

Nucleic Acid Polymers and Their Application in Hepatitis B infection:

Efficacy and Safety

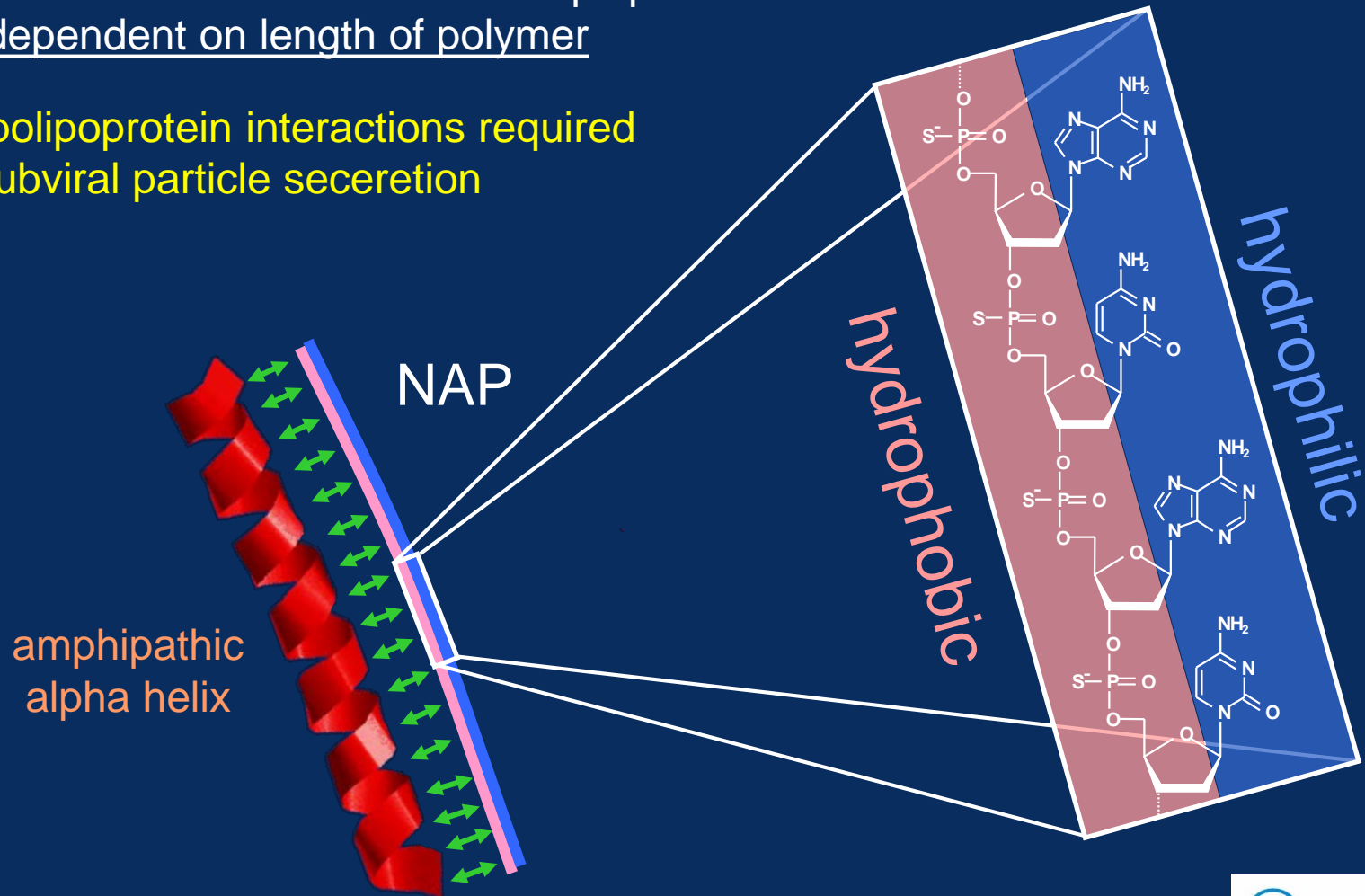
Andrew Vaillant
CSO, Replicor Inc.

TIDES 2013

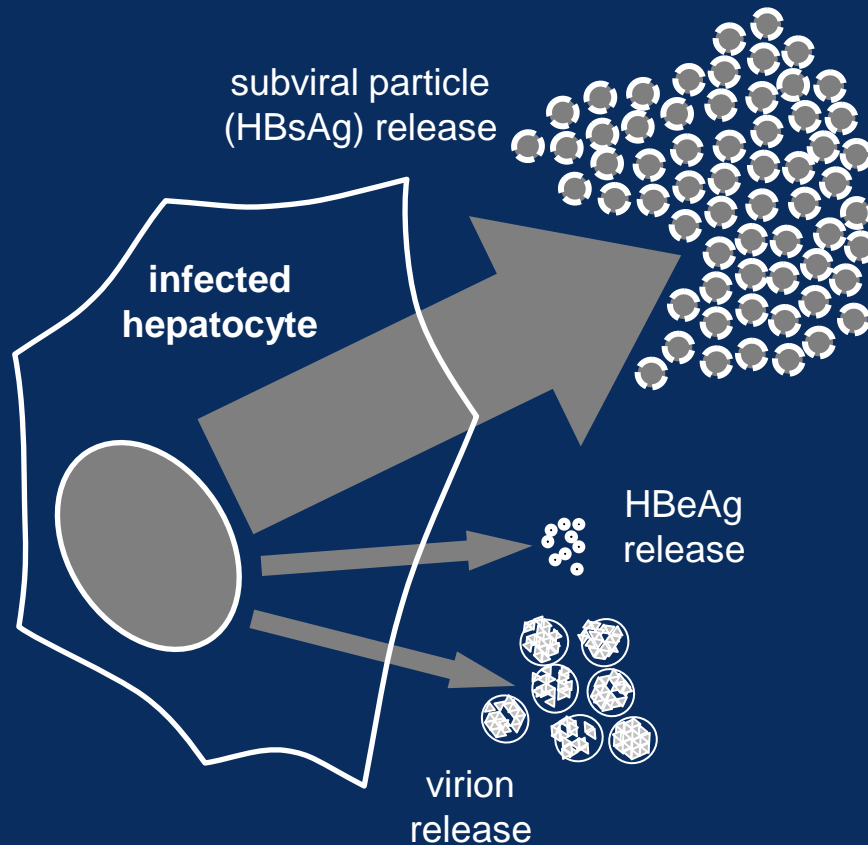


Nucleic acid-based amphipathic polymers (NAPs): A novel antiviral therapeutic potential for hepatitis B

- Activity independent of antisense or immunostimulatory mechanisms
- Co-operative lateral interaction with amphipathic domains dependent on length of polymer
- Blocks apolipoprotein interactions required for HBV subviral particle secretion



Chronic HBV infection is an immunological disorder



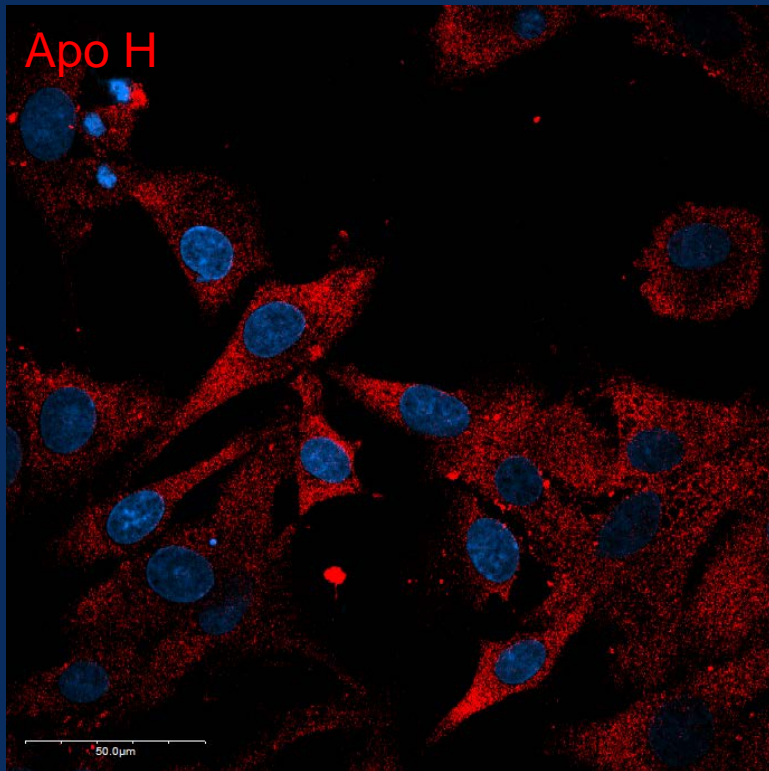
**sequestration of anti-HBs
suppresses innate immunity
suppresses T-cell proliferation
suppresses cytokine signaling**

