

Capsid assembly modulators against HBV: old molecules with new mechanisms of action

Inserm, U1110 - Institute for Translational Medicine and Liver Disease (ITM), Strasbourg

Disclosures

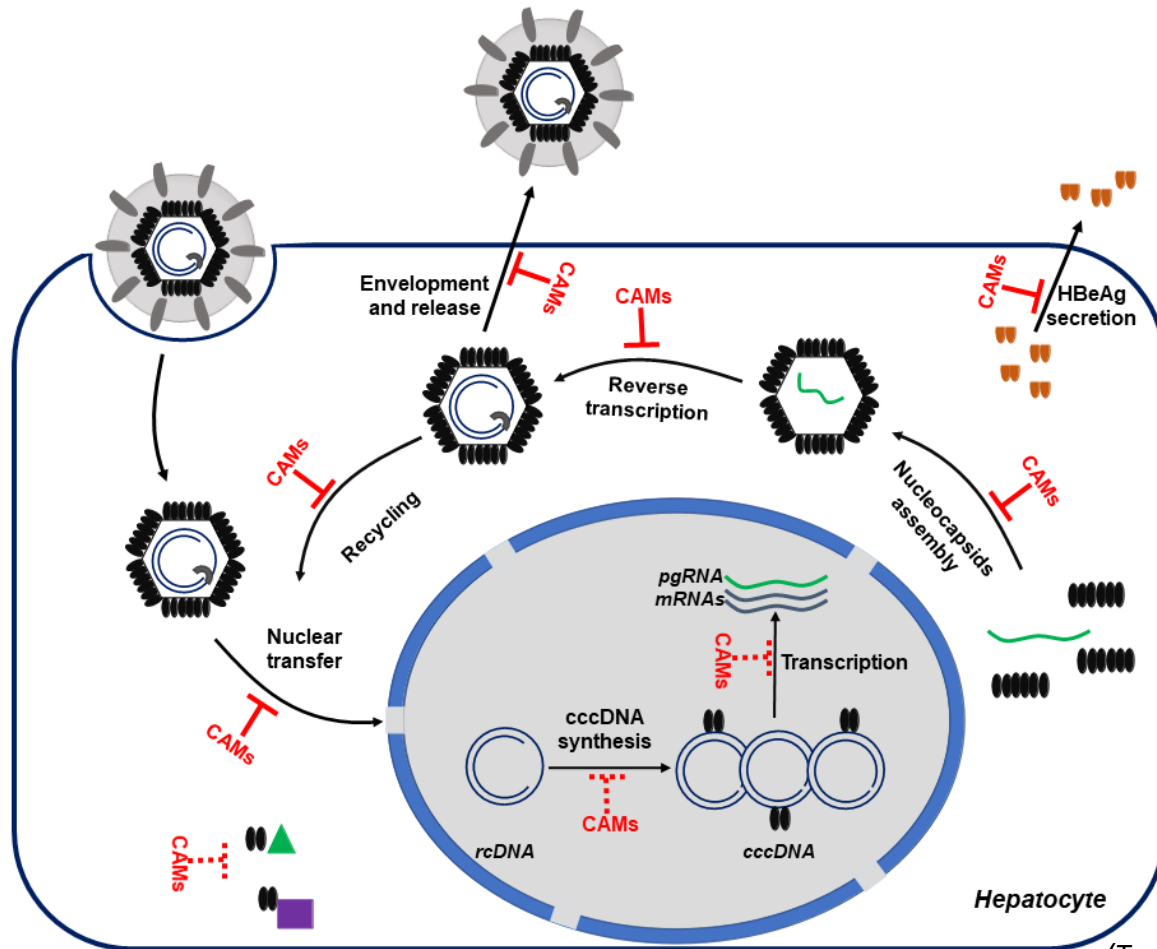
- T.F.B. and E.R.V. received funding from Aligos Belgium BV as part of the VLAIO project CoHeBA (HBC.2020.2454) with V.T.'s fellowship funded by the grant.
- Y.D. and D.B.K. are employees of Aligos Belgium BV.

Endorsed by



HBV core protein is central in HBV life cycle

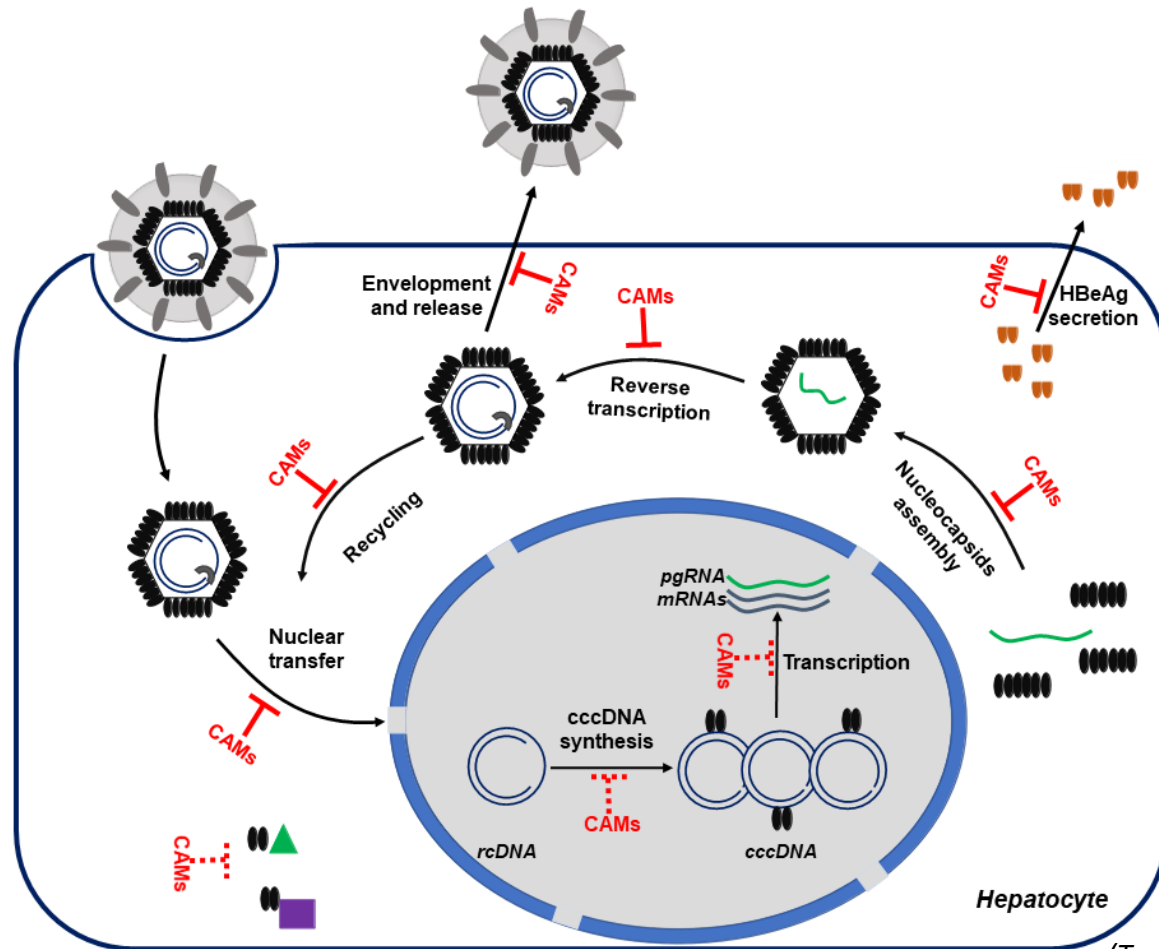
- Around 300 million people chronically infected by HBV
- NUCs and pegINF are the only available therapies
- Needs for new therapies to reach a functional cure
- HBV Core protein is a good target



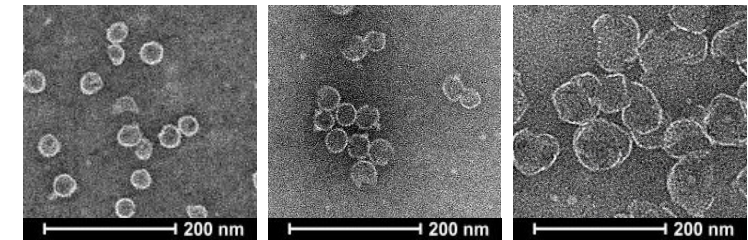
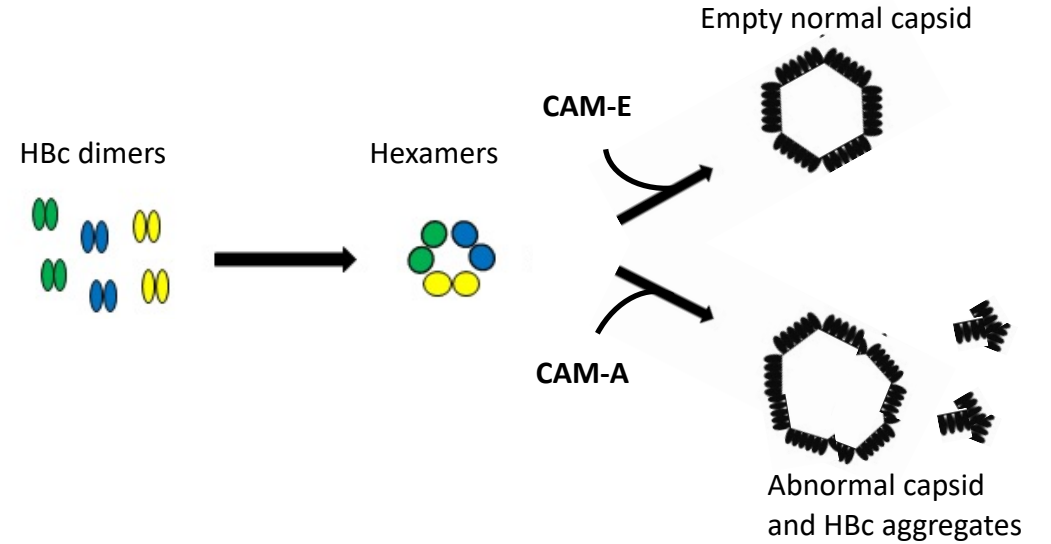
(Taverniti et al. 2022)

