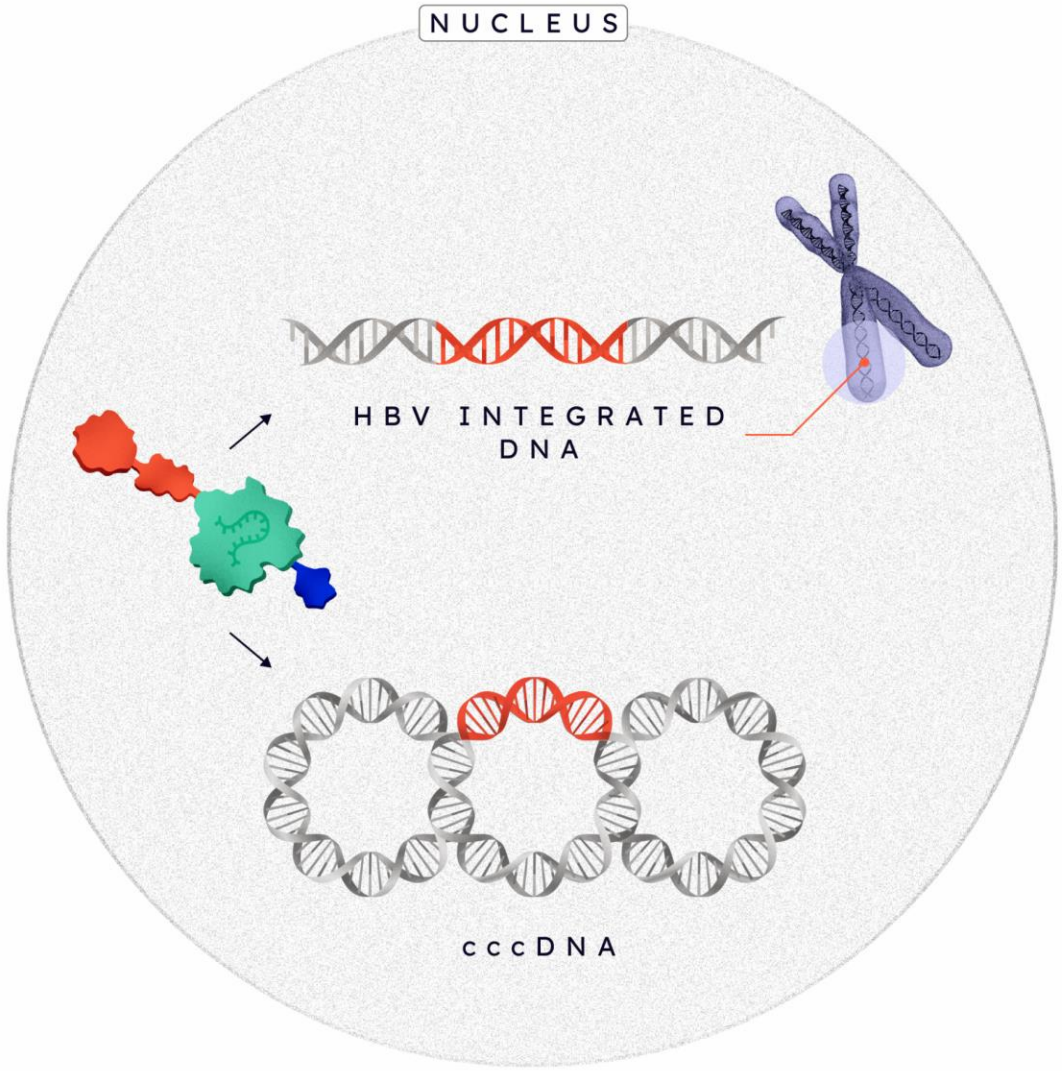
Abbreviations: cccDNA (covalently closed circular DNA); HBV (hepatitis B virus); IV (intravenous), LNP (lipid nanoparticle); RNP (ribonucleoprotein)

CRMA-1001 silences both HBV integrated and cccDNA



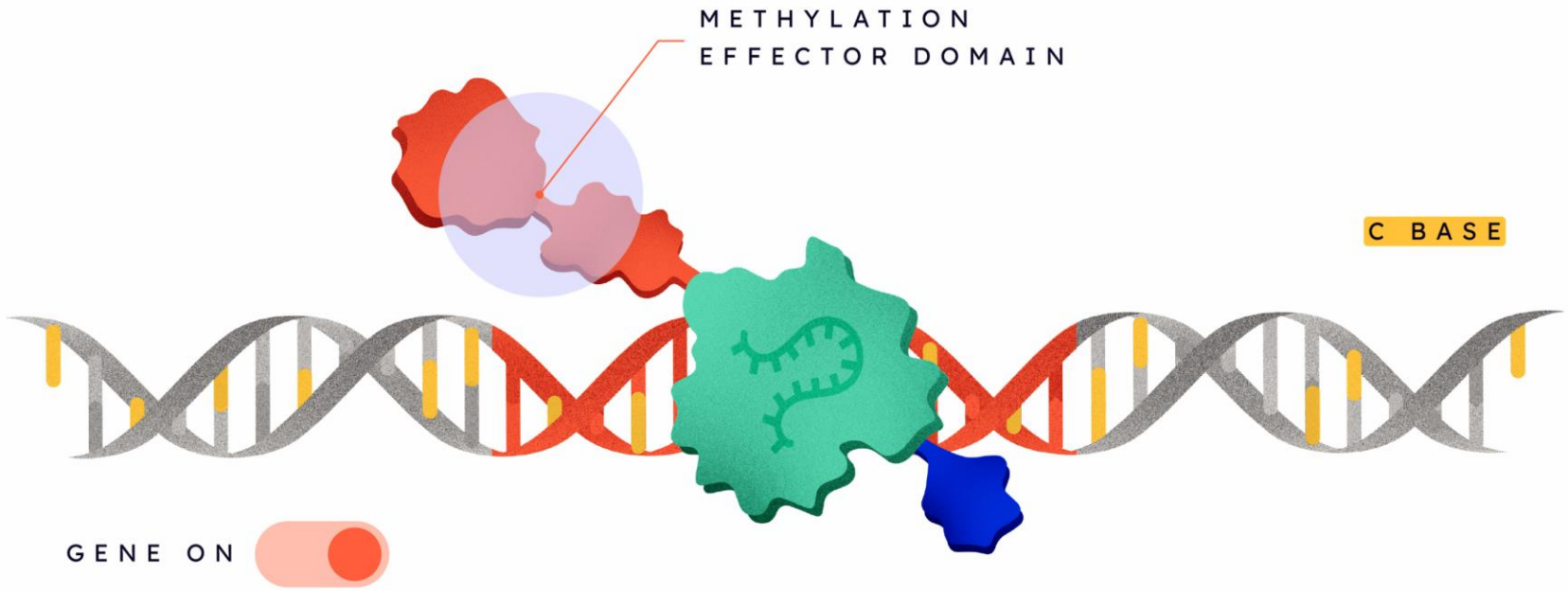
Abbreviations: cccDNA (covalently closed circular DNA); HBV (hepatitis B virus); IV (intravenous), LNP (lipid nanoparticle); RNP (ribonucleoprotein)

CRMA-1001 silences both HBV integrated and cccDNA



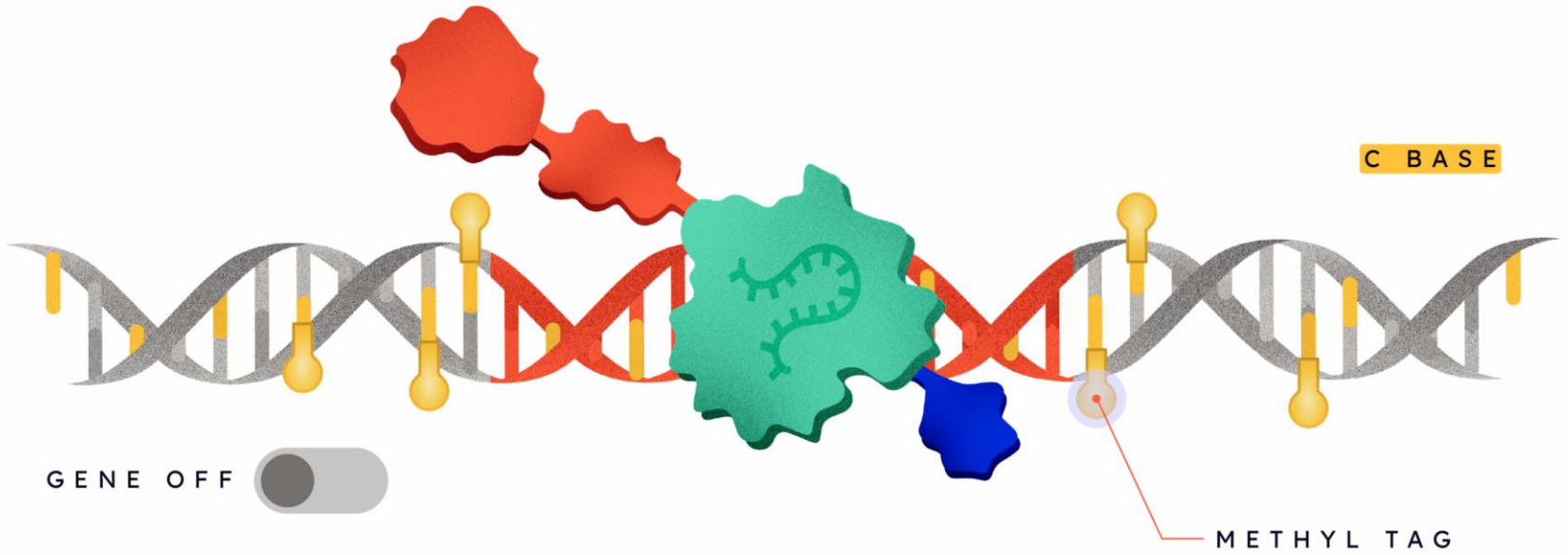
Abbreviations: cccDNA (covalently closed circular DNA); HBV (hepatitis B virus); IV (intravenous), LNP (lipid nanoparticle); RNP (ribonucleoprotein)