**dominant immunosuppressive
effect in HBV infection**

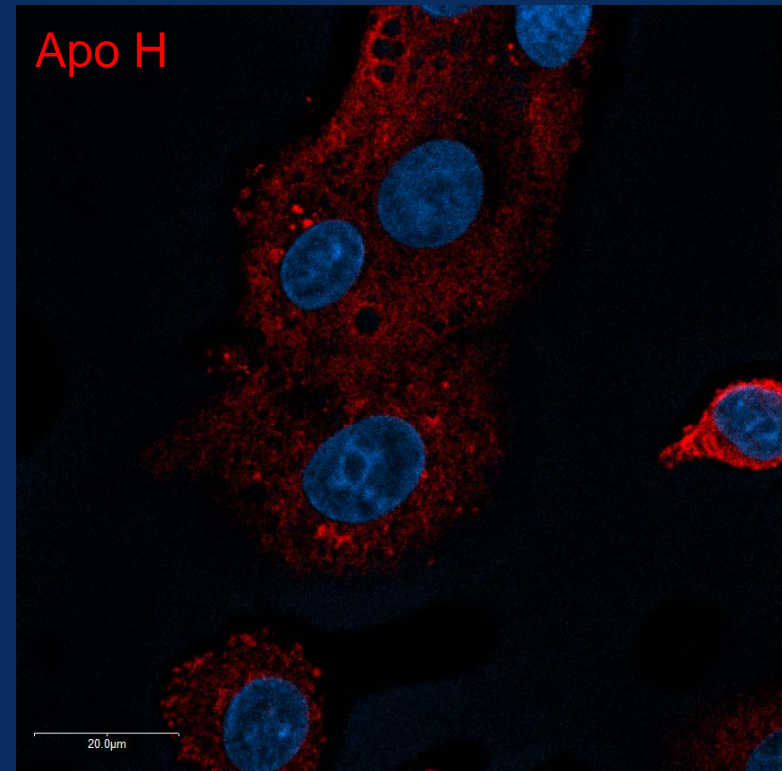
1. Cheng et al., 2005. Journal of Hepatology, 43:4 65-471
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4. Xu et al., 2009. Molecular immunology, 46: 2640-2646
5. Wu et al., 2009. Hepatology, 49: 1132-1140