HBV core protein is central in HBV life cycle

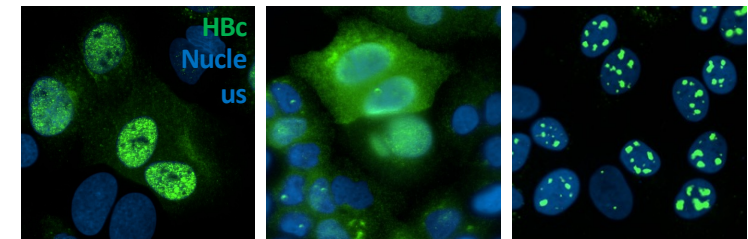
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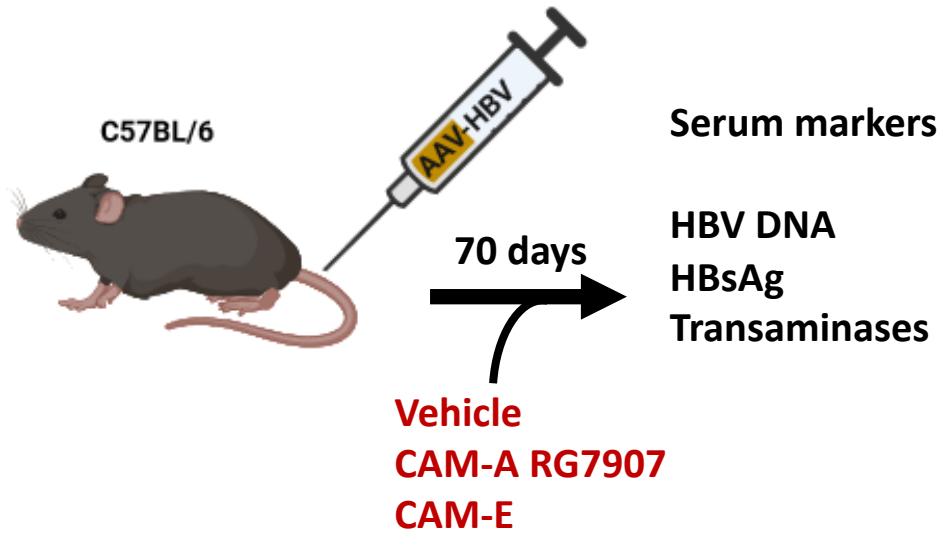
NaCl CAM-E CAM-A



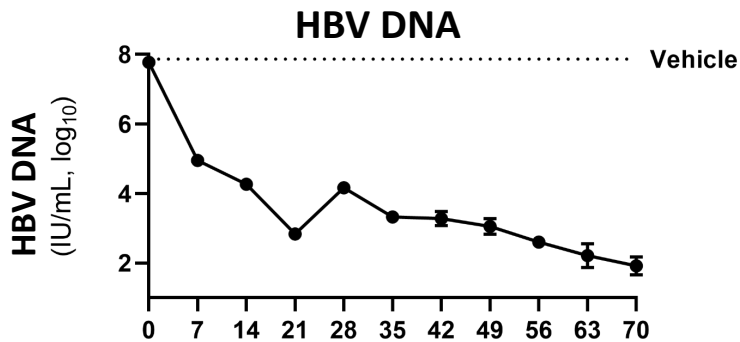
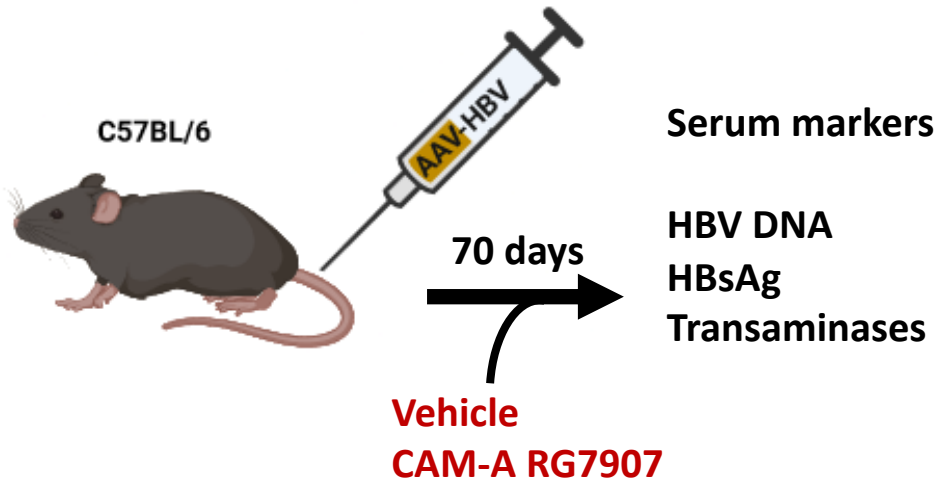
DMSO CAM-E CAM-A

(Kum et al. 2023)

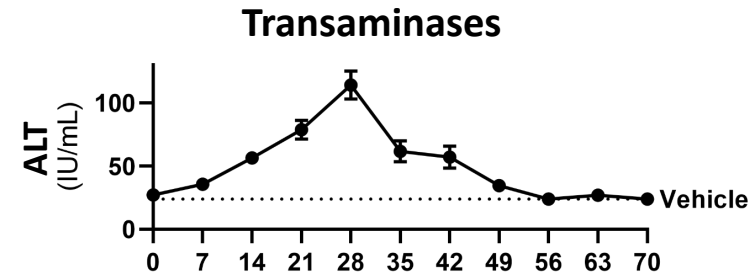
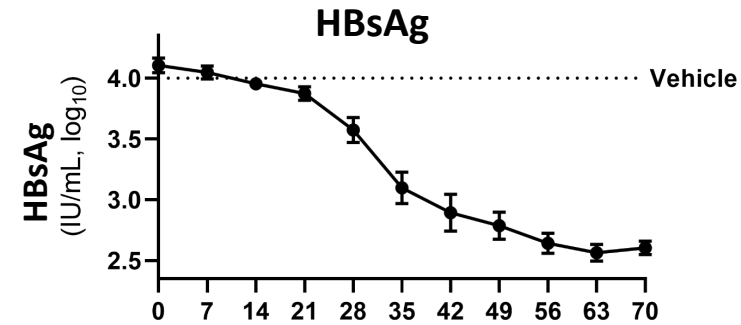
CAM-A RG7907 treatment decreases levels of HBsAg in AAV-HBV mice



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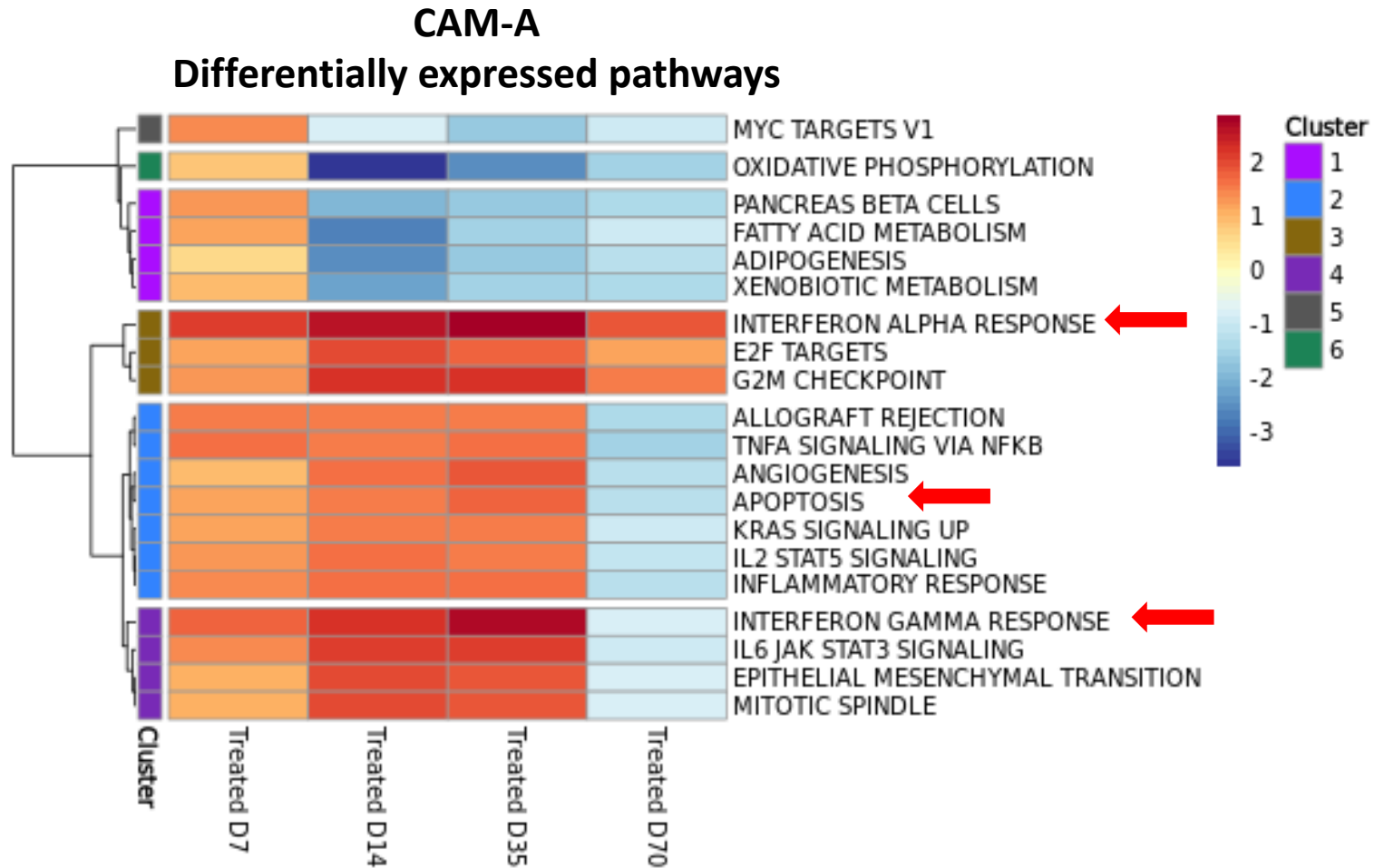
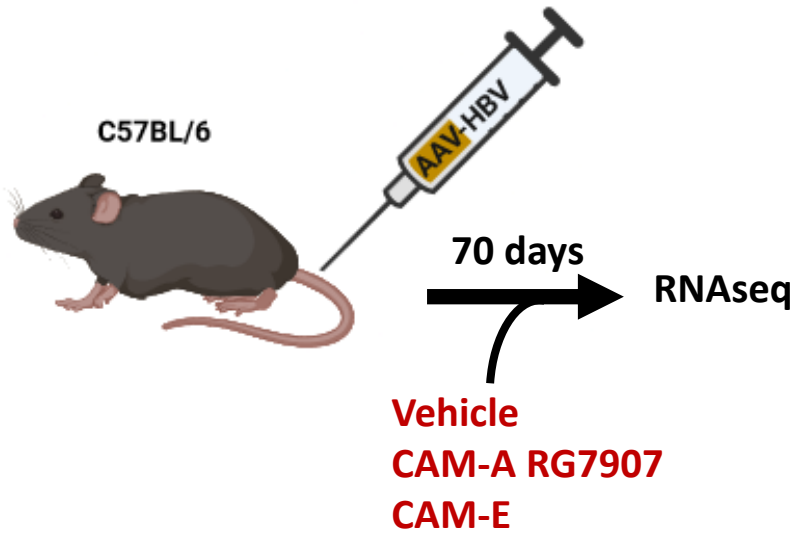