CRMA-1001 silences both HBV integrated and cccDNA



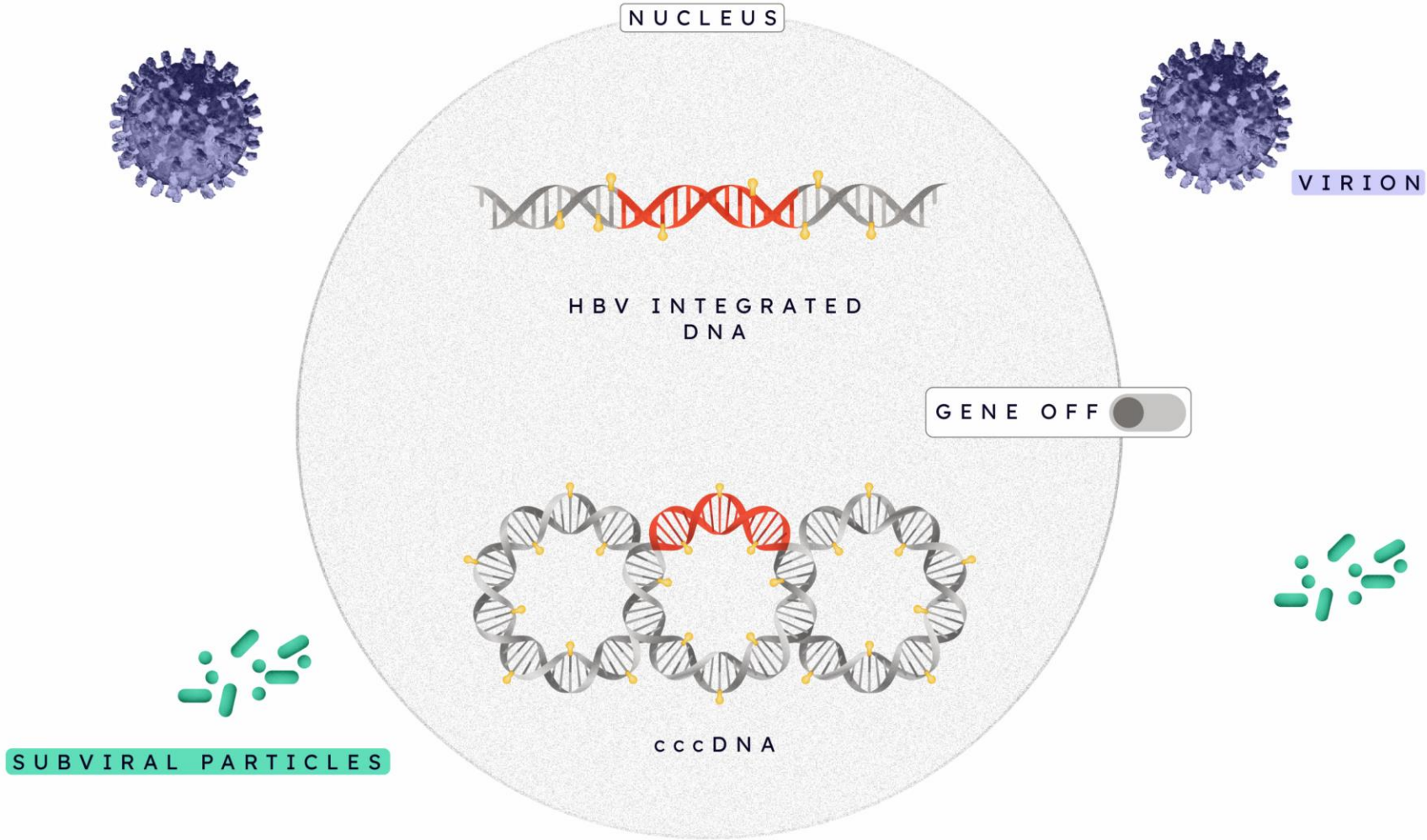
Abbreviations: cccDNA (covalently closed circular DNA); HBV (hepatitis B virus); IV (intravenous), LNP (lipid nanoparticle); RNP (ribonucleoprotein)

CRMA-1001 silences both HBV integrated and cccDNA



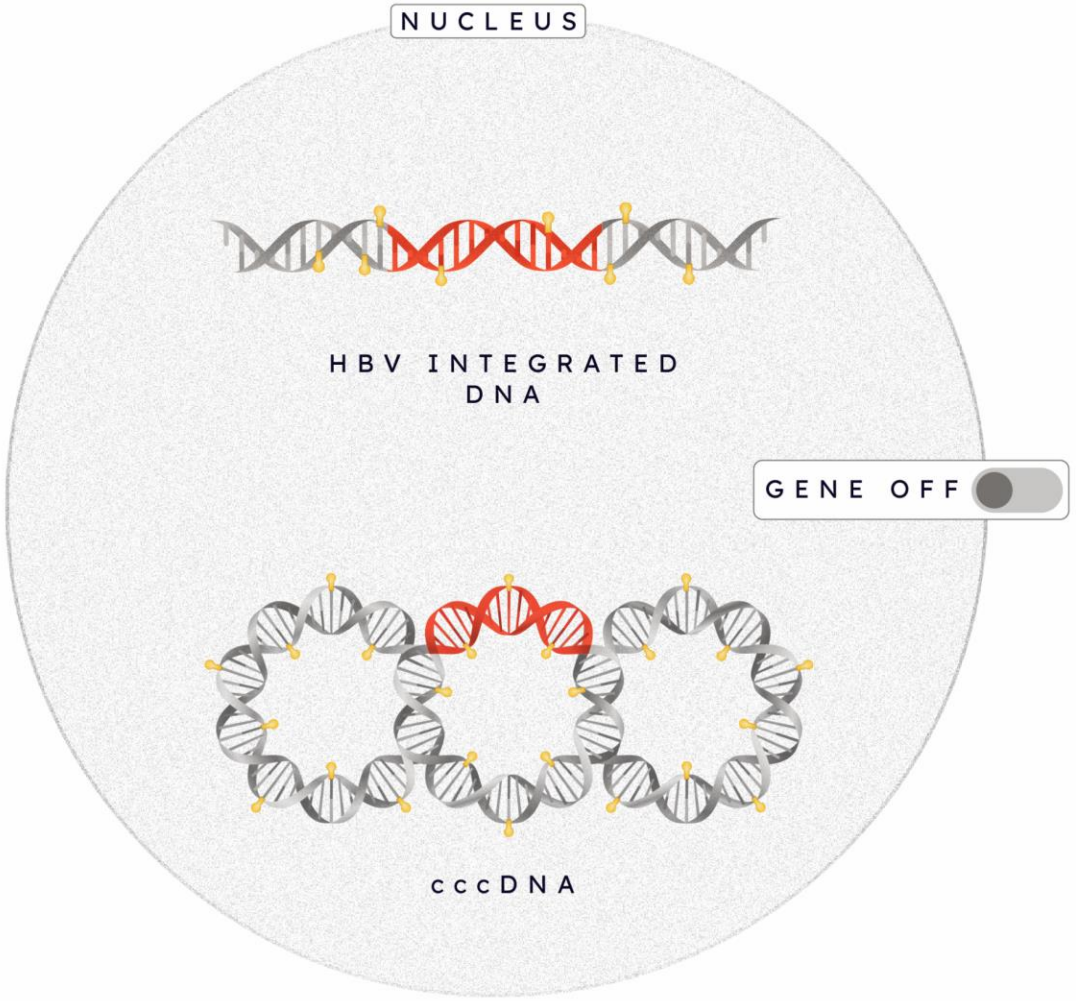
Abbreviations: cccDNA (covalently closed circular DNA); HBV (hepatitis B virus); IV (intravenous), LNP (lipid nanoparticle); RNP (ribonucleoprotein)

CRMA-1001 silences both HBV integrated and cccDNA



Abbreviations: cccDNA (covalently closed circular DNA); HBV (hepatitis B virus); IV (intravenous), LNP (lipid nanoparticle); RNP (ribonucleoprotein)