ApoH plays a role in SVP formation

BHK 21 cells

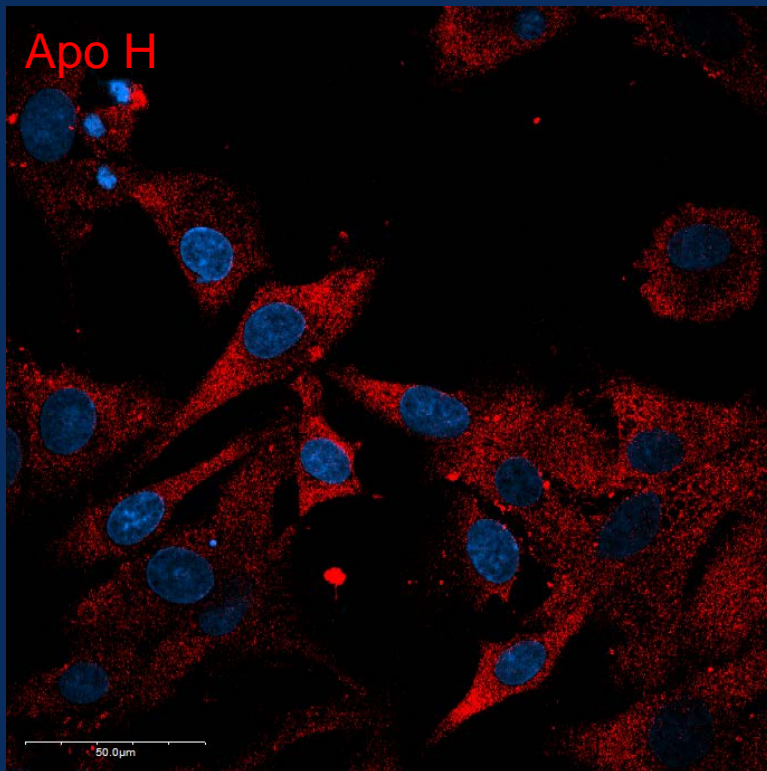


BHK-21 cells + sHBsAg

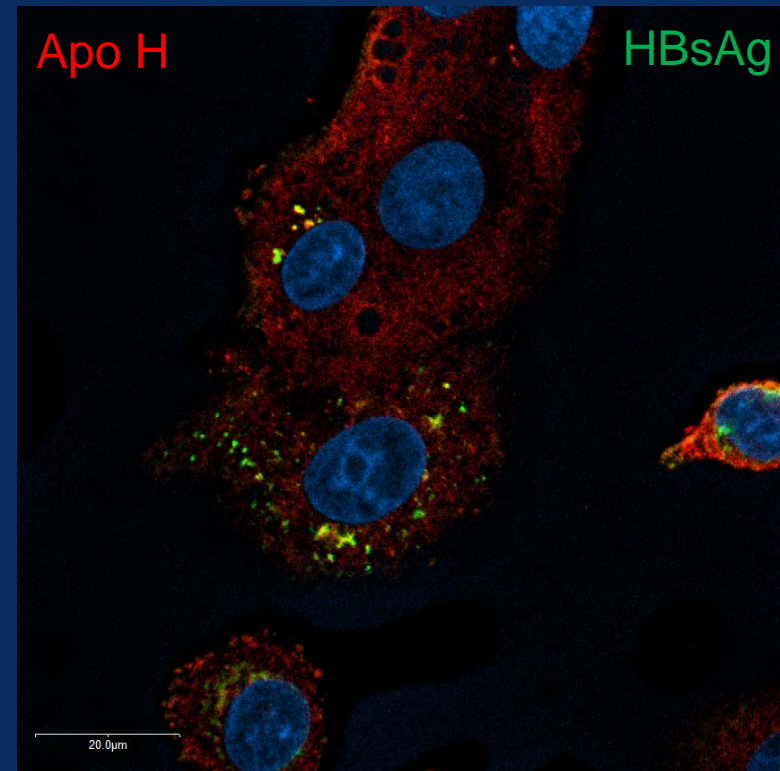


ApoH plays a role in SVP formation

BHK 21 cells

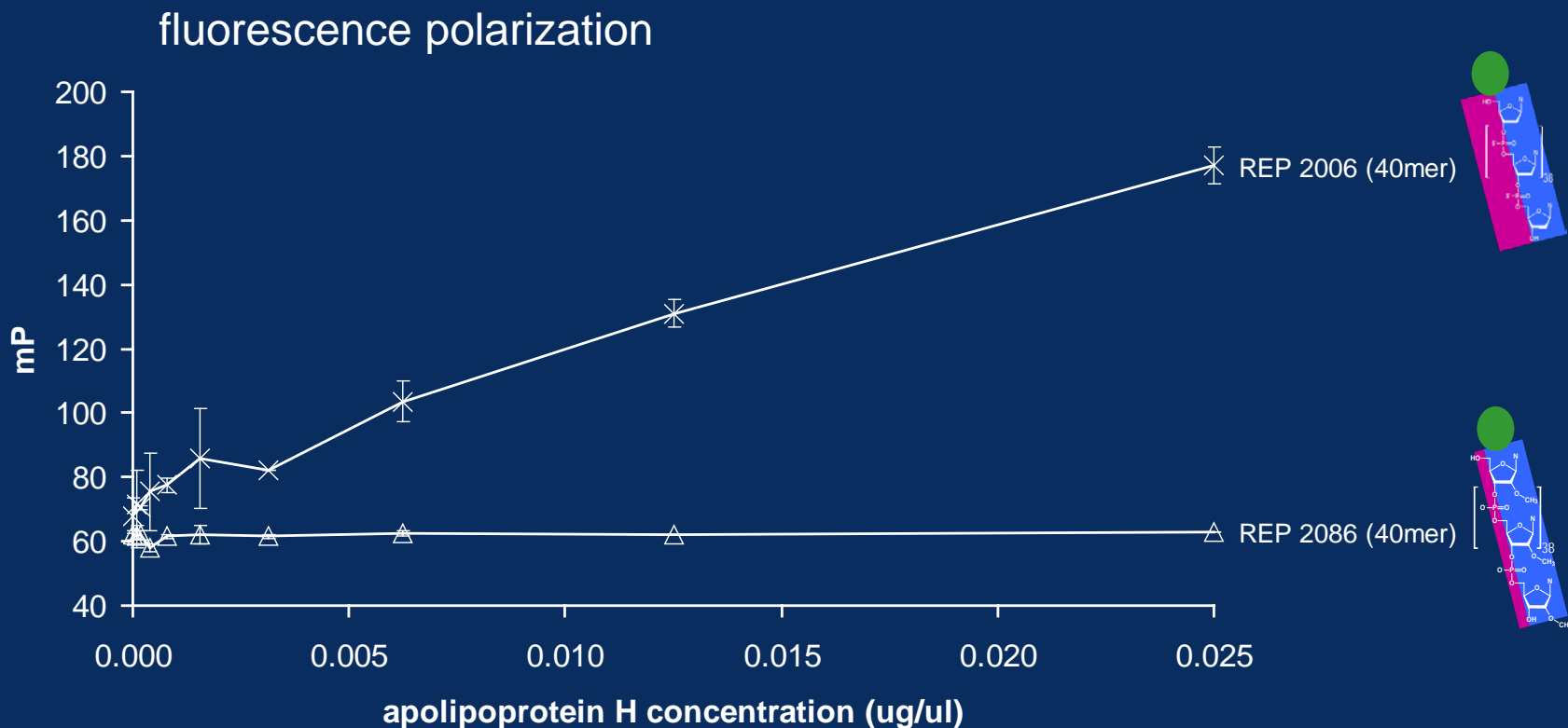


BHK-21 cells + sHBsAg



ApoH is enriched in HBsAg containing compartments

NAPs interact with ApoH



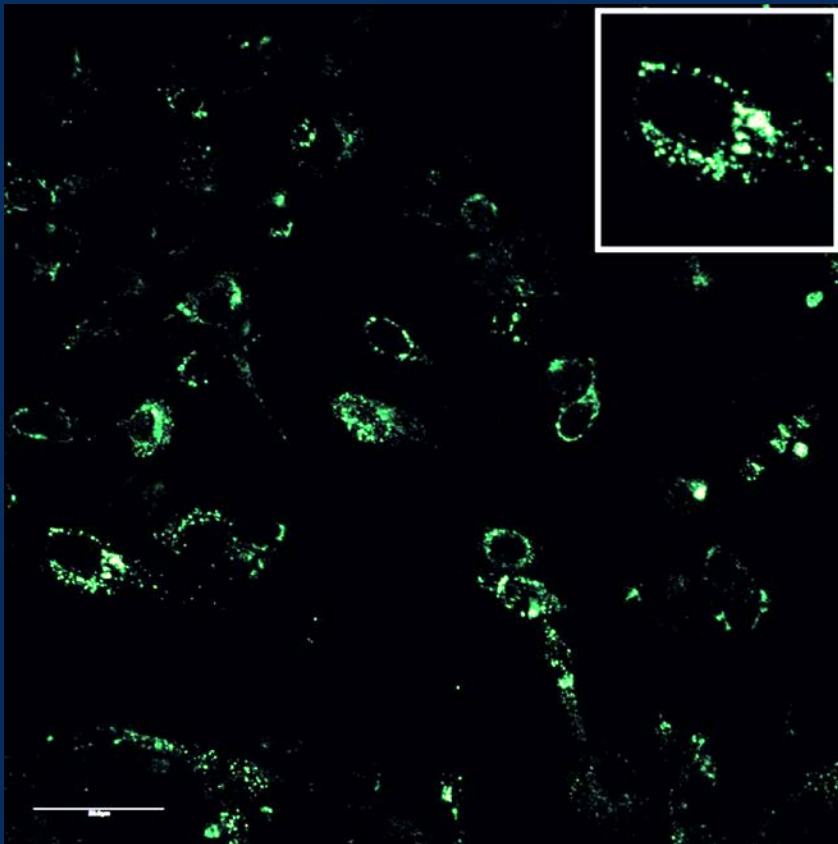
Amphipathic interactions with ApoH require phosphorothioation

NAPs block intracellular transit of SVP

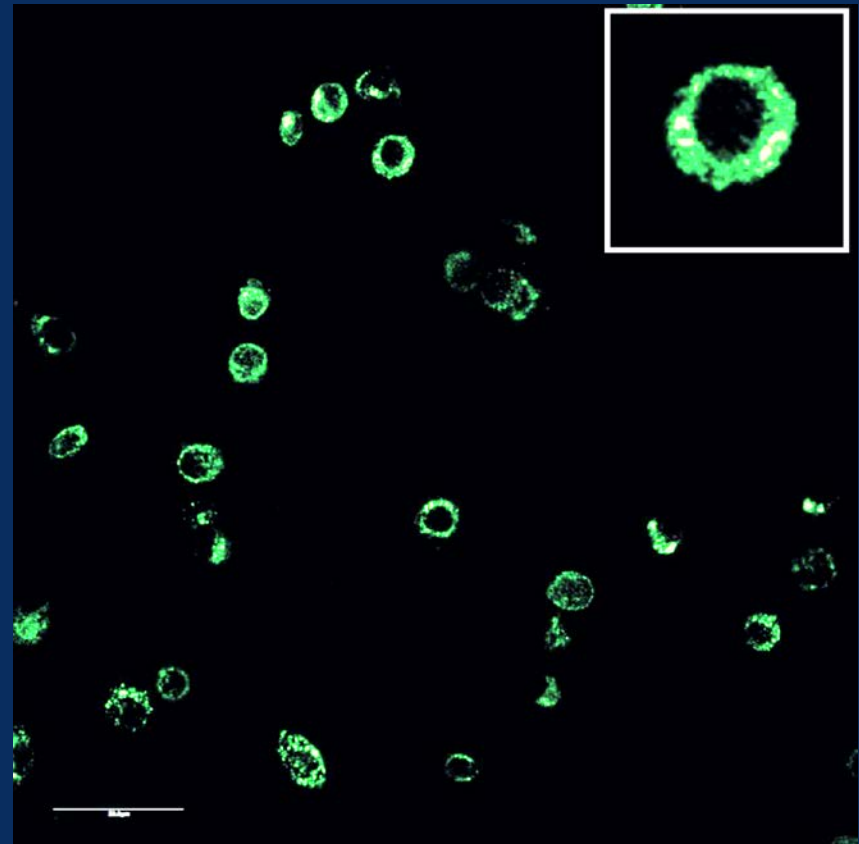
BHK-21 cells expressing sHBsAg are a model for SVP morphogenesis

Patient et al. 2007 J. Virol 81: 3842-3851

Untreated



NAP-treated



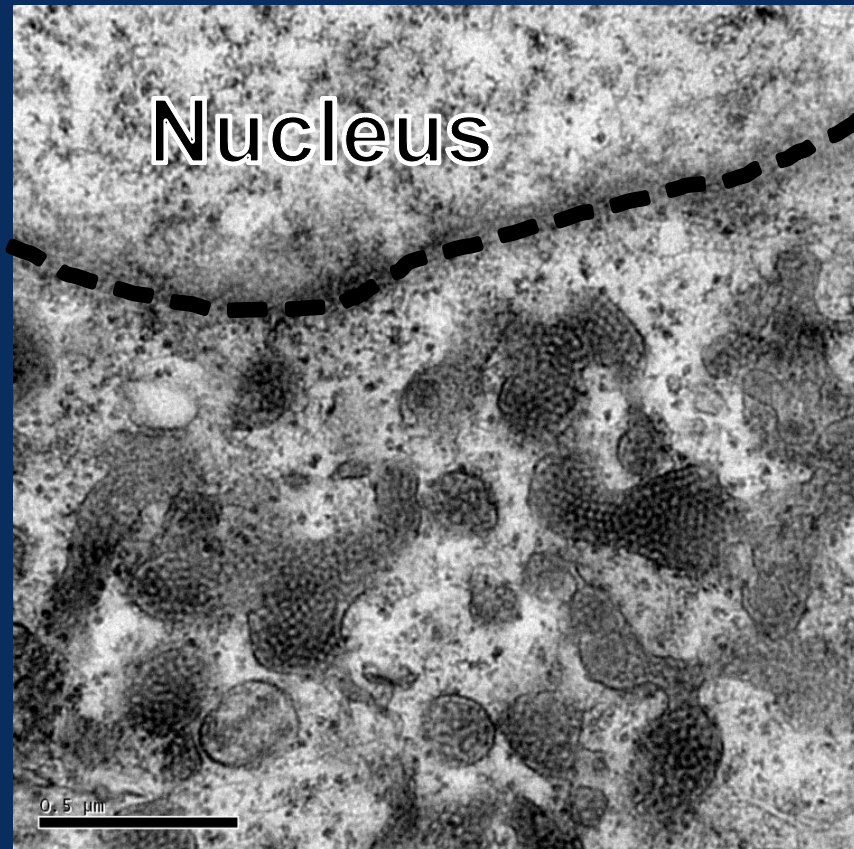
(HBsAg immunofluorescence)

NAPs block SVP formation.