CAM-A RG7907 treatment



- ✓ CAM-A but not CAM-E treatment reduces the levels of circulating HBsAg
- ✓ Liver damage suggests a CAM-A induced cell death of HBV-infected hepatocytes

CAM-A RG7907 treatment activates apoptosis in AAV-HBV mice



CAM-A treatment activates apoptosis and the innate immunity in AAV-HBV mice

Main objectives

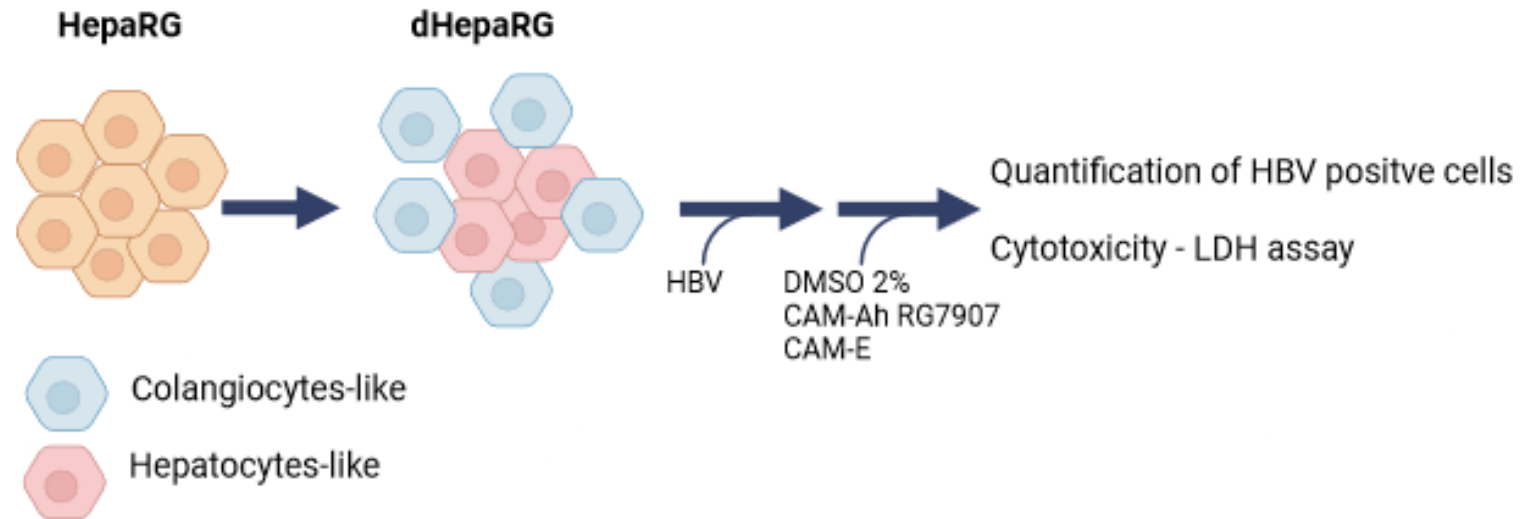
1. Elucidating the fate of HBV-infected hepatocytes that accumulates core nuclear aggregates after CAM-A treatment
2. Deciphering the response of HBV-infected hepatocytes to the cytoplasmic accumulation of HBV genetic material

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University of Strasbourg

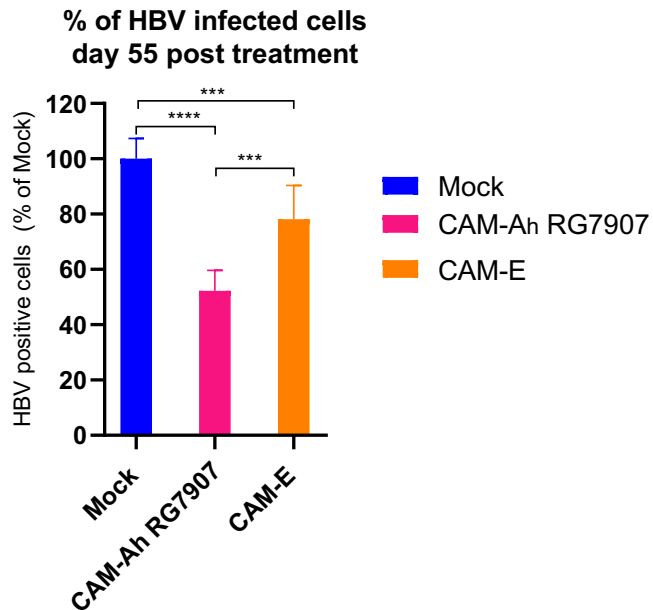
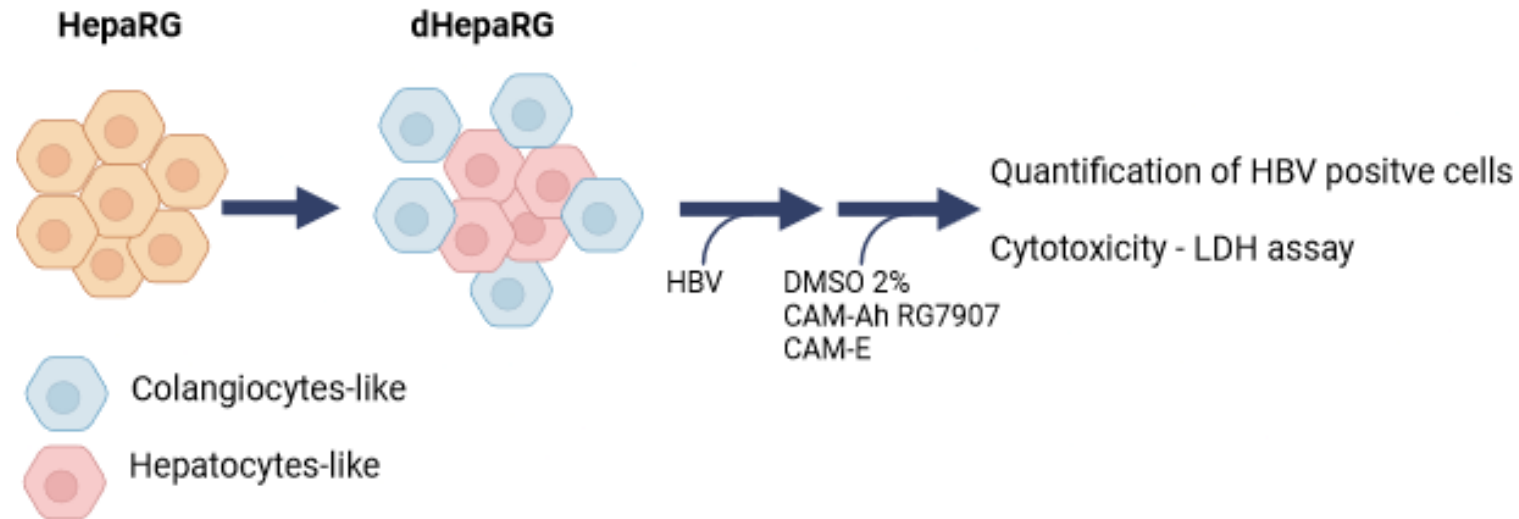


ALIGOS
THERAPEUTICS
Belgium

CAM-A RG7907 treatment increases cellular toxicity in HBV-infected dHepaRG cells

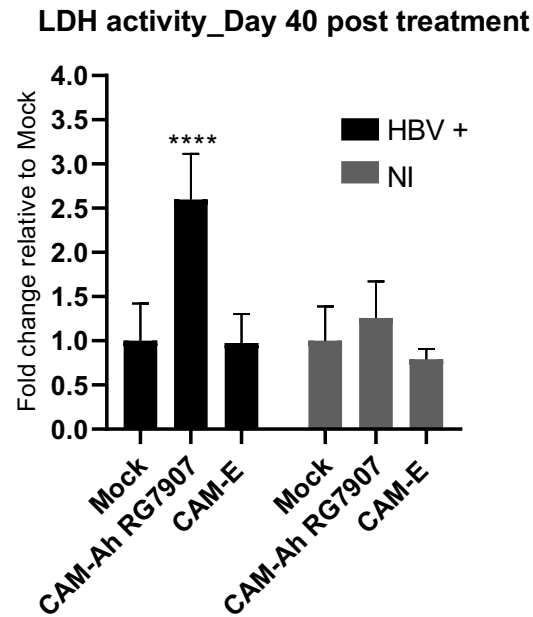
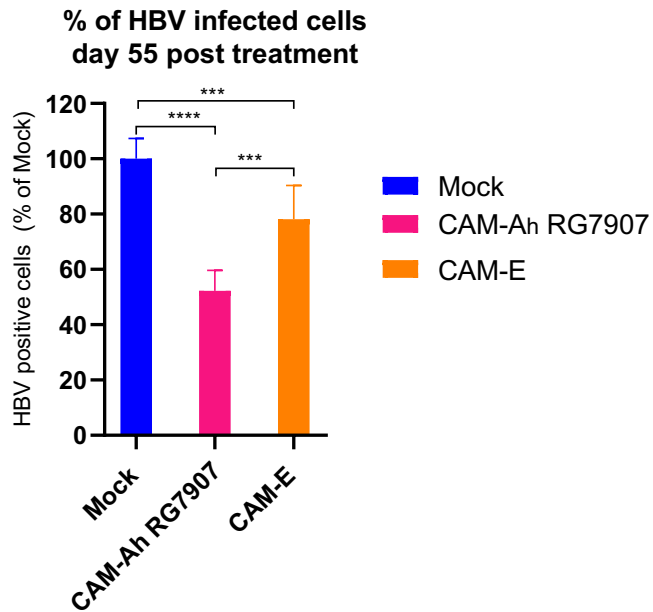
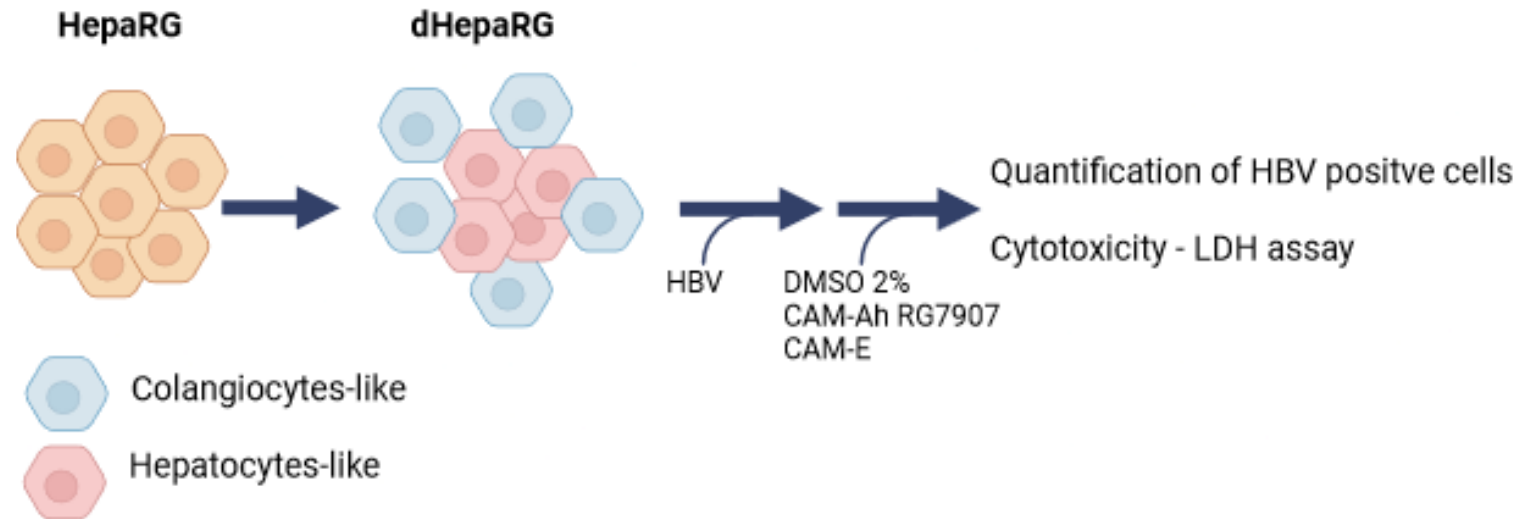