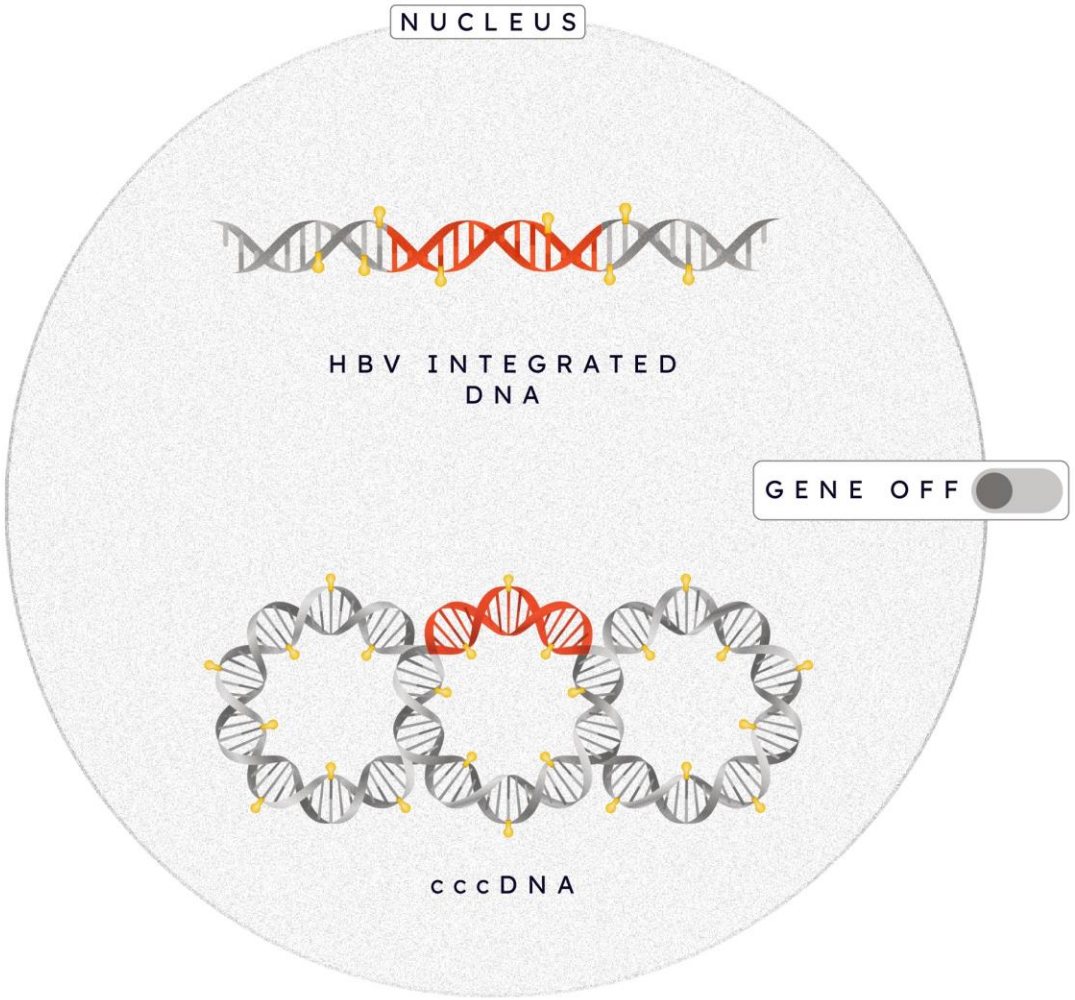
CRMA-1001 silences both HBV integrated and cccDNA



Abbreviations: cccDNA (covalently closed circular DNA); HBV (hepatitis B virus); IV (intravenous), LNP (lipid nanoparticle); RNP (ribonucleoprotein)

Epigenetic silencing is uniquely suited to address chronic HBV

- ✓ **Durably silences both forms of the genome,** HBV cccDNA and intDNA, at the level of transcription
- ✓ **Conserved** target site across HBV genotypes (>94% across genotypes A-H)
- ✓ **Highly potent with 99.9% silencing** of viral antigen after a single dose in vivo, supporting delivery to virtually all hepatocytes
- ✓ **Potential for clinically meaningful rates of functional cure with a single course of treatment**
- ✓ **Mechanism avoids unintended cutting or nicking DNA** as compared to other gene editing approaches



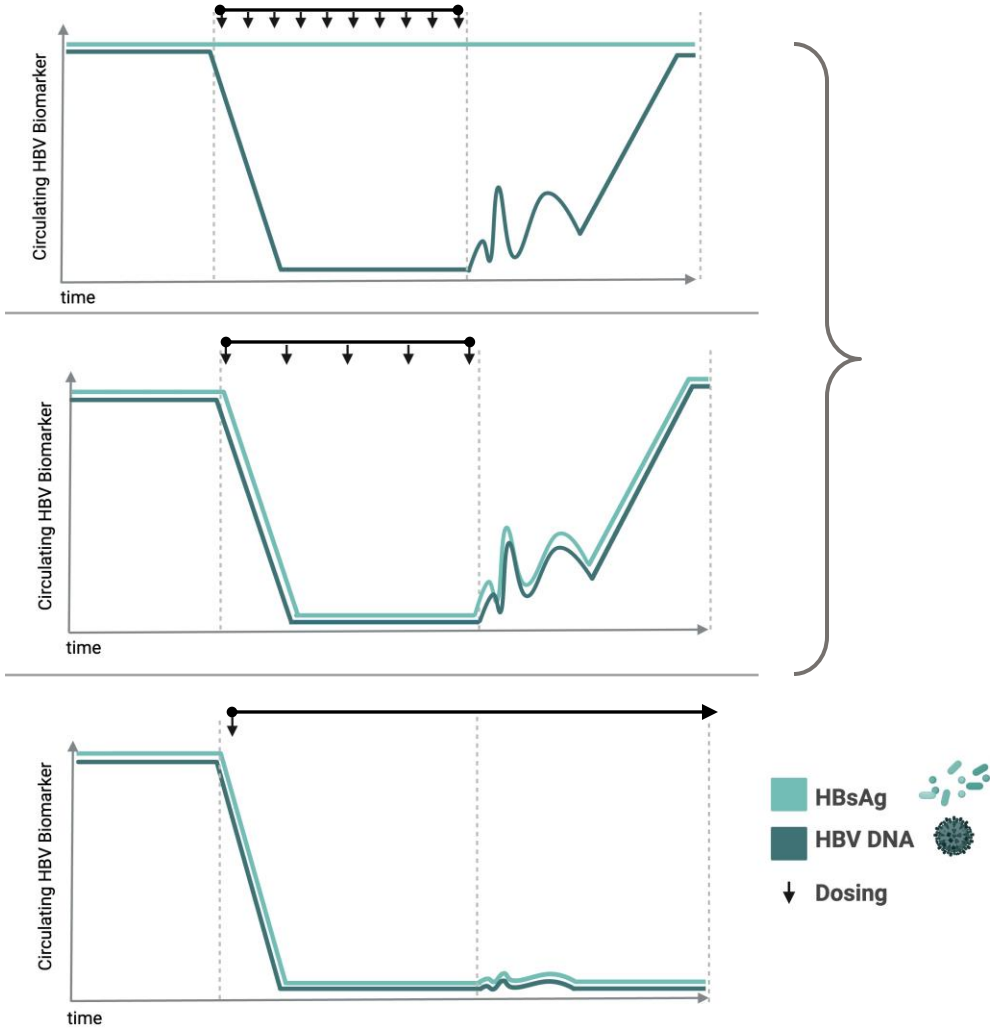
Abbreviations: cccDNA (covalently closed circular DNA); gRNA (guide RNA), HBV (hepatitis B virus); intDNA (integrated HBV DNA)

CRMA-1001 will potentially enable functional cures in chronic HBV where other technologies may be limited

Nucleos(t)ide Analog

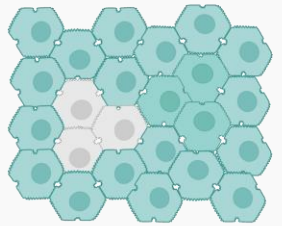
ASO/siRNA

CRMA-1001



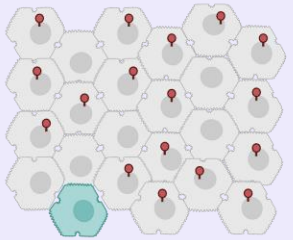
Plots are illustrative

Nucleos(t)ide Analog and ASO/siRNA



At cessation of treatment, infected cells are **functionally active** producing virions and antigens. Significant disease burden **overwhelms the immune system**, limiting clearance of infected cells and rates of functional cure.

CRMA-1001

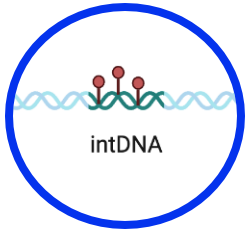


CRMA-1001 treatment is intended to **functionally inactivate** HBV, resulting in **minimal residual disease burden** for immune system to clear, enabling functional cure.