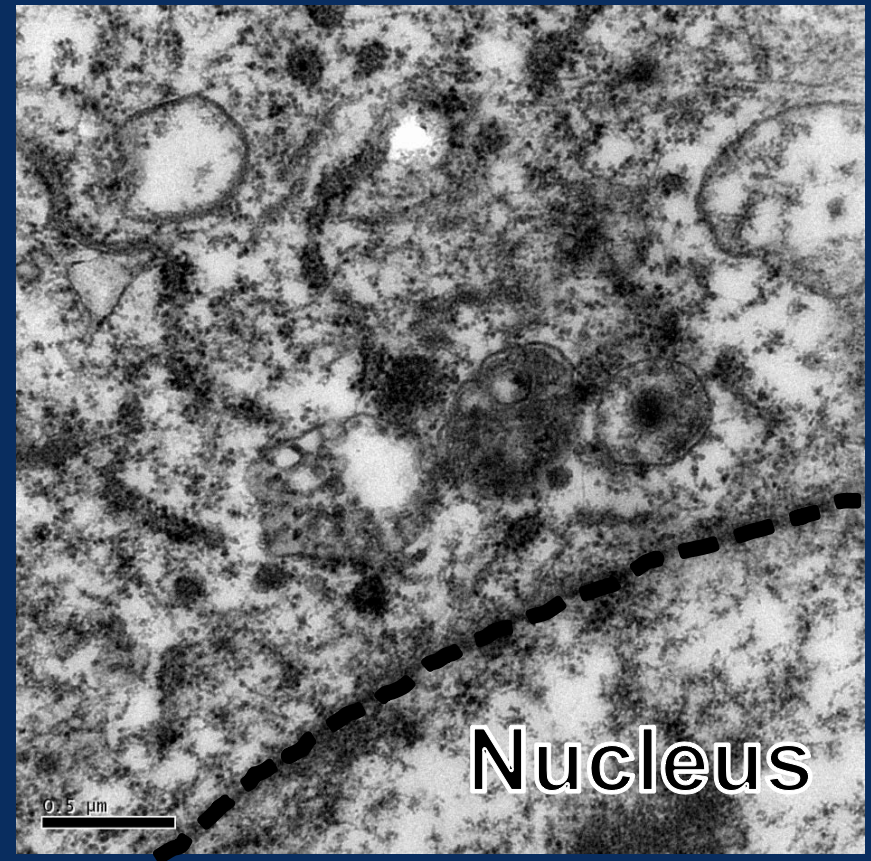
8

BHK-21 cells expressing sHBsAg
(Negative stained TEM)

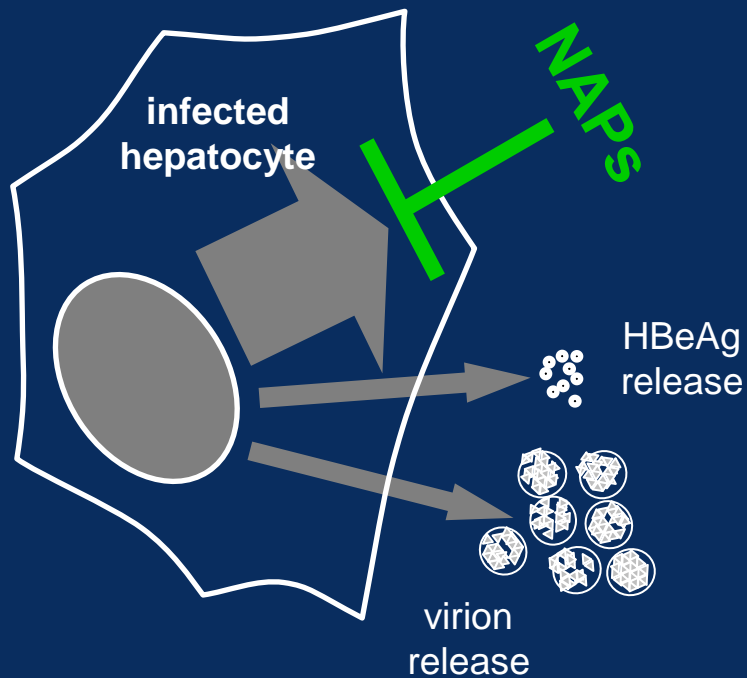
Untreated



NAP-treated



NAPs block the release of subviral particles



**HBsAg-mediated
immunosuppression
is removed**



**Restoration of host
immune response?**

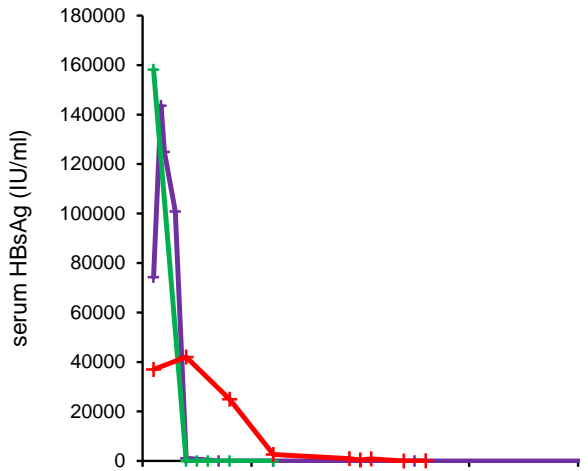
Clinical NAP species

NAP	REP 9AC (REP 2055)	REP 9AC' (REP 2139)
sequence	(AC) ₂₀	
backbone	phosphorothioate	
base modification	none	5' methylcytosine
ribose modification	none (DNA)	2' O methyl (RNA)
ability to block HBsAg release	comparable	
immunostimulatory activity	none detectable	
Biodistribution	Accumulation in Ki, Lv, Lu, Sp	Accumulation in Ki, Lv, Lu, Sp Higher steady state levels in the blood

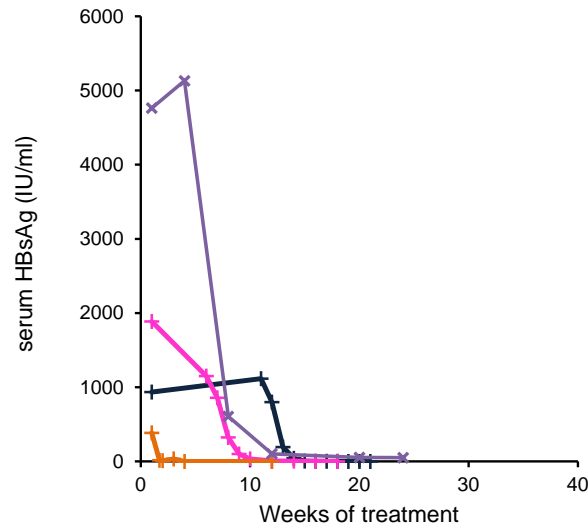
Effect of NAPs on serum HBsAg levels in HBV infected human patients

REP 2055

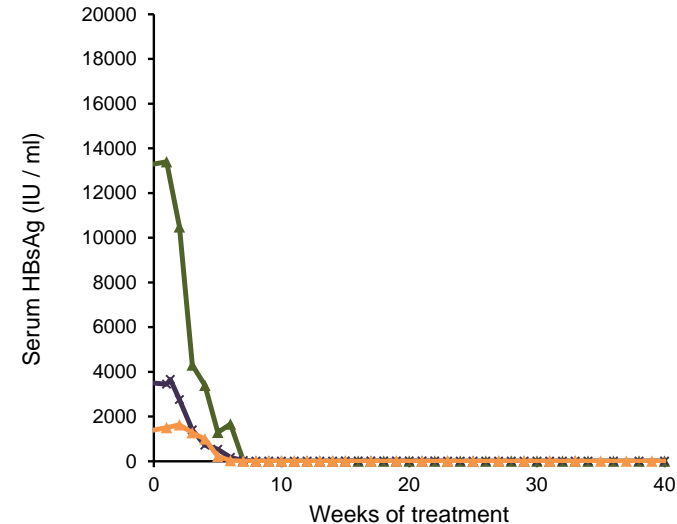
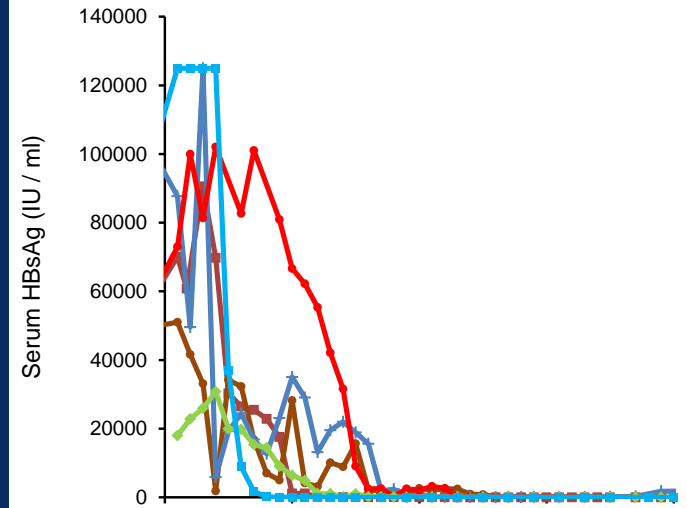
High pre-treatment
HBsAg