CAM-A RG7907 treatment increases cellular toxicity in HBV-infected dHepaRG cells



✓ **CAM-Ah RG7907 treatment induces loss HBV infected cells**

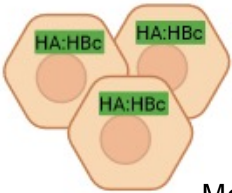
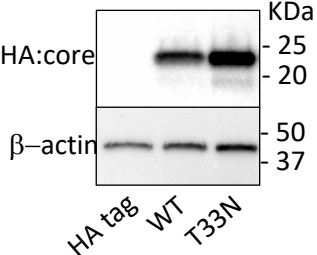
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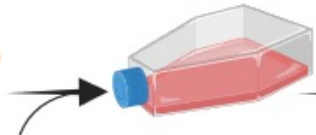
- ✓ CAM-Ah RG7907 treatment induces loss HBV infected cells
- ✓ Long CAM-Ah RG7907 treatment increases cytotoxicity in HBV-infected dHepaRG

CAM-A dependent core aggregation induces apoptosis in HepG2-NTCP cells expressing core

HepG2-NTCP

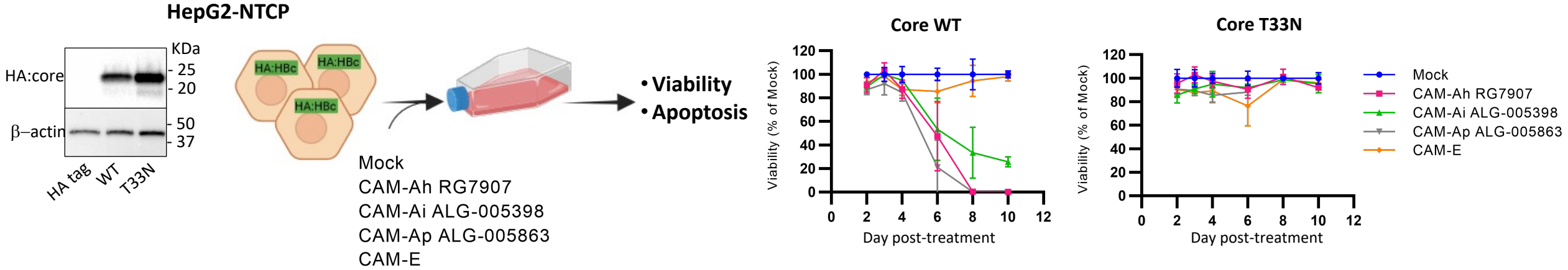


- Mock
- CAM-Ah RG7907
- CAM-Ai ALG-005398
- CAM-Ap ALG-005863
- CAM-E



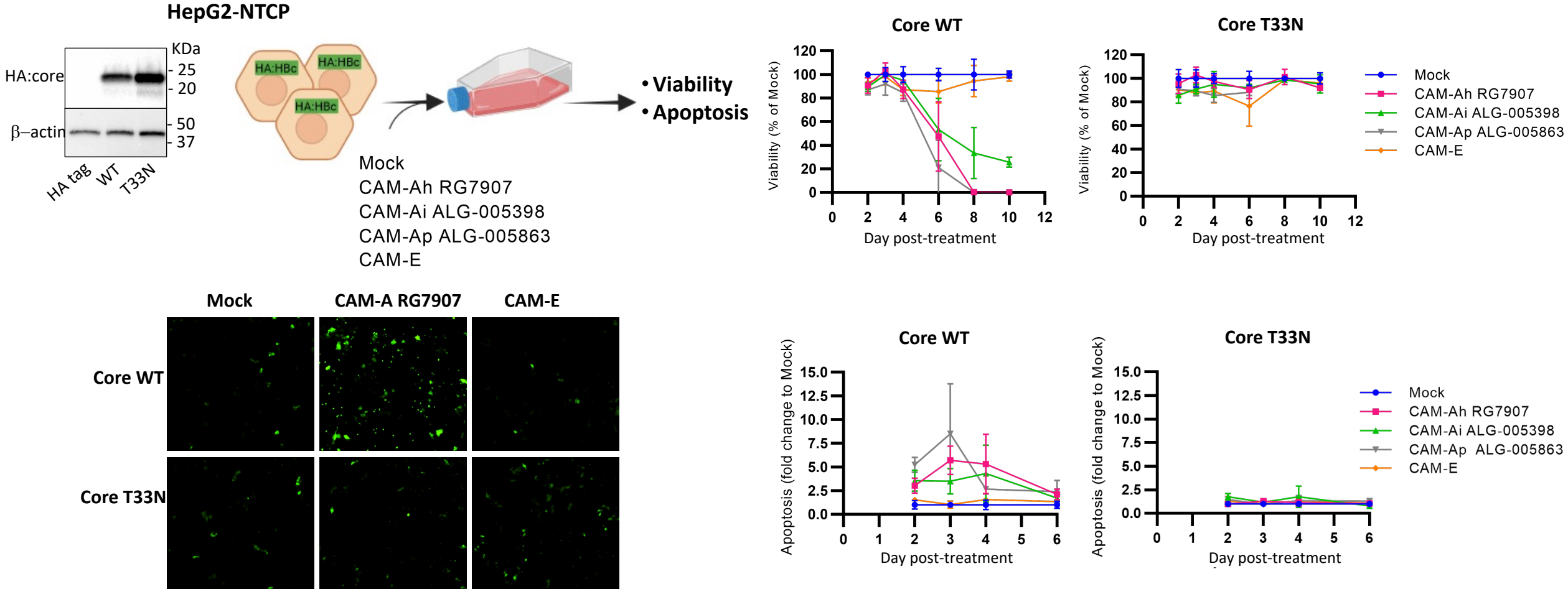
- Viability
- Apoptosis

CAM-A dependent core aggregation induces apoptosis in HepG2-NTCP cells expressing core



✓ CAM-A treatment causes cell death of cells expressing core WT but not the T33N mutant.