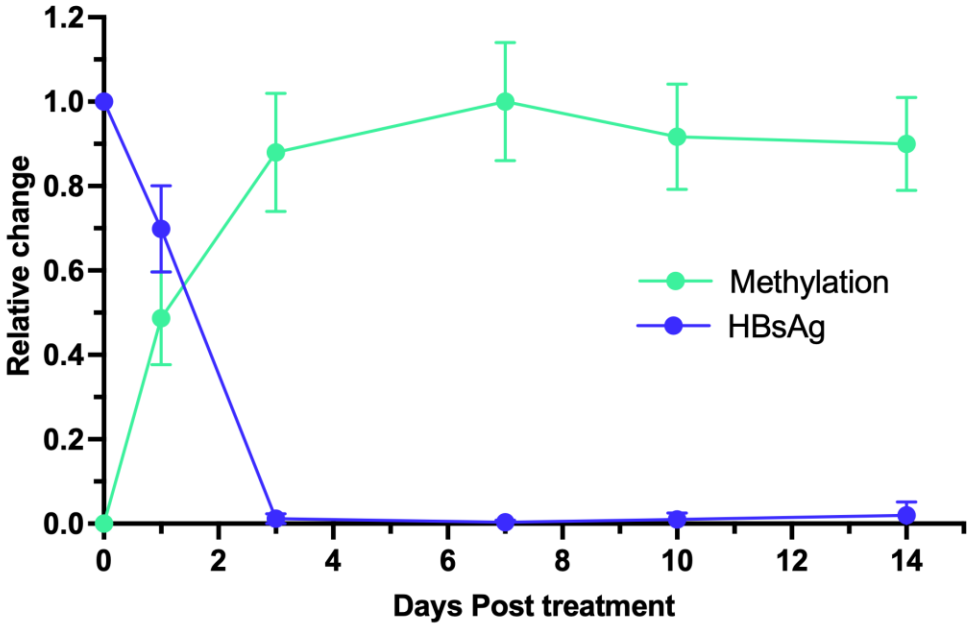
Hepatocyte infected with HBV Healthy Hepatocyte Methylated HBV DNA

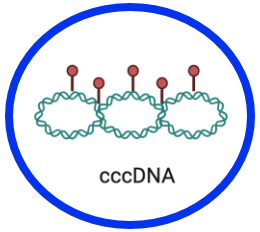
Abbreviations: ASO (antisense oligonucleotide); HBsAg (hepatitis B surface antigen); HBV (hepatitis B virus); siRNA (small interfering RNA)

Increase of HBV CpG methylation in both intDNA and cccDNA correlates with reduction of viral biomarkers

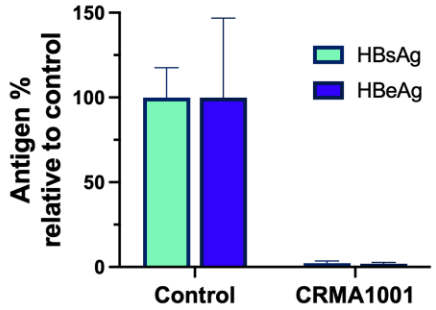


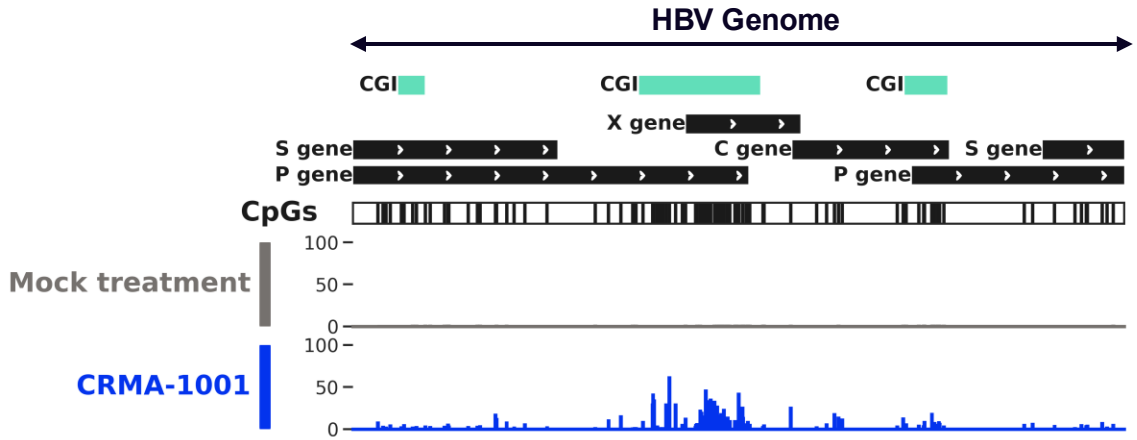
HepG2.2.15 cells 14 days after treatment with CRMA-1001





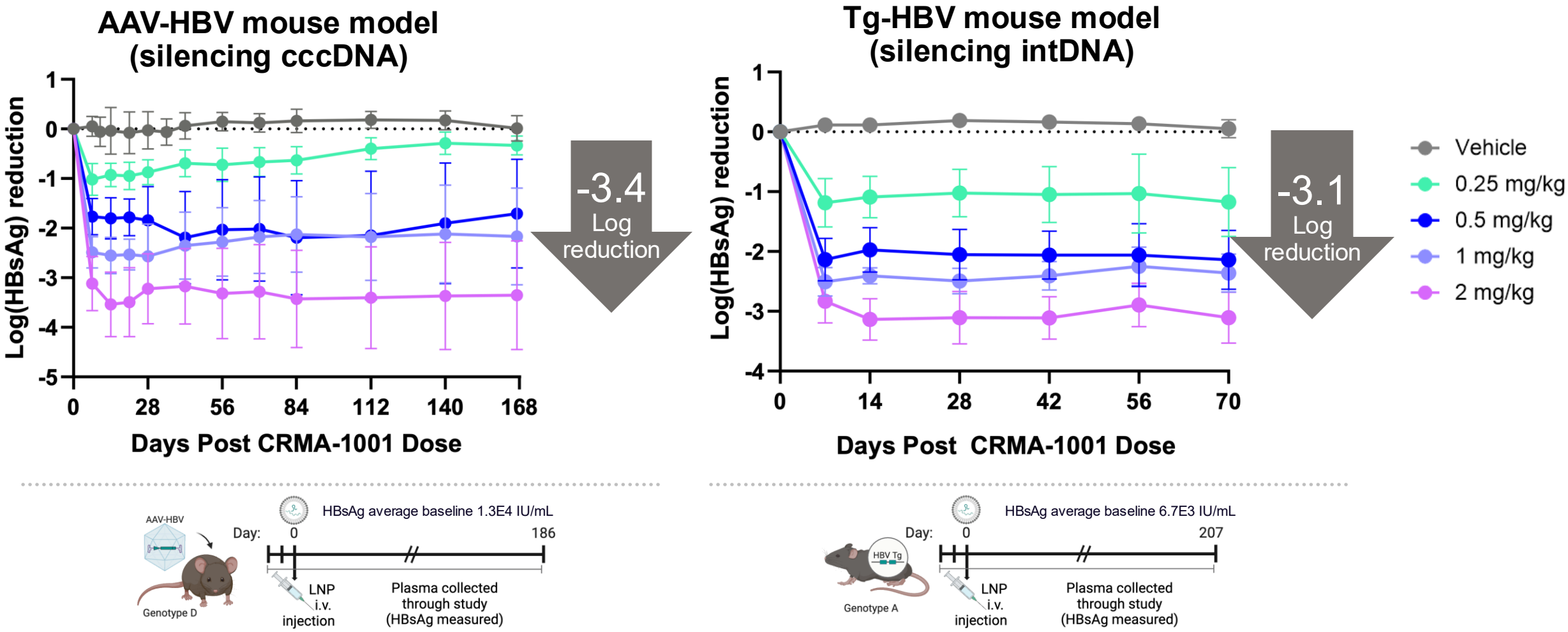
Infected PHH cells 14 days after treatment with CRMA-1001





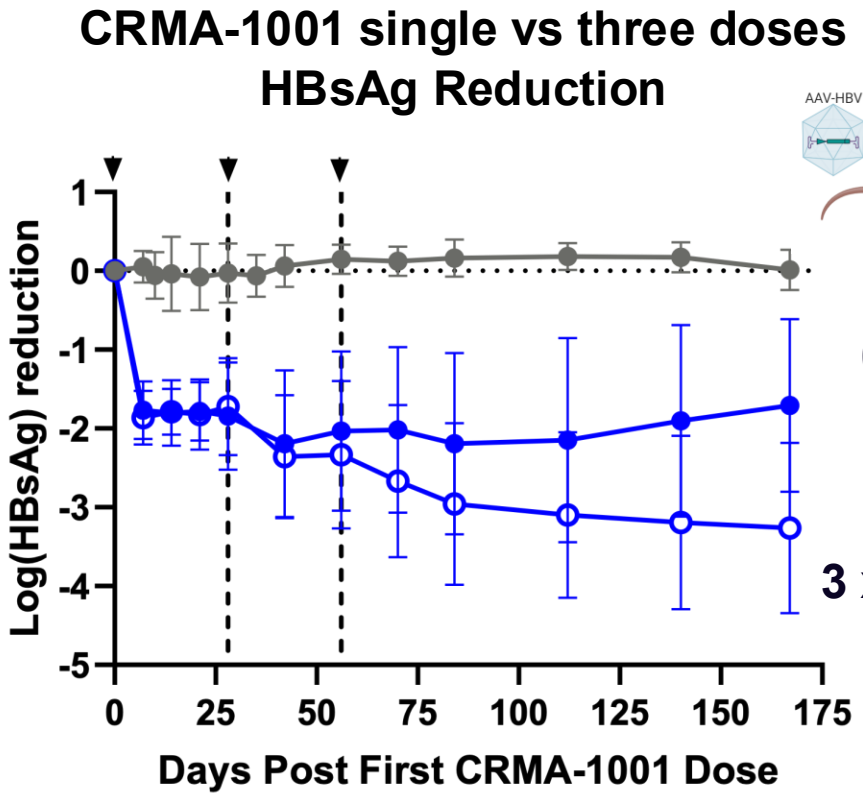
Abbreviations: cccDNA (covalently closed circular DNA); CGI (CpG islands); HBeAg (hepatitis B e-antigen), HBsAg (hepatitis surface antigen); HBV (hepatitis B virus); intDNA (integrated HBV DNA); PHH (primary human hepatocytes)