Low pre-treatment
HBsAg



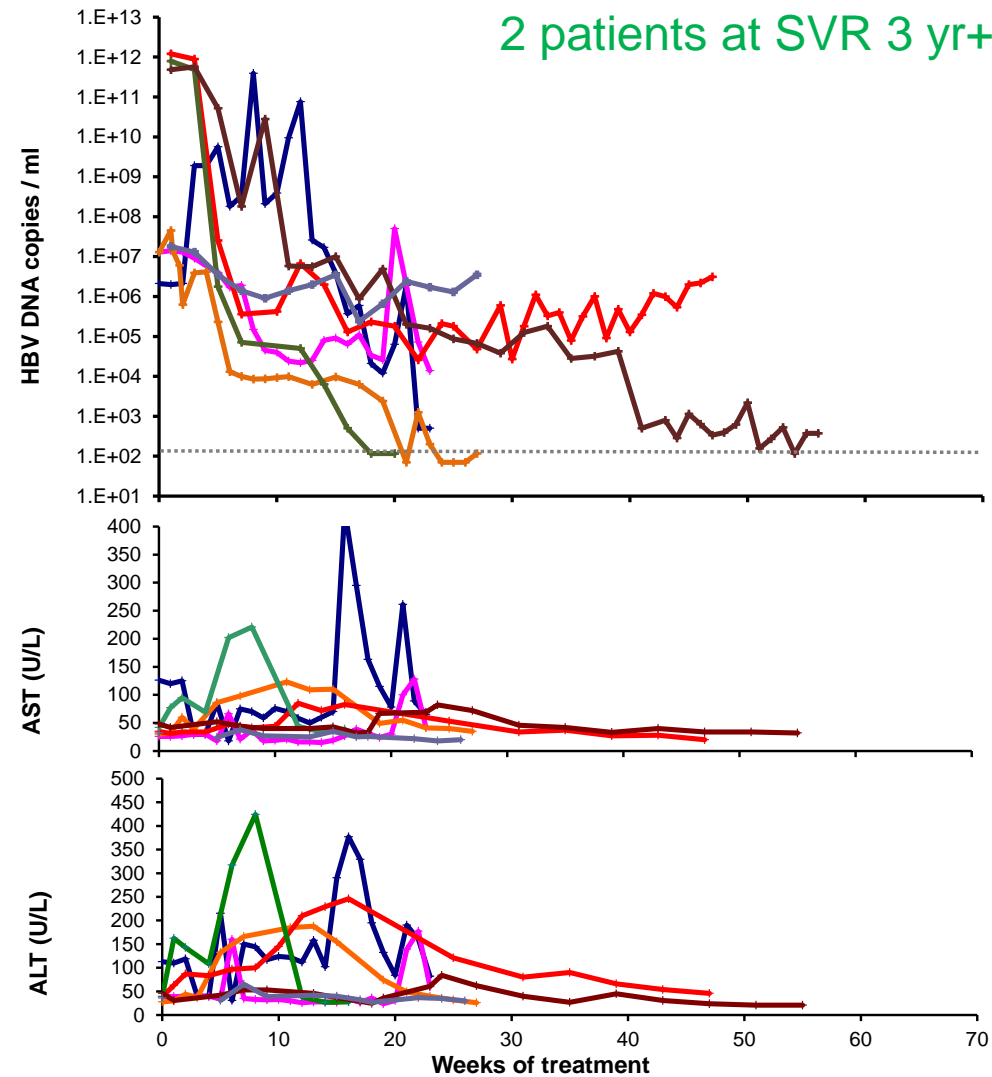
REP 2139-Ca



Therapeutic effect of REP 2055-mediated HBsAg clearance

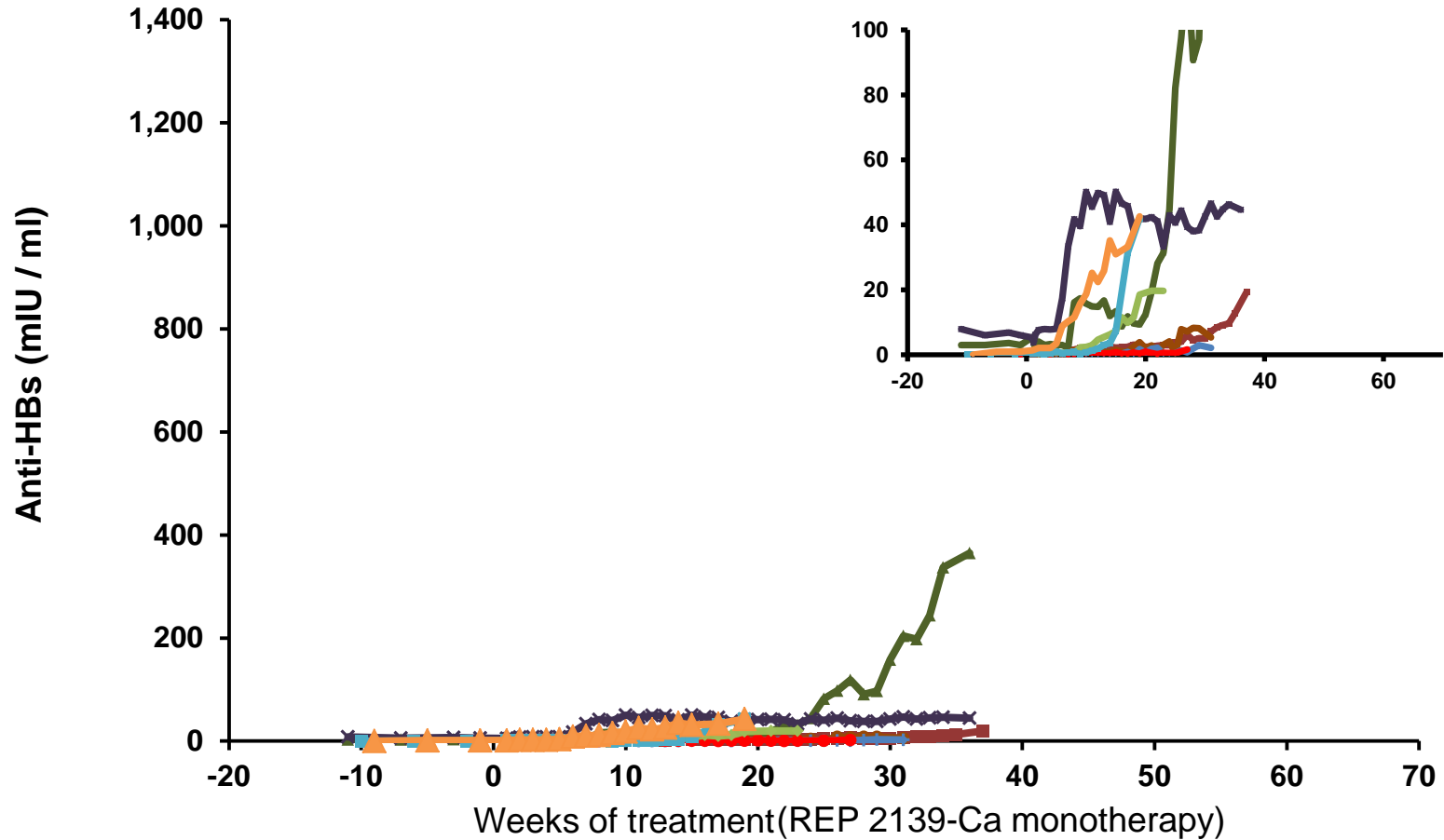
HBV
viremia

Activation of
immunity

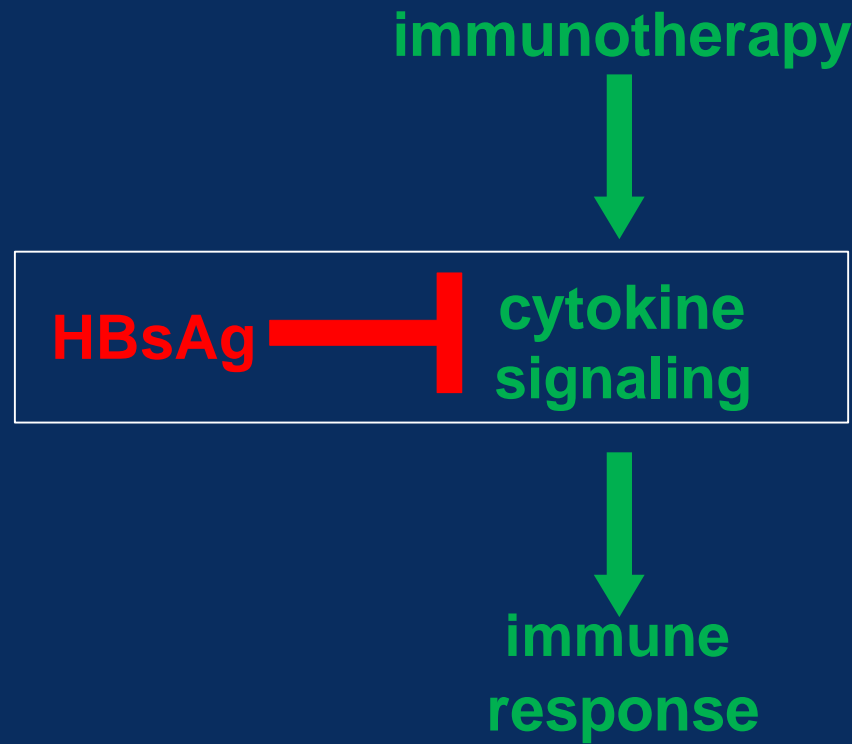


Anti-HBsAg (HBV) titers with REP 2139-Ca mediated HBsAg clearance

13

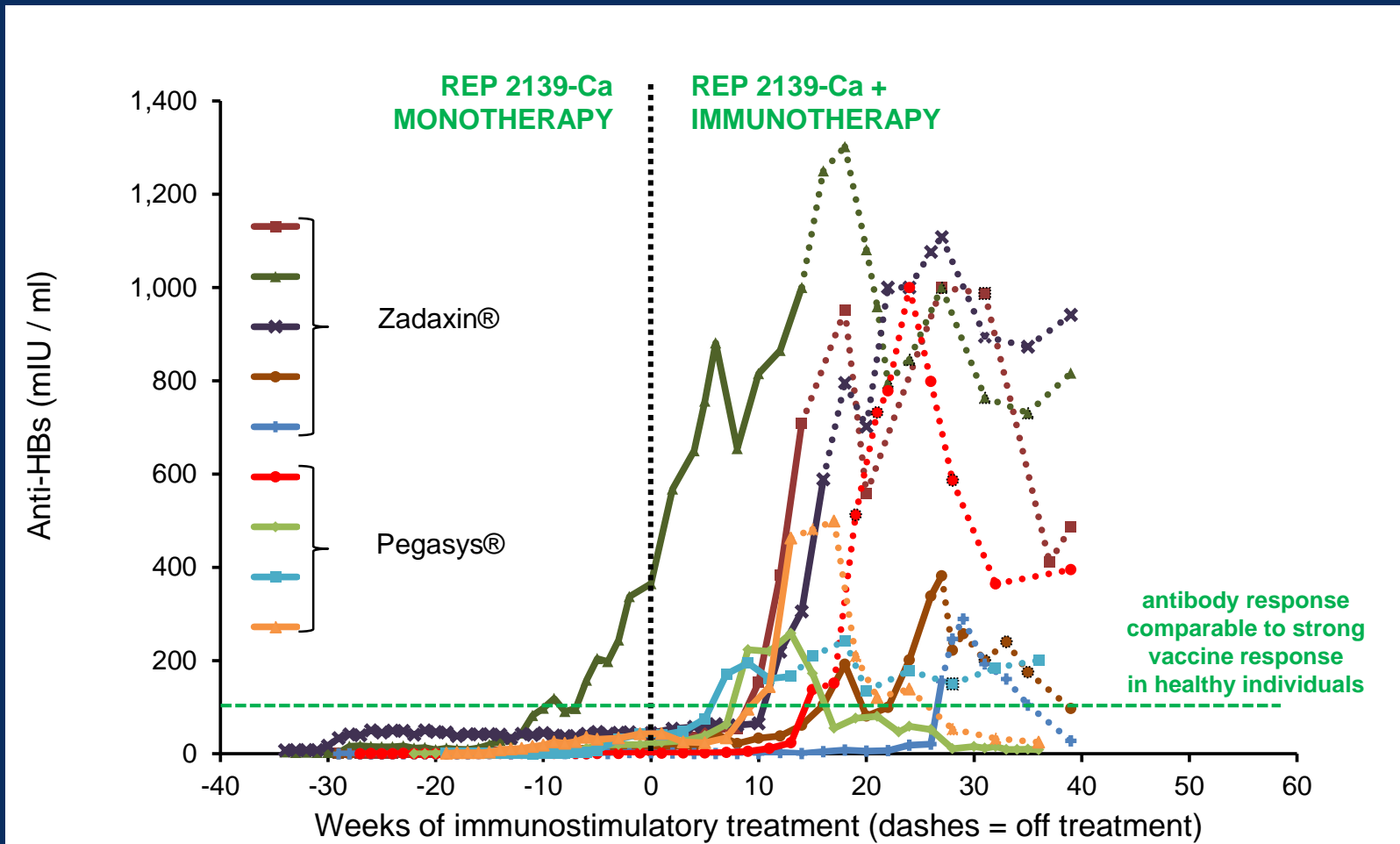


Can HBsAg removal potentiate the response to immunotherapy in patients with HBV infection?



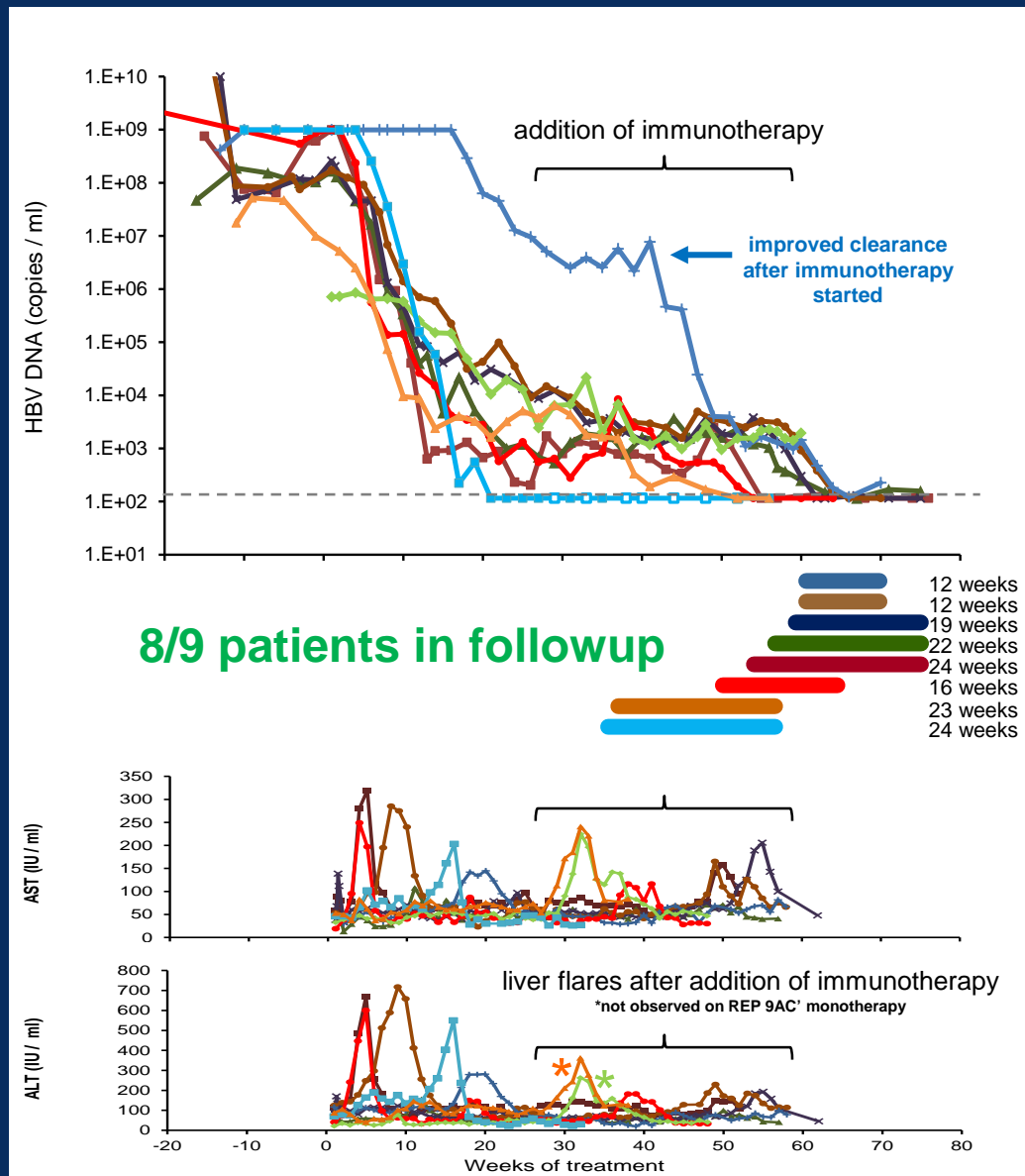
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Increased anti-HBs production continues off treatment