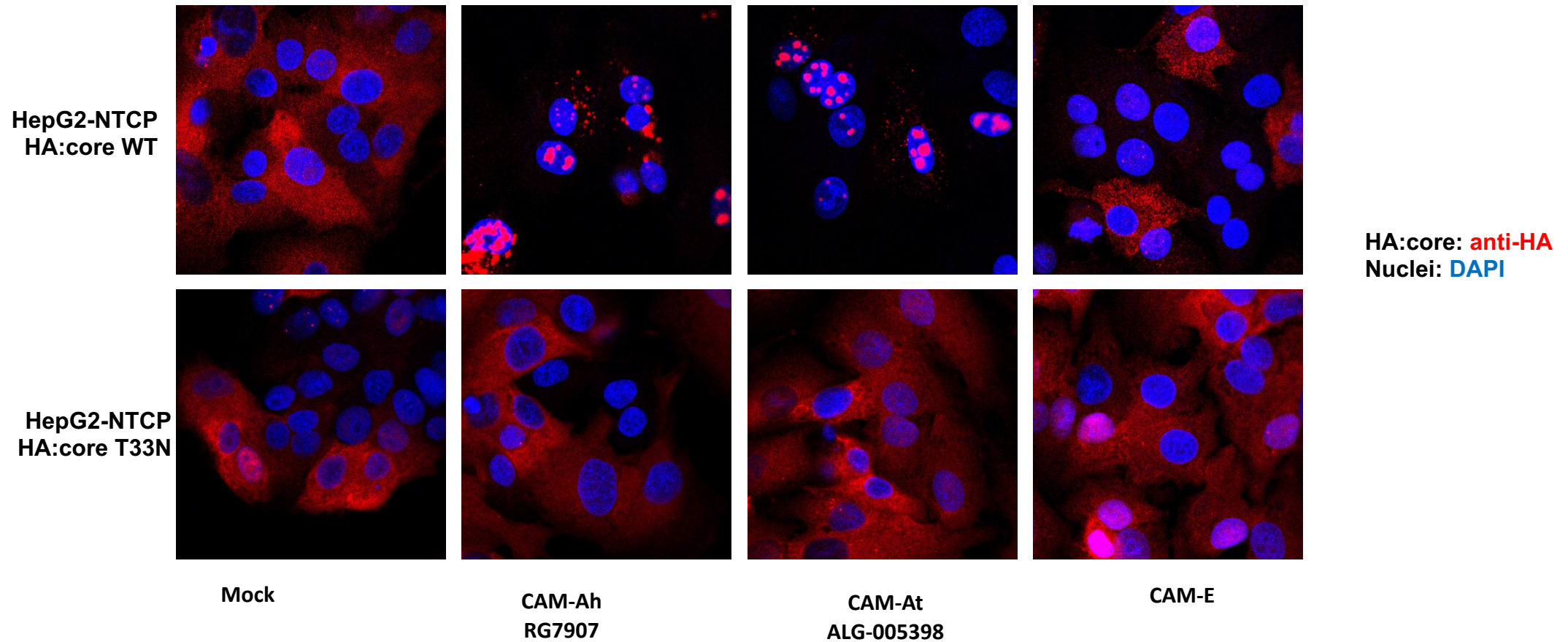
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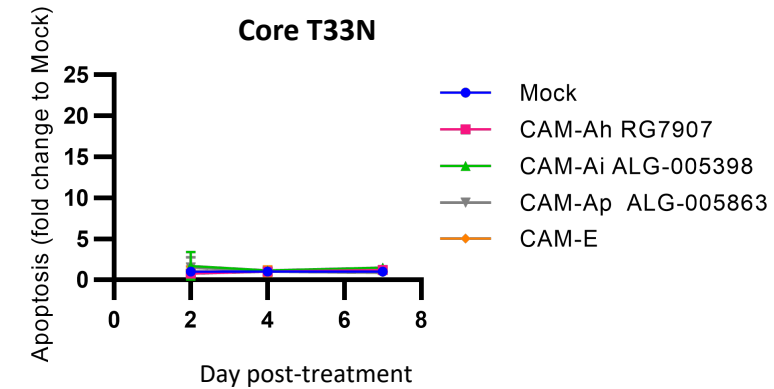
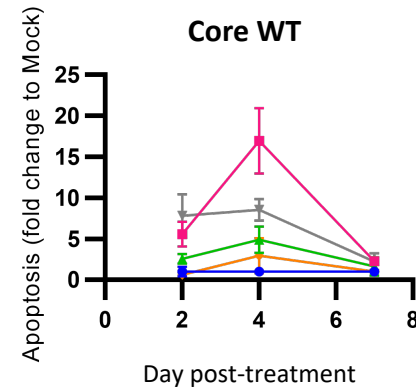
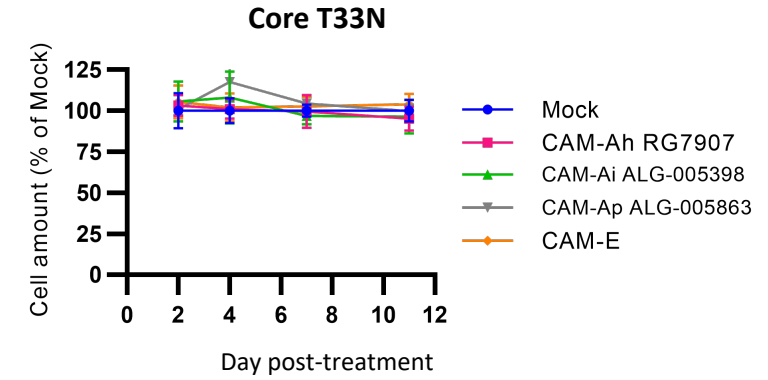
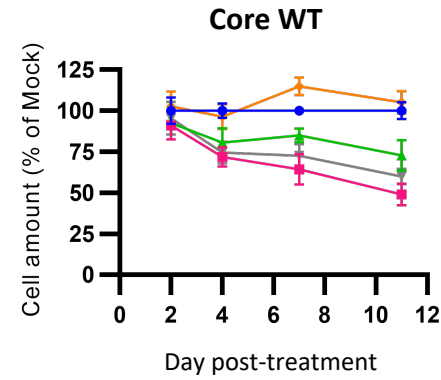
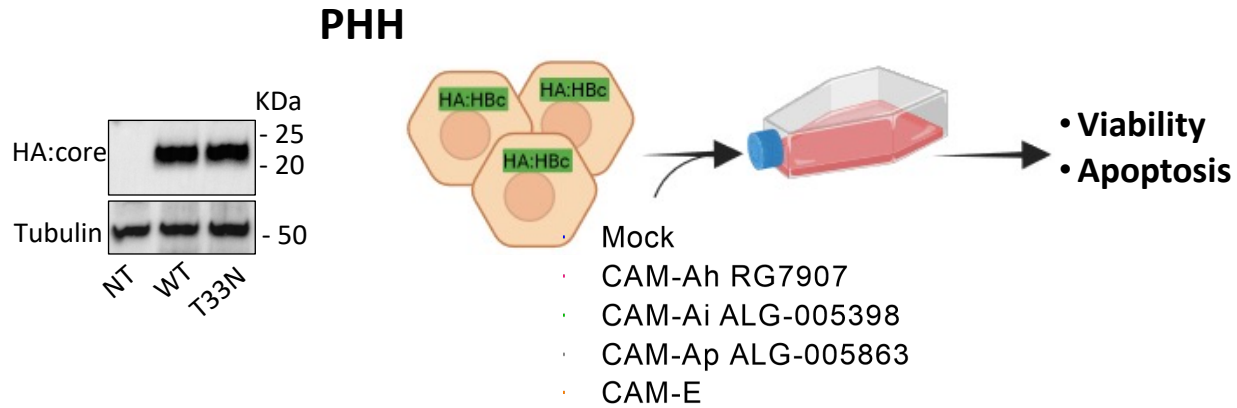
✓ CAM-A treatment induces apoptosis in cells expressing core WT.

CAM-A treatment causes the nuclear accumulation of core aggregates



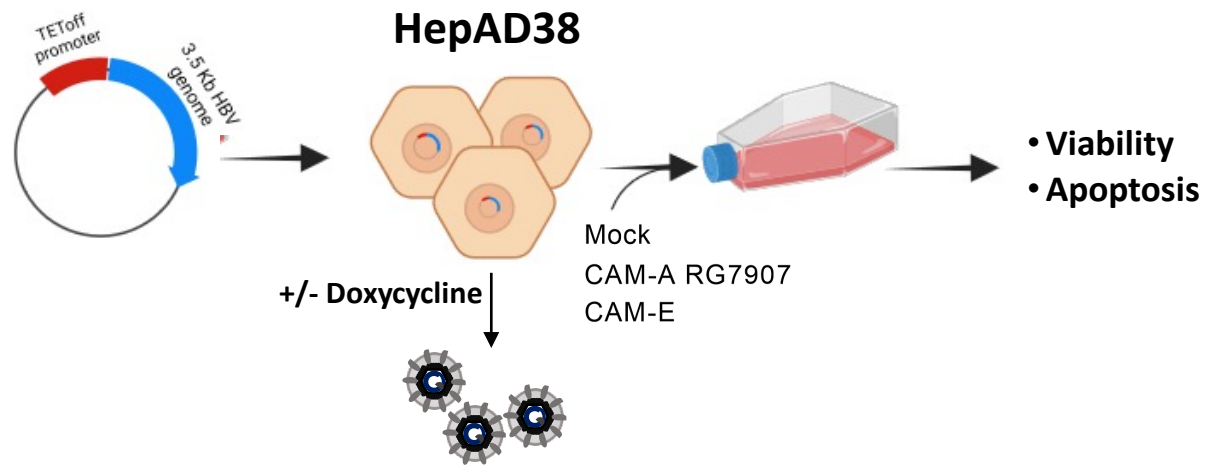
✓ CAM-A treatment causes the nuclear accumulation of core aggregates only in cells expressing core WT

CAM-A dependent core aggregation induces apoptosis in primary human hepatocytes (PHH)

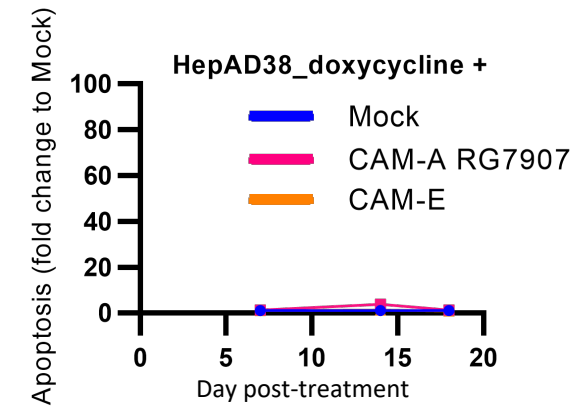
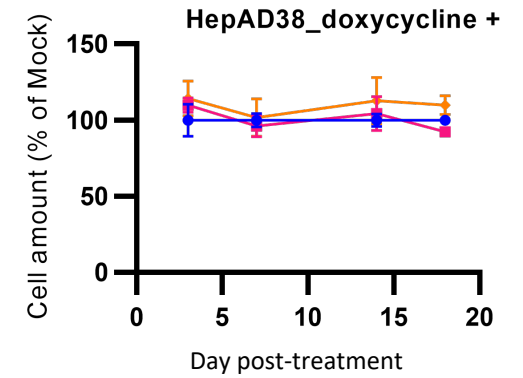
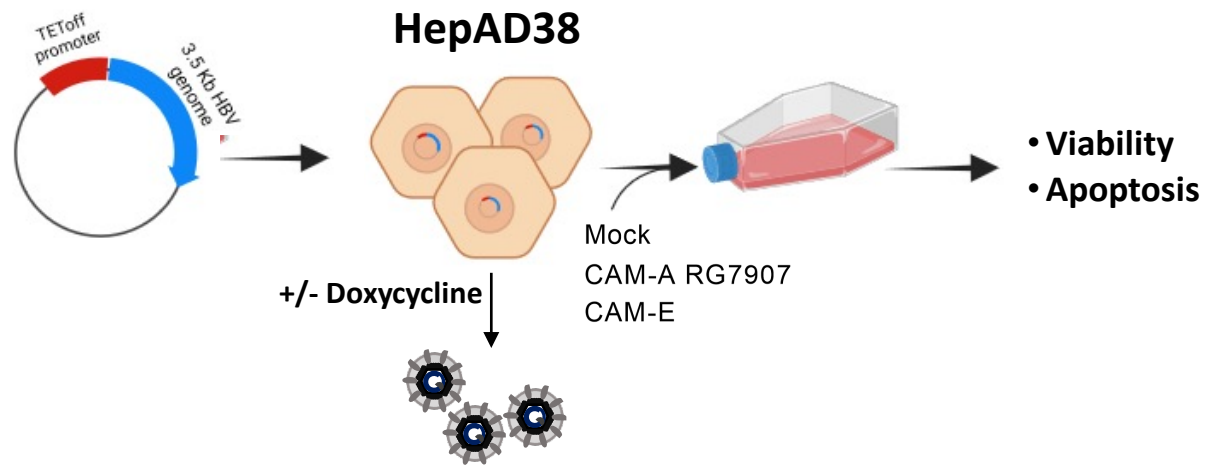