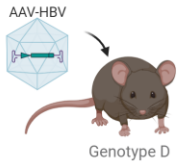
CRMA-1001 durably reduces HBsAg in HBV mouse models for at least 6 months following a single dose



Abbreviations: AAV (adeno-associated virus); HBsAg (hepatitis B surface antigen); HBV (hepatitis B virus); LNP (lipid nanoparticle); i.v. (intravenous); Tg (transgenic)

CRMA-1001 repeat dosing regimen drives additive pharmacology and results in more animals with HBsAg loss

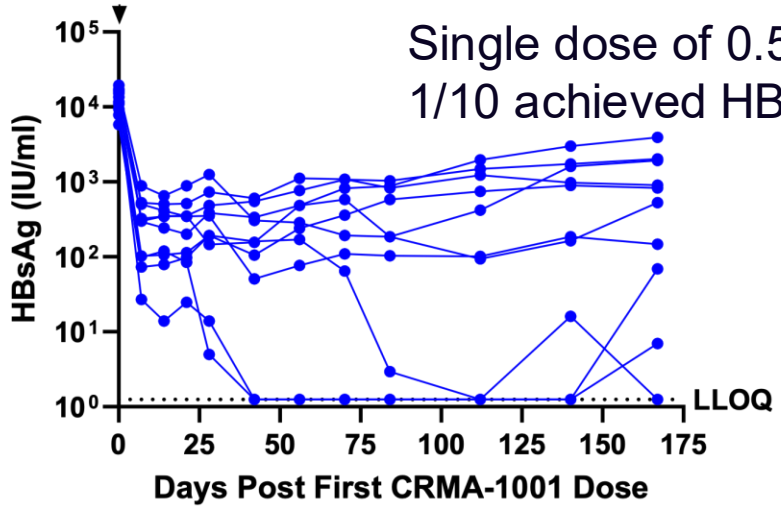




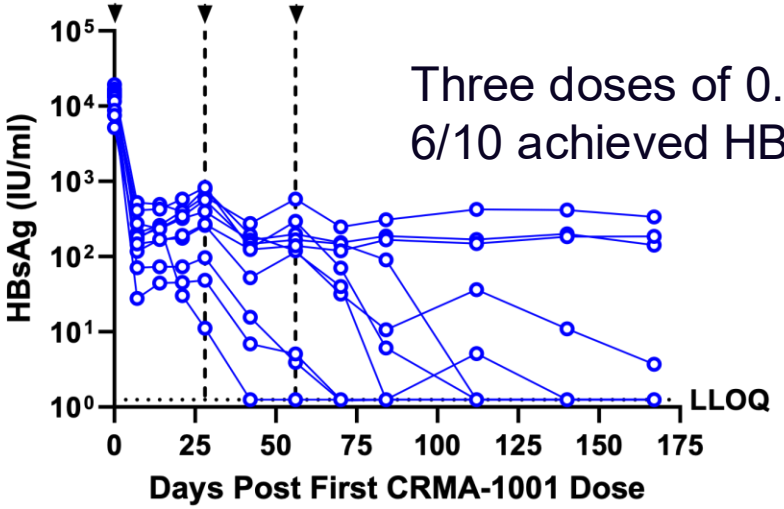
0.5 mg/kg

-1.6 Log

3 x 0.5 mg/kg



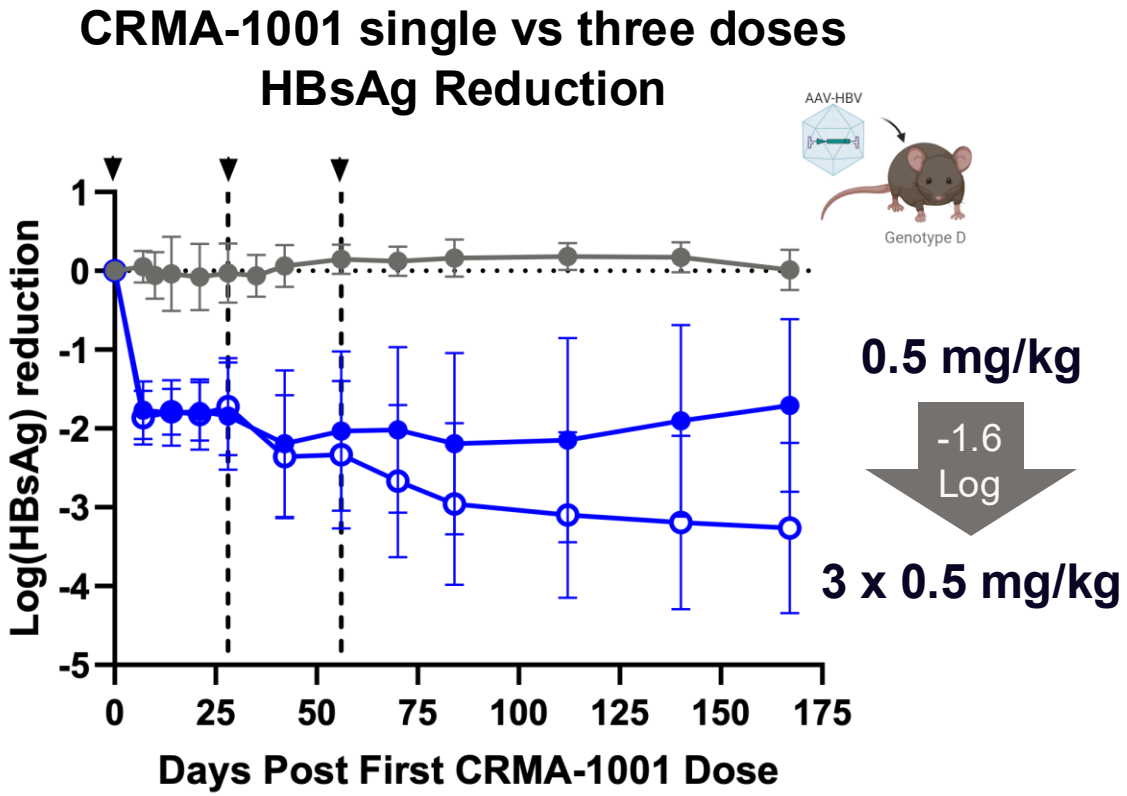
Single dose of 0.5 mg/kg:
1/10 achieved HBsAg loss

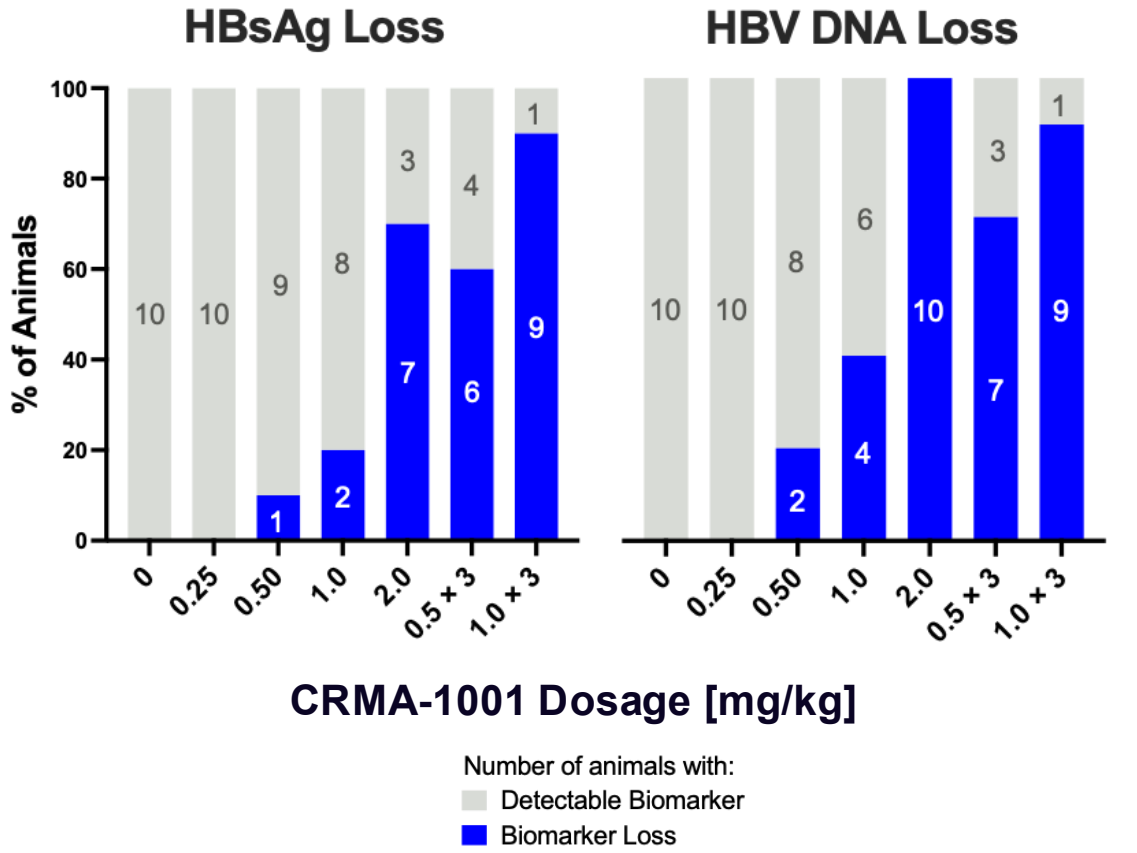


Three doses of 0.5 mg/kg:
6/10 achieved HBsAg loss

Abbreviations: AAV (adeno-associated virus); HBsAg (hepatitis B surface antigen); HBV (hepatitis B virus); LLOQ (lower limit of quantification)
Note: Average baseline of HBsAg ~1.3E4 IU/mL in AAV model.