Therapeutic effect of REP 2139-Ca mediated HBsAg clearance (with add-on immunotherapy)

HBV
viremia



Activation of
immunity

REP 2055 vs REP 2139-Ca

COMPARATIVE TOXICOLOGY

NAPs do not have any nucleic acid target

Both REP 2055 and REP 2139 have the same target interface (Apo H)

Unique capability to evaluate toxicology of PS-ONs:

- in the absence of any antisense effects
- comparing the effect of 5'MeC and 2'Ome modifications in the same sequence context

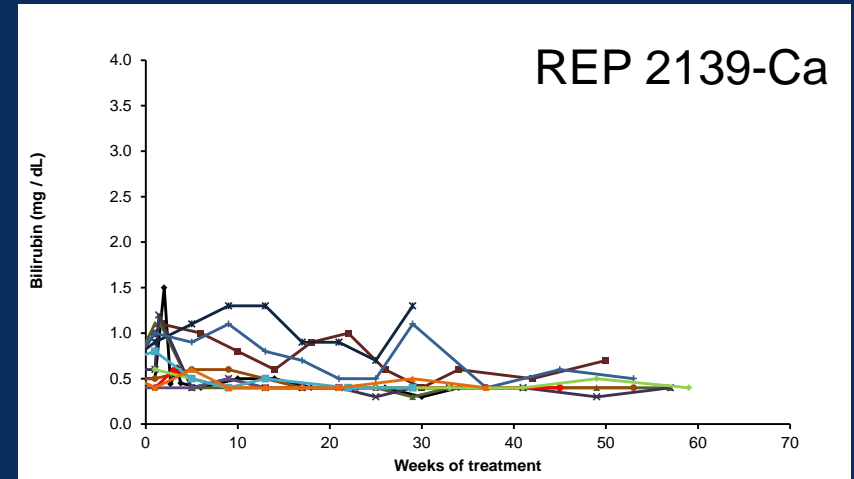
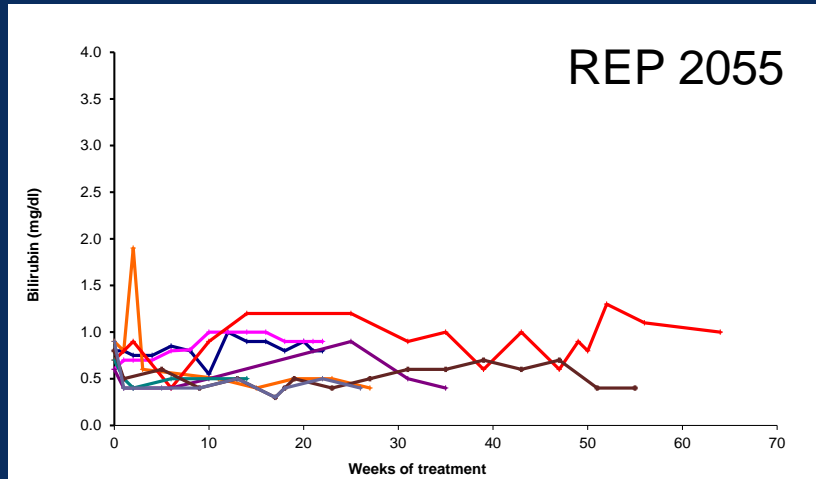
REP 2055 dosing (n=8, typically 400mg / week)