✓ CAM-A treatment induces apoptosis in PHH expressing core WT

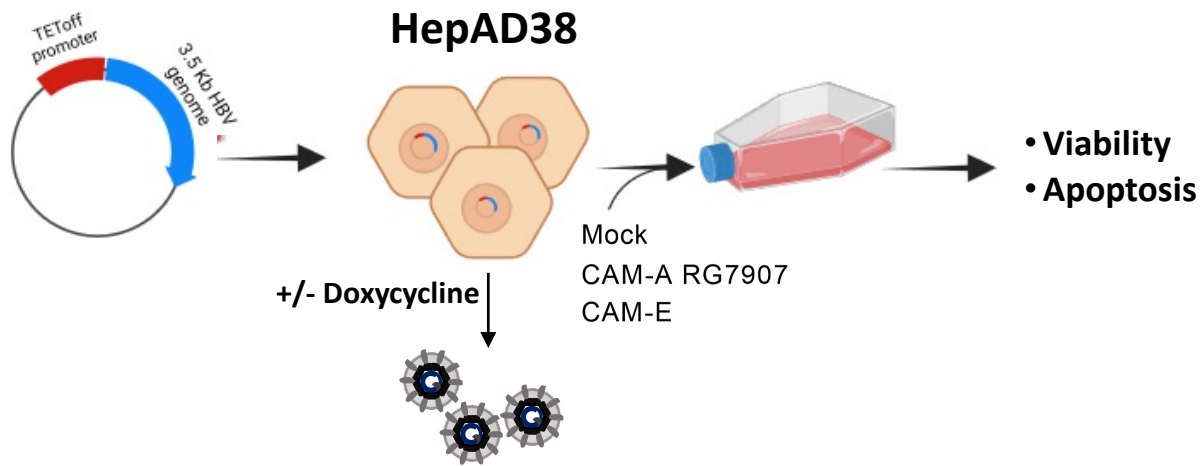
CAM-A dependent core aggregation induces apoptosis in HepAD38 replicating HBV



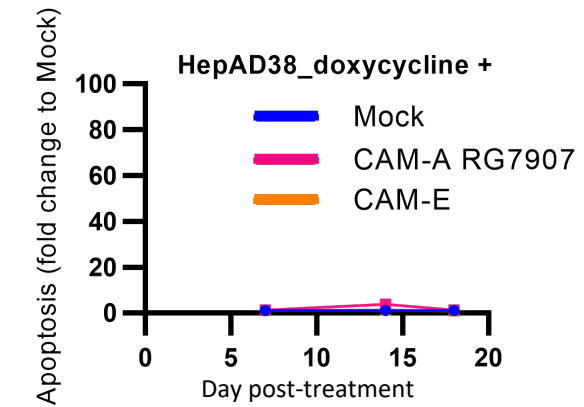
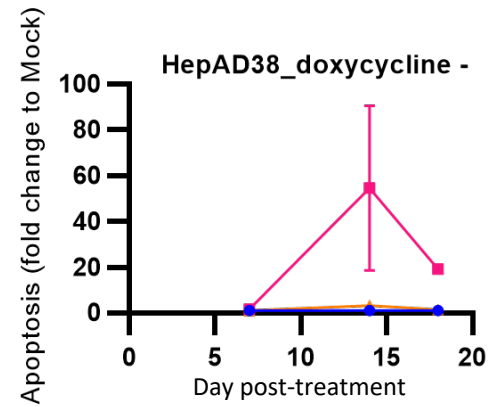
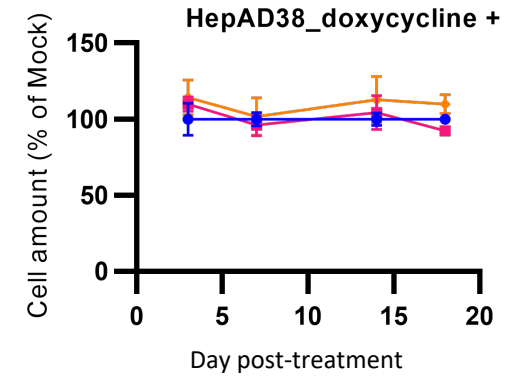
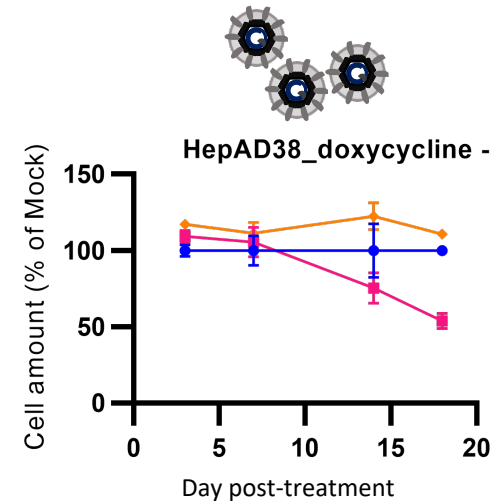
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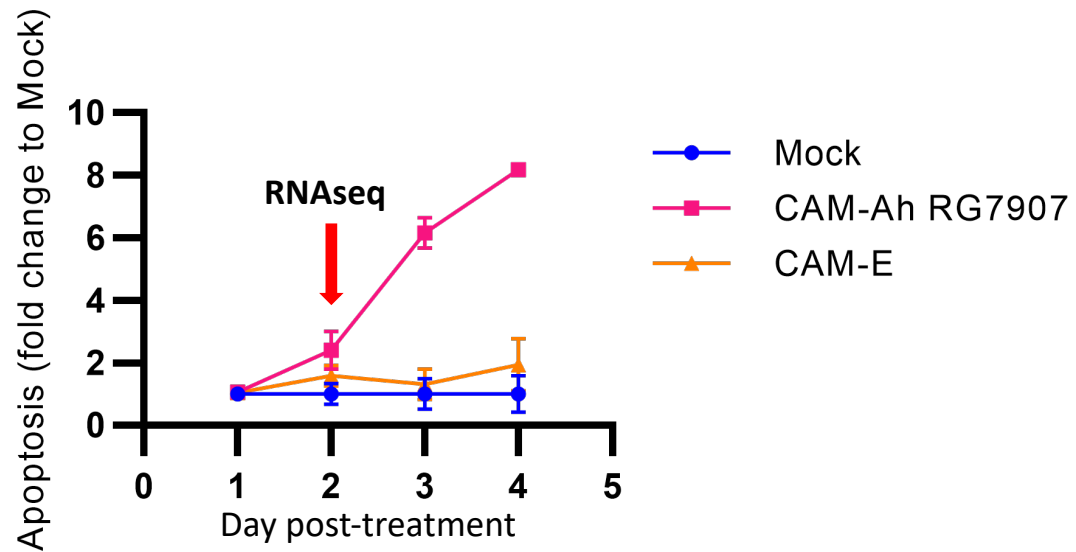
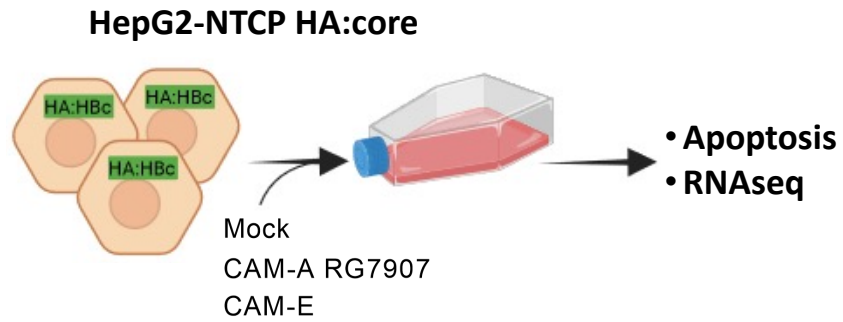
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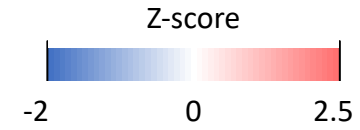
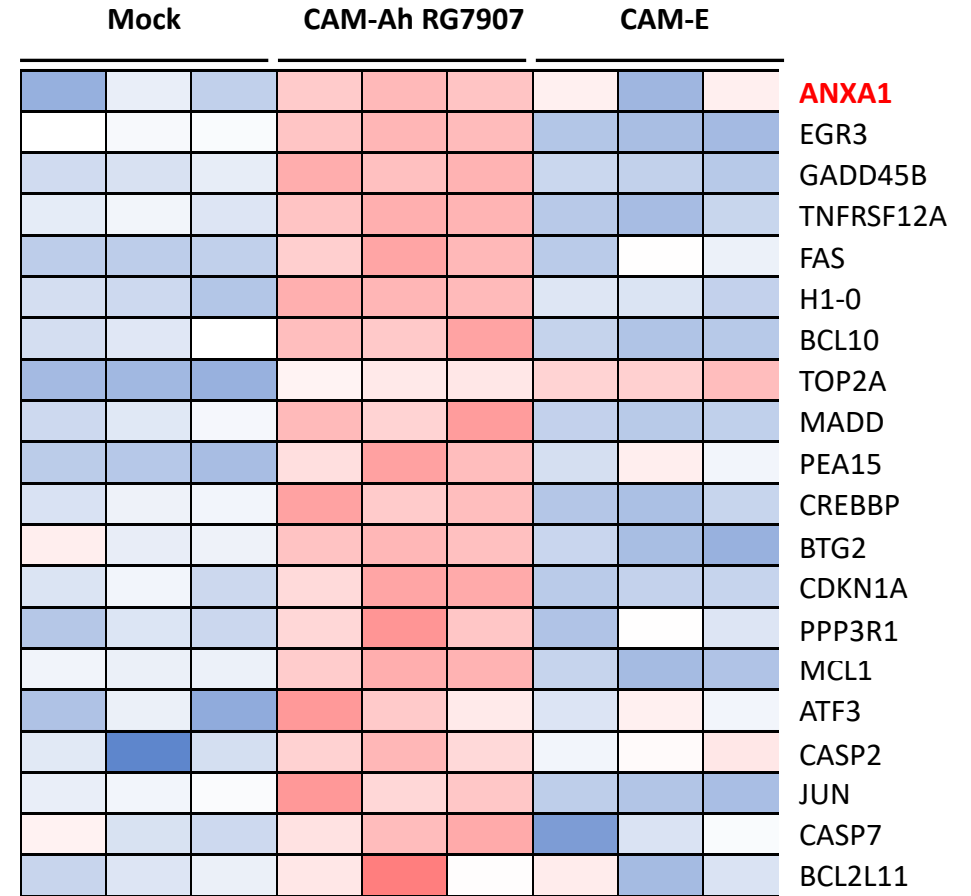
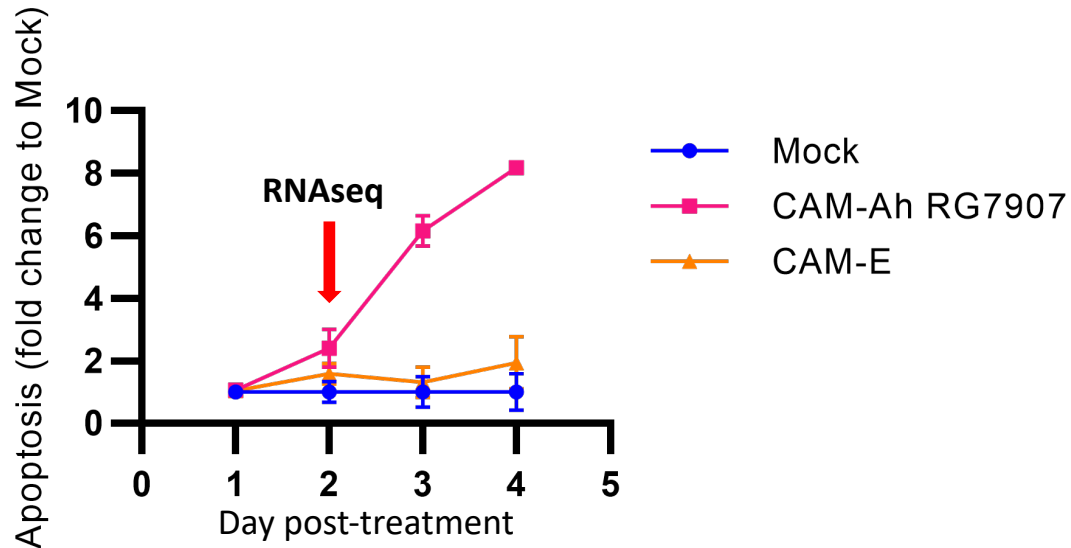
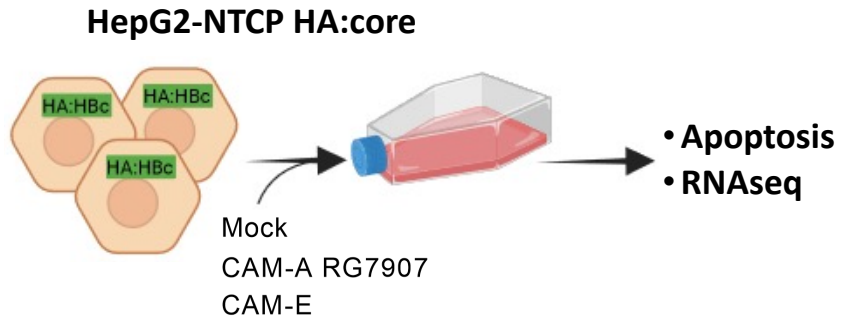
- ✓ Both CAM-A and CAM-E inhibit HBV replication
- ✓ Only CAM-A treatment induces apoptosis in HepAD38 producing HBV