CRMA-1001 repeat dosing regimen drives additive pharmacology and results in more animals with HBsAg loss

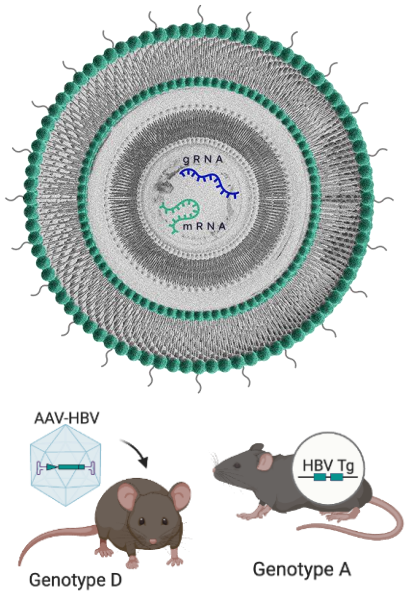




Abbreviations: AAV (adeno-associated virus); HBsAg (hepatitis B surface antigen); HBV (hepatitis B virus); LLOQ (lower limit of quantification);
Note: Average baseline of HBsAg ~1.3E4 IU/mL in AAV model.

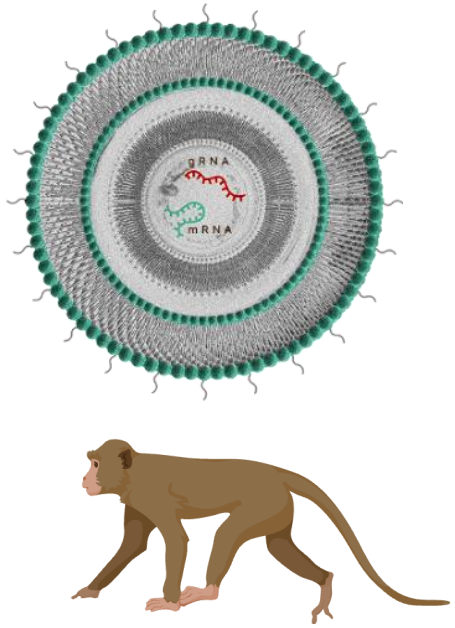
Epigenetic silencing of PCSK9 in NHPs informs efficiency, durability, and tolerability of silencing HBV with CRMA-1001

CRMA-1001



No large animal models available for HBV

PCSK9-EE

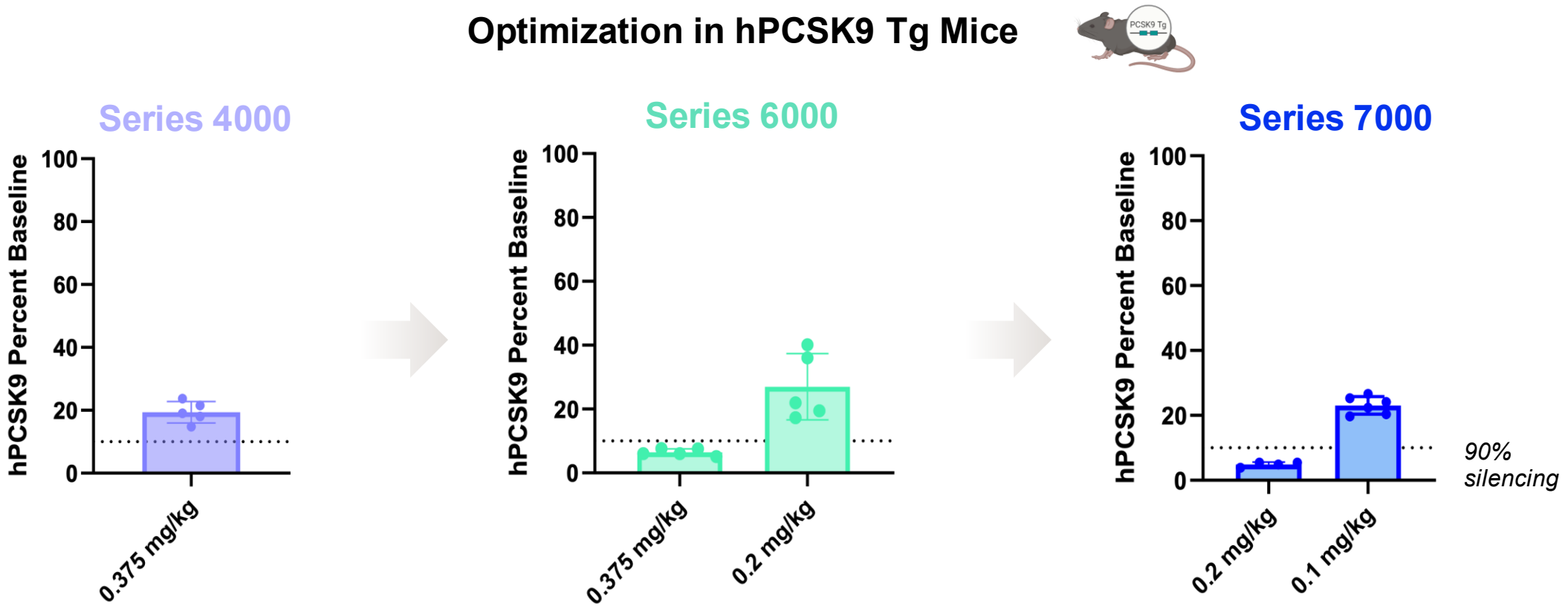


PCSK9 silencing can be evaluated in NHPs

- CRMA-1001 and PCSK9-EE use the same mRNA epigenetic effector construct and LNP delivery vehicle to silence the target, only the gRNA is different
- As HBV does not have a large animal model, nChroma Bio is leveraging *PCSK9* to evaluate the efficiency, durability, and tolerability of epigenetically silencing HBV

Abbreviations: EE (epigenetic editor); gRNA (guide RNA); HBV (hepatitis B virus); NHP (non-human primate); PCSK9 (proprotein convertase subtilisin/kexin type 9)

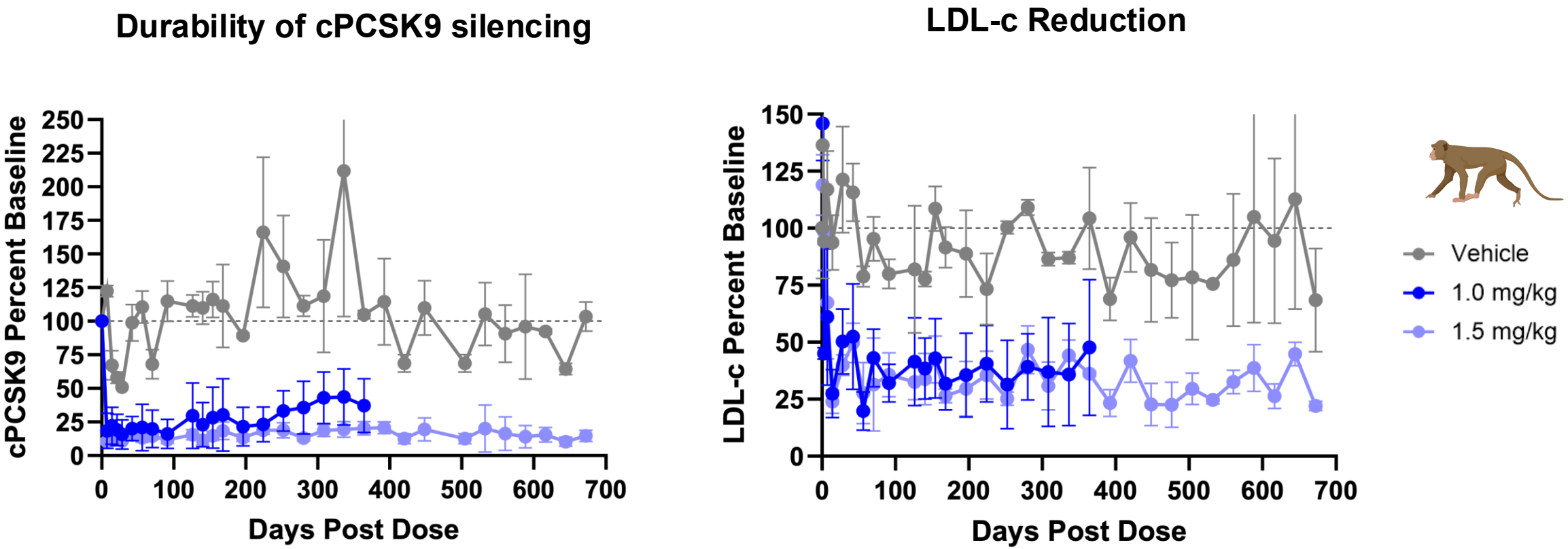
Construct optimization efforts have led to a significant increase in potency in animal models