REP 2139-Ca dosing (n=12, typically 500mg / week) ~equimolar to REP 9AC

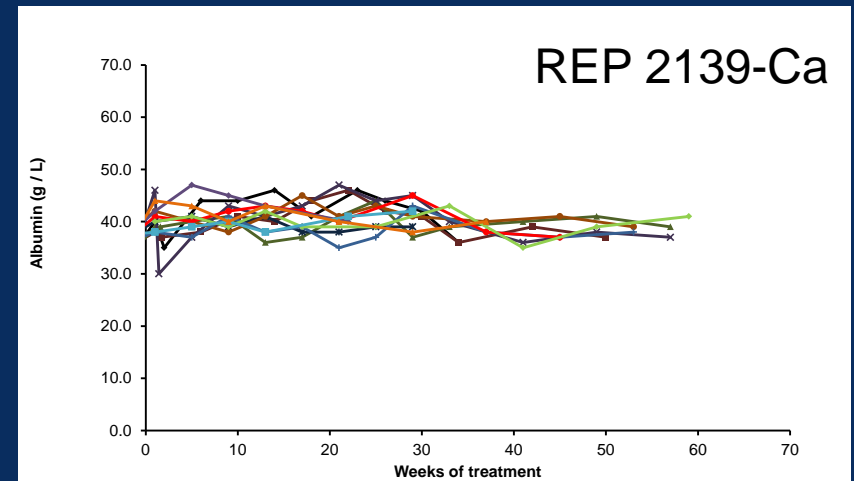
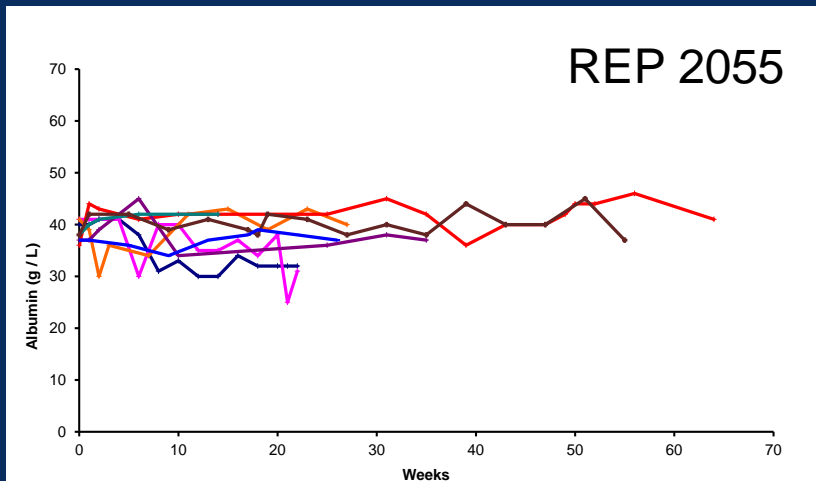
Examination of NAP monotherapy exposure only.

REP 2055 vs REP 2139-Ca COMPARATIVE LIVER FUNCTION

SERUM BILIRUBIN

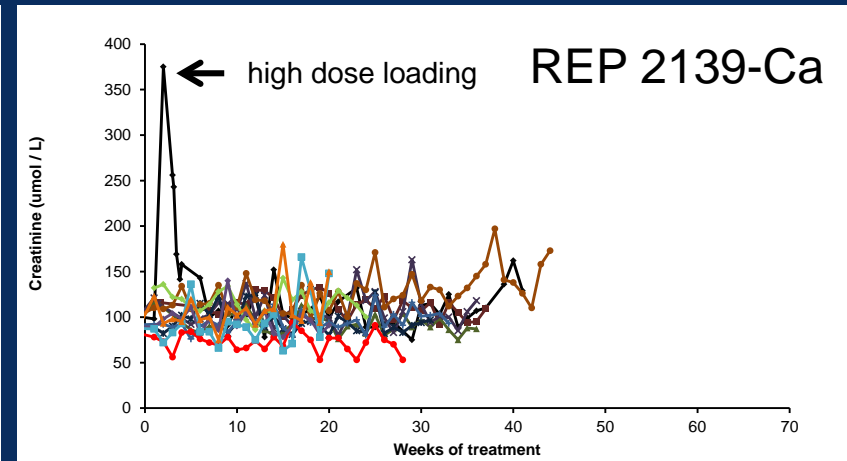
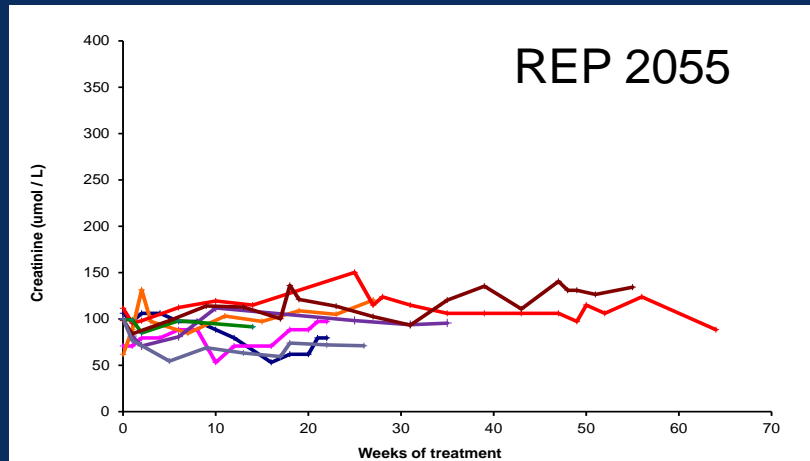


SERUM ALBUMIN



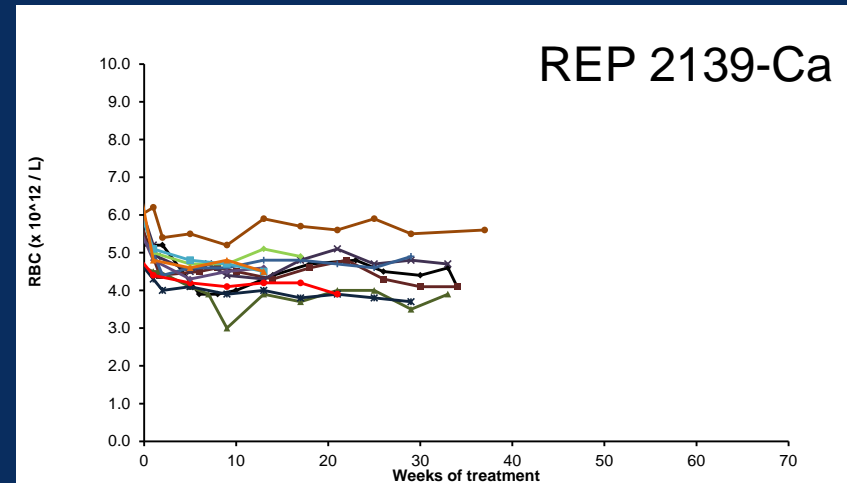
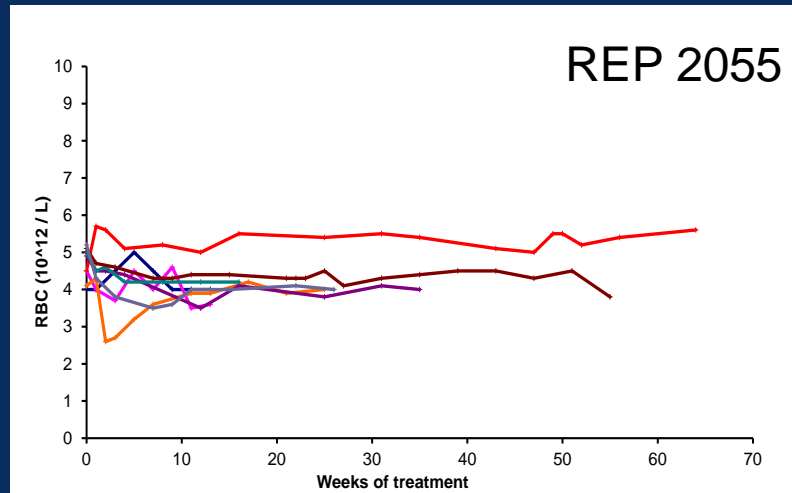
REP 2055 vs REP 2139-Ca COMPARATIVE KIDNEY FUNCTION