CAM-A dependent core aggregation induces the deregulation of host genes



CAM-A dependent core aggregation induces the deregulation of host genes

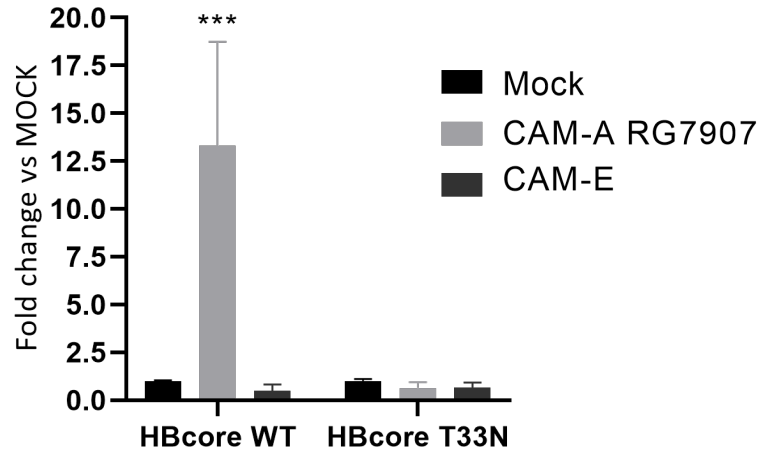


- ✓ Several upregulated genes play a role in apoptosis
- ✓ ANXA1 is a good candidate driver of apoptosis

ANXA1 expression is upregulated after CAM-A induced core aggregation

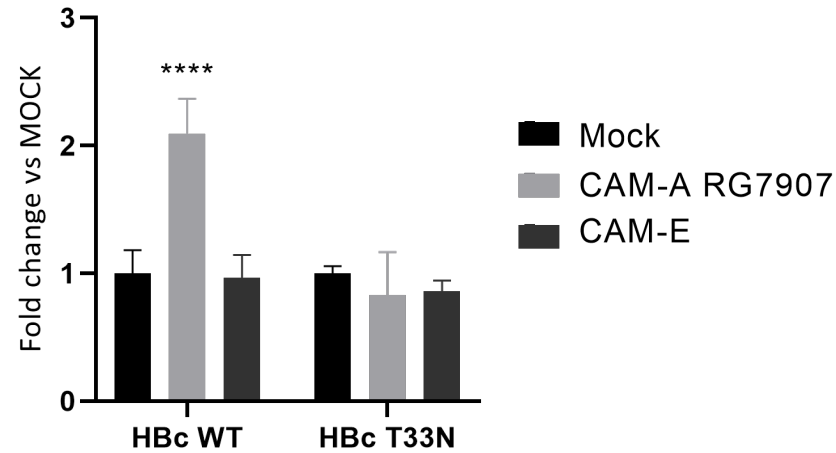
HepG2-NTCP HA:core

ANXA1 level Day 4 post-treatment



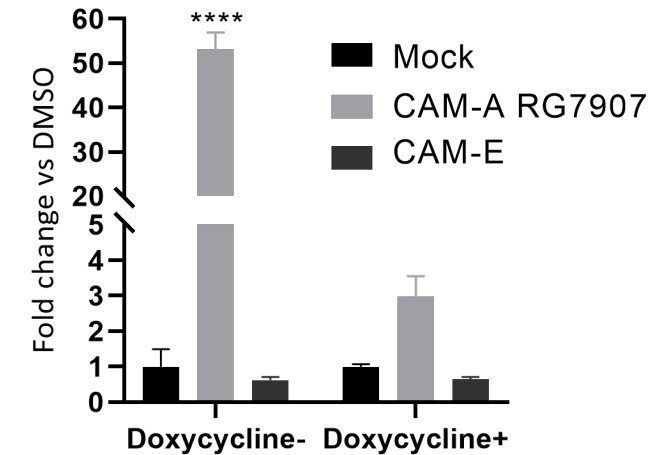
PHH HA:core

ANXA1 level Day 4 post-treatment



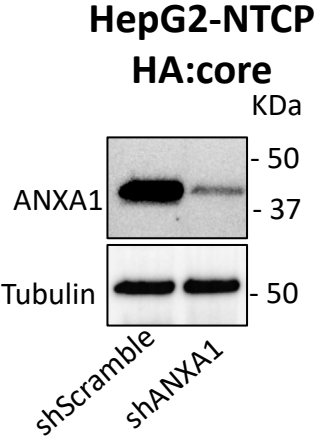
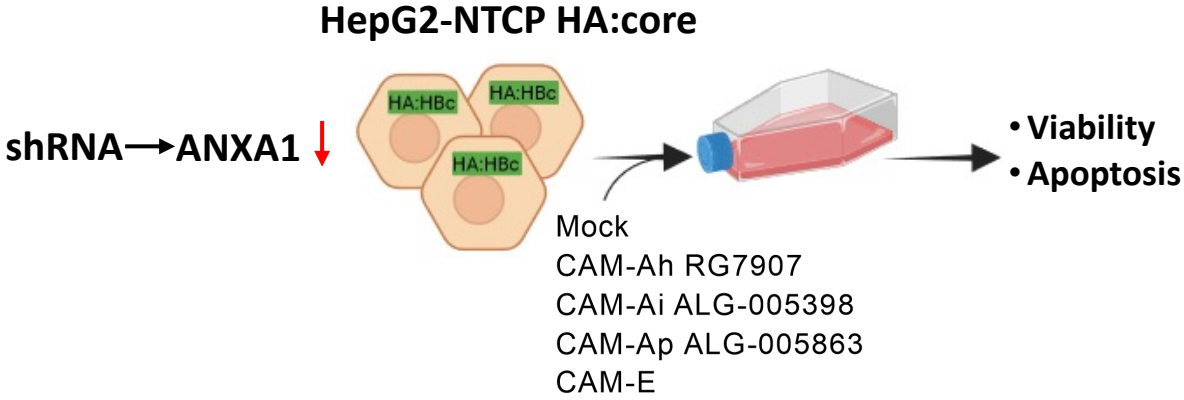
HepAD38