- Construct optimization has yielded a significant increase in epigenetic silencer potency in hPCSK9 Tg-mice
- NHP study with 7000 construct (used in CRMA-1001) demonstrated potency gains and >22 months durability

Abbreviations: hPCSK9 (human proprotein convertase subtilisin/kexin type 9); NHP (non-human primate); Tg (transgenic)

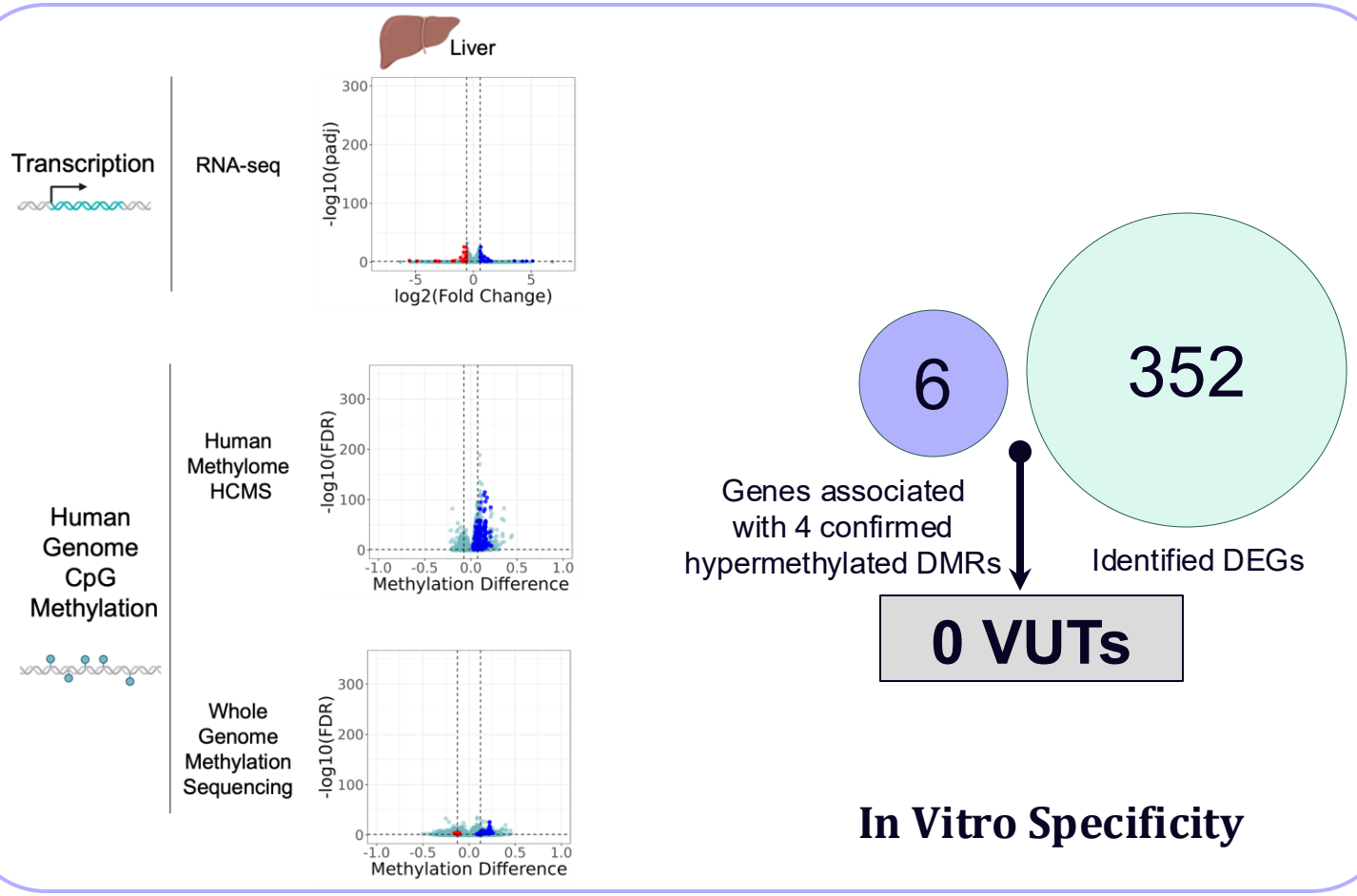
PCSK9-EE (Series 7000) achieved saturating pharmacology at ≥ 1 mg/kg in NHPs with durability beyond 22 months



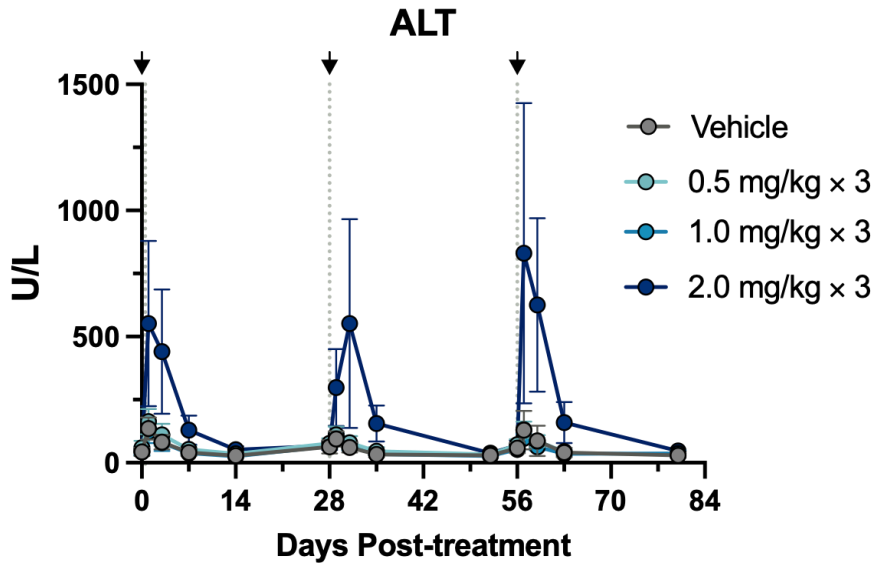
Abbreviations: cPCSK9 (cyno proprotein convertase subtilisin/kexin type 9); EE (epigenetic editor); LDL-c (low-density lipoprotein cholesterol); NHP (non-human primate)

No verified unintended targets (VUTs) have been identified in the human genome

A comprehensive evaluation of CRMA-1001 specificity, and safety in NHPs supported clinical trial initiation



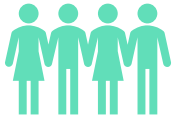
In Vitro Specificity



NHP GLP Toxicology

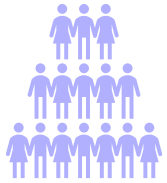
Abbreviations: ALT (alanine transaminase); CpG (cytosine guanine dinucleotide); DEG (differentially expressed gene); DMR (differentially methylated region); GLP (Good Laboratory Practice); HCMS (hybrid capture methylation sequencing); NHP (non-human primate); VUT (verified unintended target)

CRMA-1001-101: A Phase 1/2, open-label, SAD/MAD study of CRMA-1001 in adults with chronic hepatitis B



SINGLE ASCENDING DOSE

MULTIPLE ASCENDING DOSE



EXPANSION

Key Eligibility Criteria
Inclusion Criteria: • Adults with chronic hepatitis B • On oral antiviral therapy • ALT and AST ≤ 1.5 x ULN • Total bilirubin ≤ ULN **Exclusion Criteria:** • Significant hepatic fibrosis or cirrhosis • Current or prior liver disease other than HBV

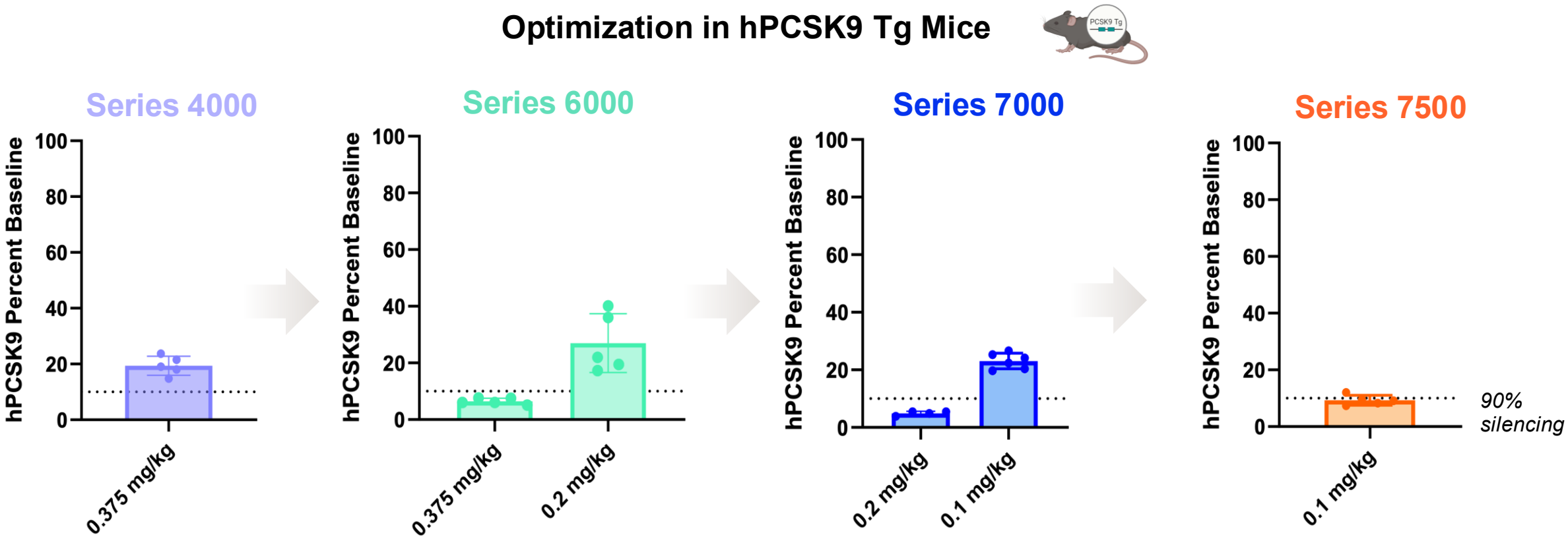
Select Endpoints
Primary • Safety and tolerability of single and multiple doses of CRMA-1001 **Secondary** • Pharmacokinetics of CRMA-1001 • Immunogenicity of CRMA-1001 • Change in HBV Biomarkers

The study is actively recruiting and dosing participants in Hong Kong and New Zealand. Additional sites are planned with CTA approvals in the United Kingdom and France.