SERUM CREATININE

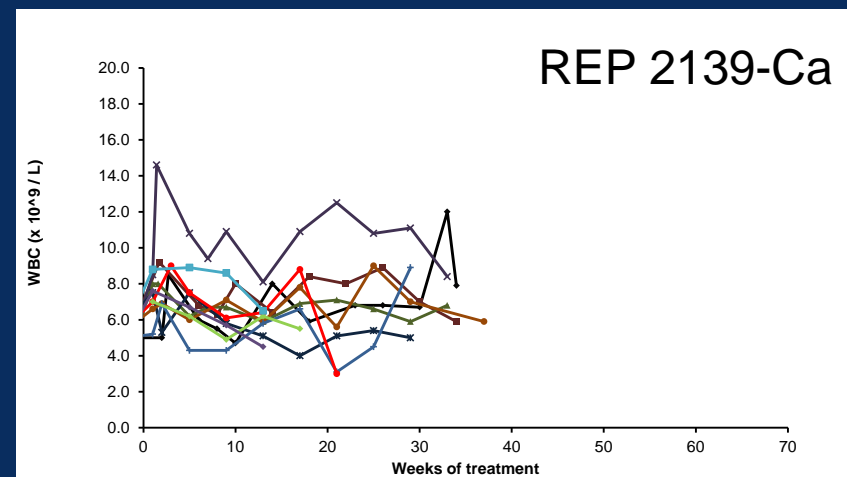
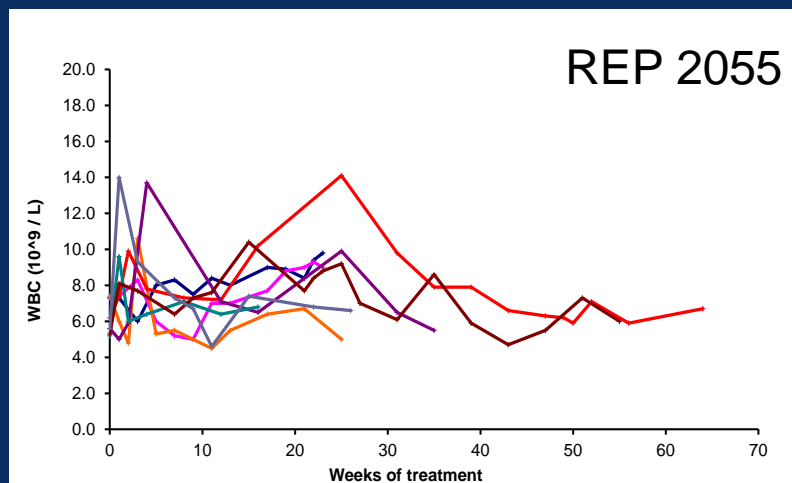


REP 2055 vs REP 2139-Ca COMPARATIVE HEMATOLOGY

RBC COUNTS



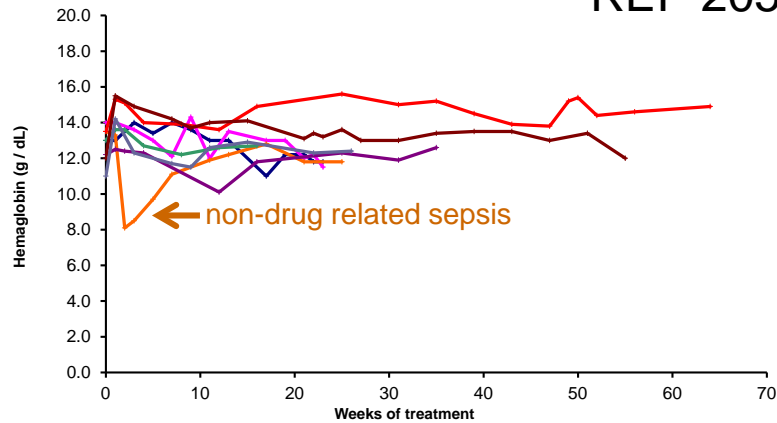
WBC COUNTS



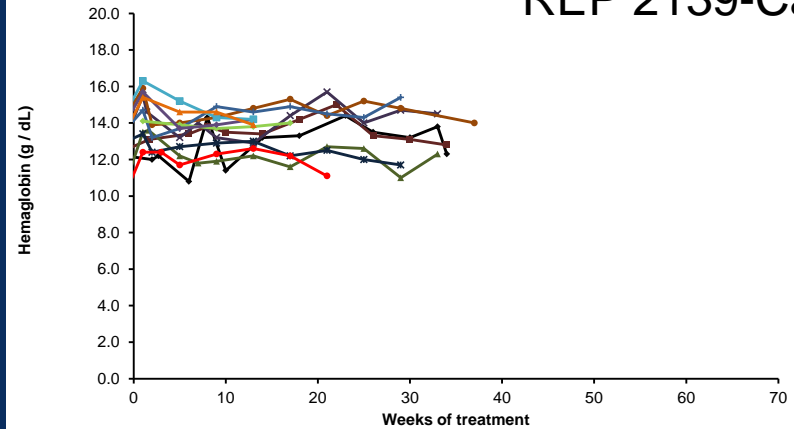
REP 2055 vs REP 2139-Ca COMPARATIVE HEMATOLOGY

HEMOGLOBIN

REP 2055

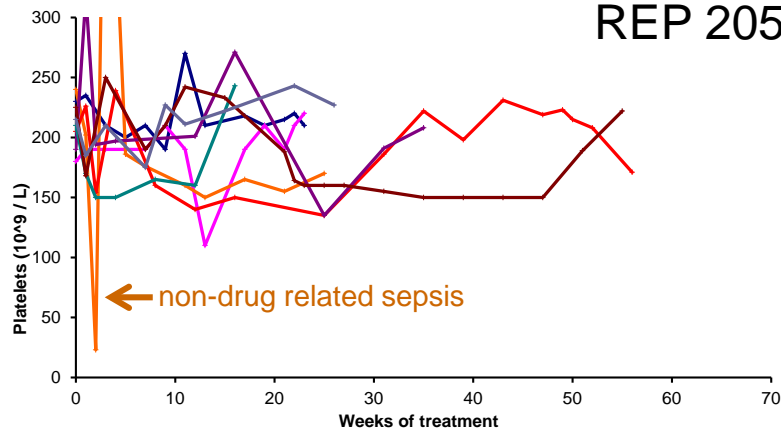


REP 2139-Ca

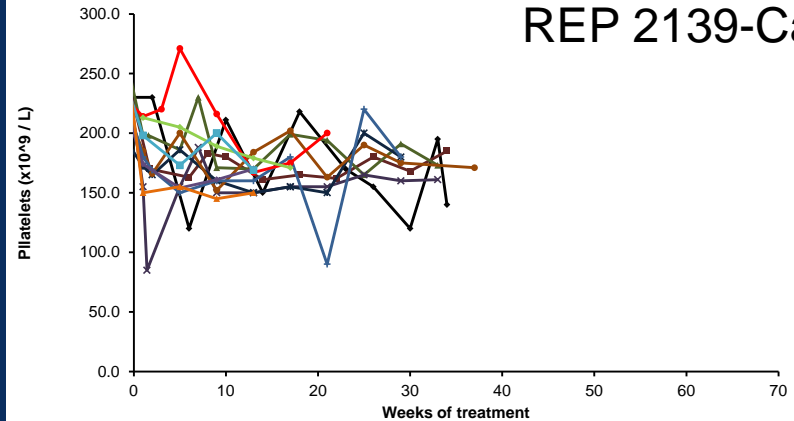


PLATELET COUNTS

REP 2055



REP 2139-Ca



REP 2055 vs REP 2139-Ca

THE ROLE OF MINERALS IN REPORTED SYMPTOMS

Major reported symptoms were all consistent with mineral deficiency:

weakness*
dyspepsia*
nausea*
transient hair loss
dysphagia

*also reported for other 2' ribose modified oligos

Frequently reported for REP 2139-Ca

severity related to accumulated drug exposure

Rare or absent with REP 2055

Absent in new REP 2139-Ca patients with optimized vitamin D3 levels and mineral supplementation at start of REP 2139-Ca therapy.

SUMMARY

NAPs effectively clear HBsAg from the blood of infected patients

HBsAg clearance allows for restoration of immunological function

Especially when combined with immunotherapy.

Combination NAP / immunotherapy can likely achieve permanent immunological control in most patients with chronic HBV infection.

NAPs have no antisense effect and show:

- PS-ON chemistry is **generally well tolerated** with no detectable liver, kidney or hematological dysfunction with long term exposure.
- Most symptoms reported with 2' ribose modified ONs may be linked to the chelation properties of ONs being more severe due to the higher circulating levels of 2' ribose modified ONs.