ANXA1 level Day 13 post-treatment



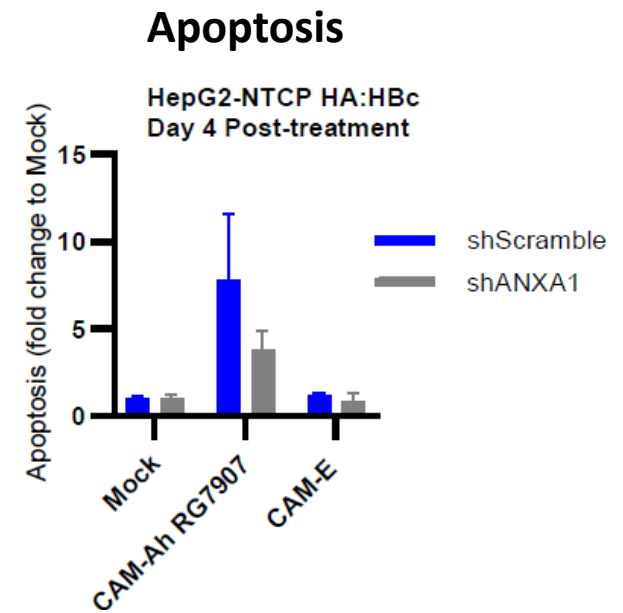
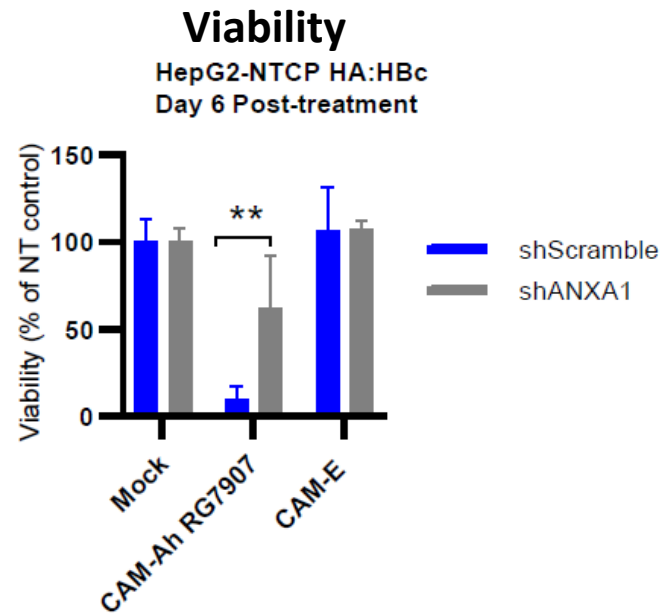
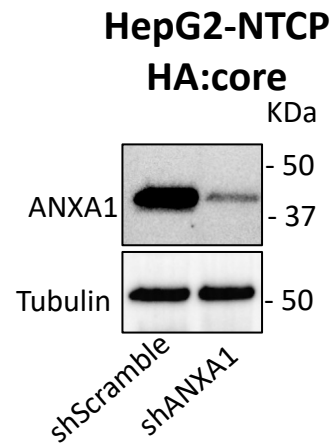
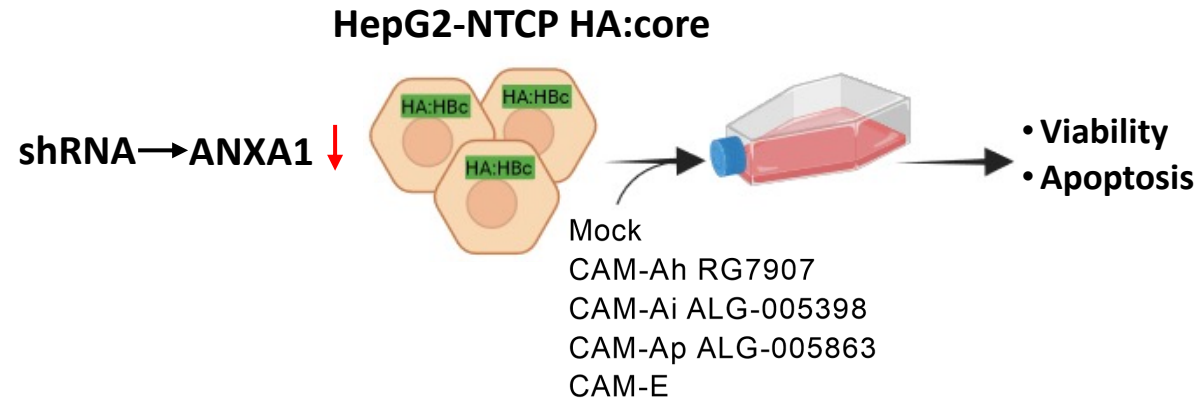
✓ ANXA1 upregulated in cells expressing core WT after CAM-A and HepAD38 replicating HBV

ANXA1 drives apoptosis activation induced by CAM-A treatment



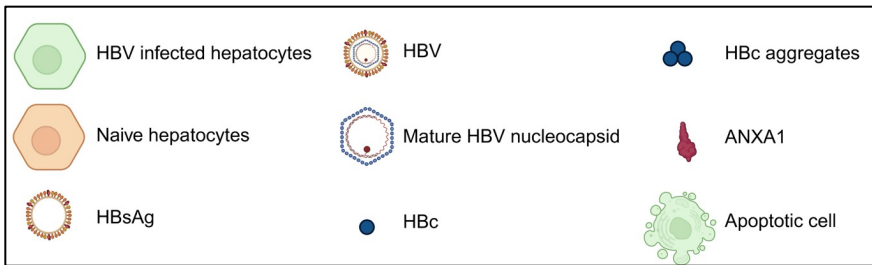
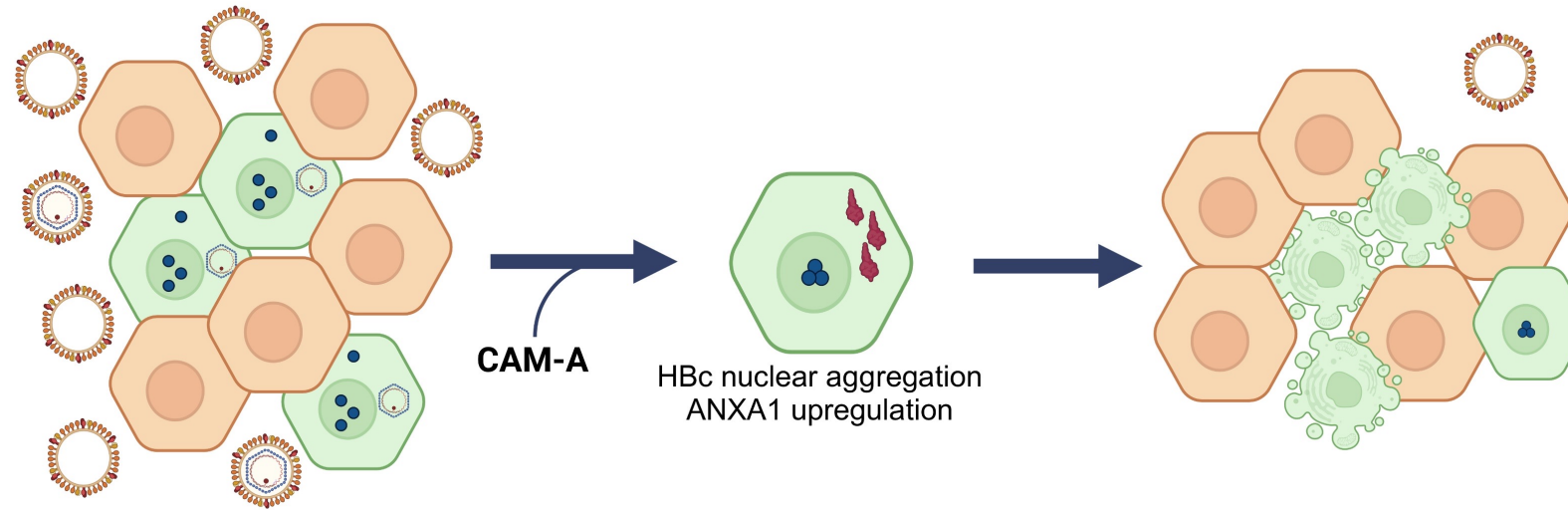
(Taverniti et al. 2024)

ANXA1 drives apoptosis activation induced by CAM-A treatment



✓ ANXA1 knockdown reduces cell death and apoptosis activation after CAM-A treatment

Conclusions



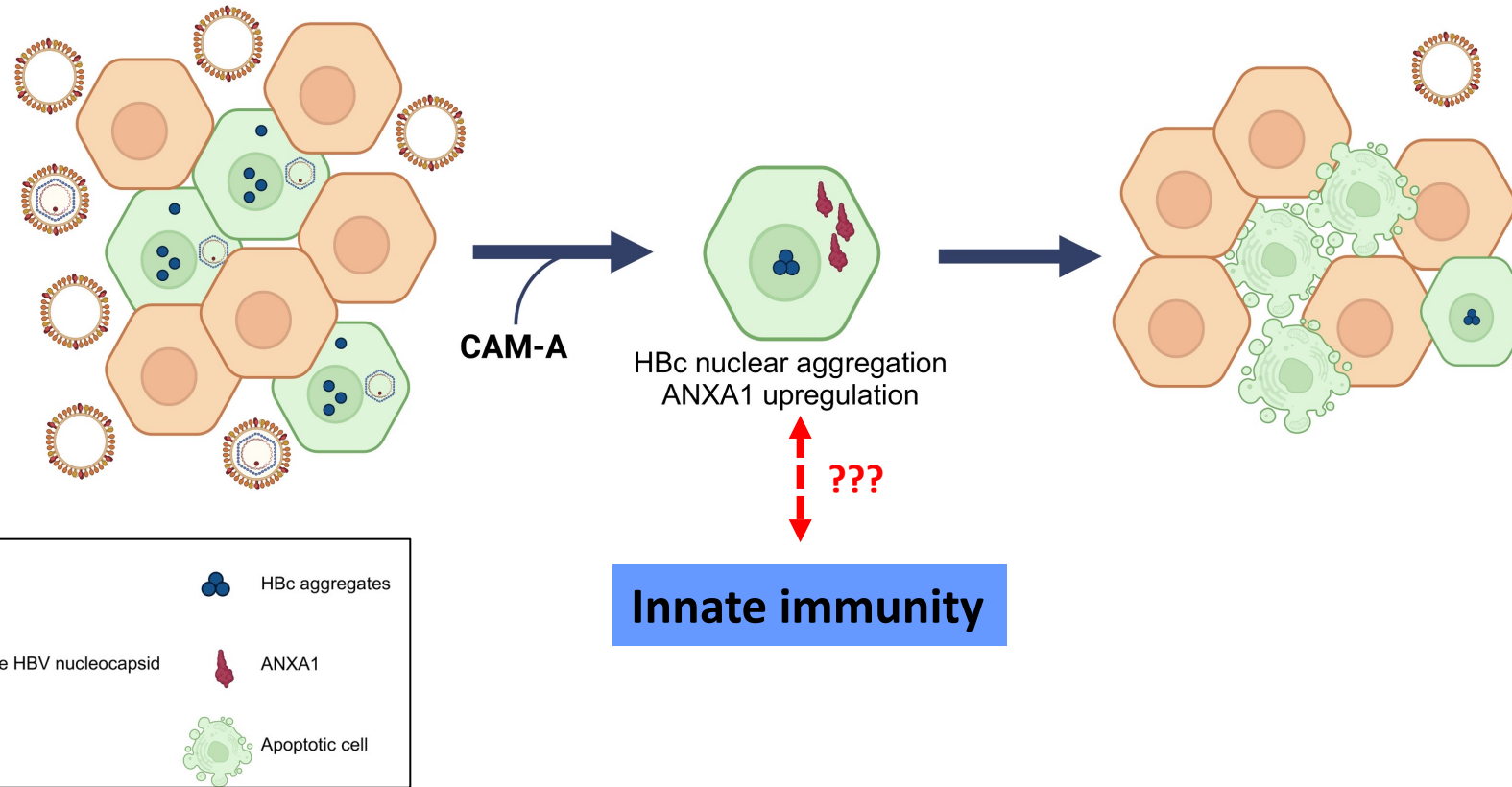
- ✓ **CAM-A dependent core aggregation causes cell death via activation of apoptosis**
- ✓ **ANXA1 is a driver of apoptosis**
- ✓ **The clinical impact needs to be determined – high levels of core are required**

Taverniti et al. 2024

Berke et al. 2024

Kornyeyev et al. 2024

Conclusions



- ✓ **CAM-A dependent core aggregation causes cell death via activation of apoptosis**
- ✓ **ANXA1 is a driver of apoptosis**
- ✓ **The clinical impact needs to be determined – high levels of core are required**

Taverniti et al. 2024

Berke et al. 2024

Kornyeyev et al. 2024

Acknowledgements



Inserm Unit 1110

ALIGOS Therapeutics



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