ClinicalTrials.gov ID: NCT07200193 EUCT number: 2025-523619-12-00

Abbreviations: ALT (alanine transaminase); AST (aspartate transaminase); EUCT (European Union Drug Regulating Authorities Clinical Trials), HBV (hepatitis B virus); MAD (multiple ascending dose); SAD (single ascending dose); ULN (upper limit of normal)

Ongoing construct optimization efforts demonstrate significant increases in potency in animal models

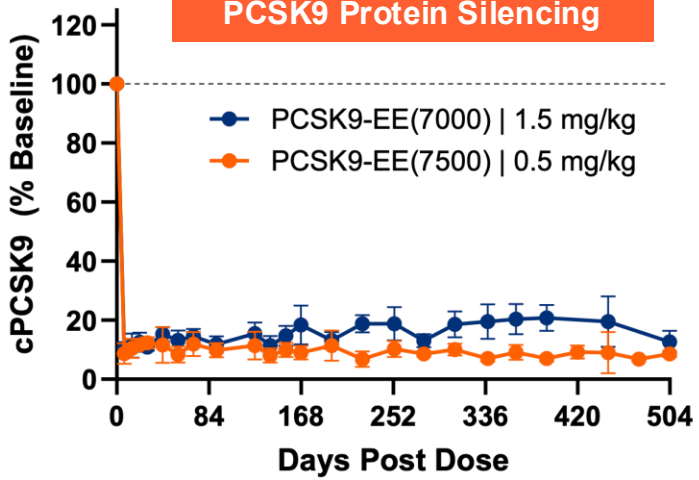


- Further construct optimization yields increased potency in epigenetic silencer potency in hPCSK9 Tg-mice
- NHP study with Series 7500 construct has demonstrated additional potency gains and >18 months durability

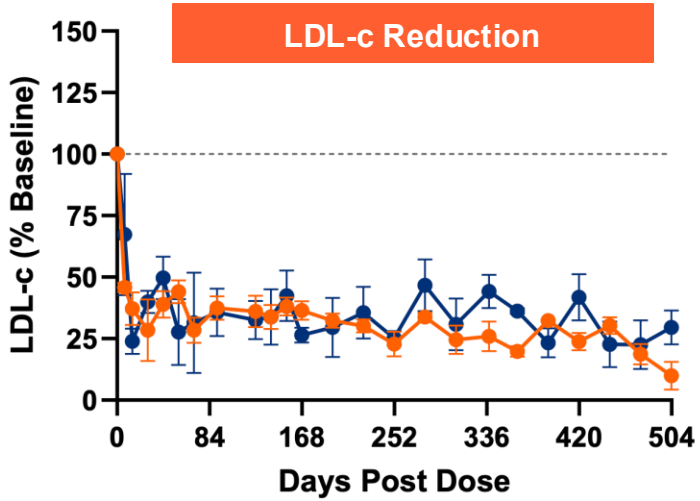
Abbreviations: NHP (non-human primate); hPCSK9 (human proprotein convertase subtilisin/kexin type 9); Tg (transgenic)

PCSK9-EE (Series 7500) achieved >3X improved potency over 7000 series editor in NHPs with durability beyond 18 months

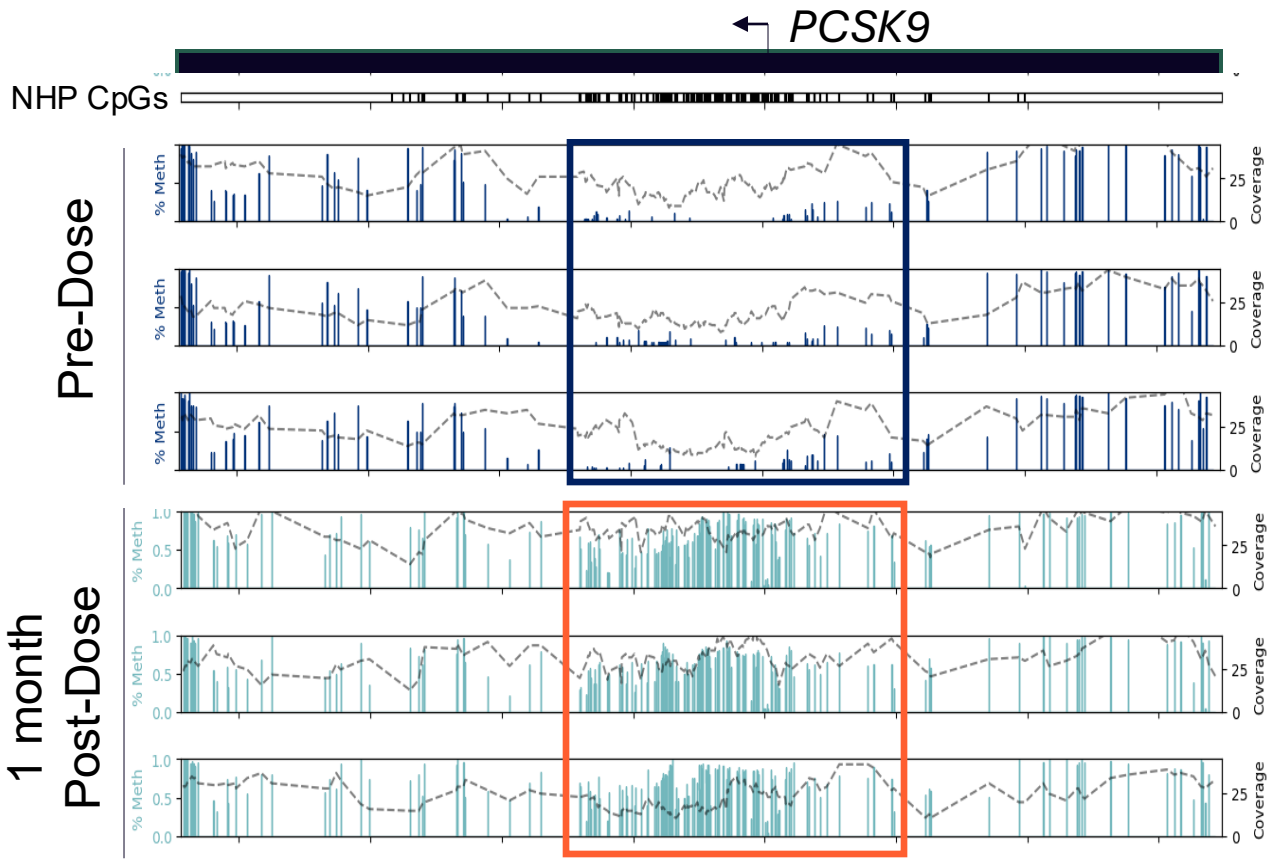
PCSK9 Protein Silencing



LDL-c Reduction



Methylation in *PCSK9* locus



Abbreviations: cPCSK9 (cyno proprotein convertase subtilisin/kexin type 9); EE (epigenetic editor); LDL-c (low-density lipoprotein cholesterol); NHP (non-human primate)

CRMA-1001: Designed to durably silence cccDNA and intDNA with the potential to achieve high rates of functional cure

- **Potency:** >3 log reduction of HBsAg at a single high dose or with repeat lower doses
- **Durability:** Suppressed HBV viral markers for over 6 months (observation period of study)
- **Translation:** Effector saturated *PCSK9* silencing at ≥1 mg/kg in NHPs for up to 22 months
- **Safety:** Confirmed methylation at target site with no detectable unintended targets in the human genome, PK/Biodistribution & Toxicology profile supported further development
- **Pipeline:** Ongoing construct optimization has demonstrated further gains in potency

CRMA-1001-101 is actively recruiting and dosing participants in multiple jurisdictions

Abbreviations: cccDNA (covalently closed circular DNA); HBsAg (hepatitis B surface antigen); HBV (hepatitis B virus); intDNA (integrated HBV DNA); PCSK9 (proprotein convertase subtilisin/kexin type 9); PK (pharmacokinetic)

Thank you to nChroma Bio team, collaborators, partners, and study participants

LNP Technology provided by
Acuitas Therapeutics, Inc.

Thank You