

# ***TLR7: A Therapeutic Target for HBV and HCV Chronic Infections***

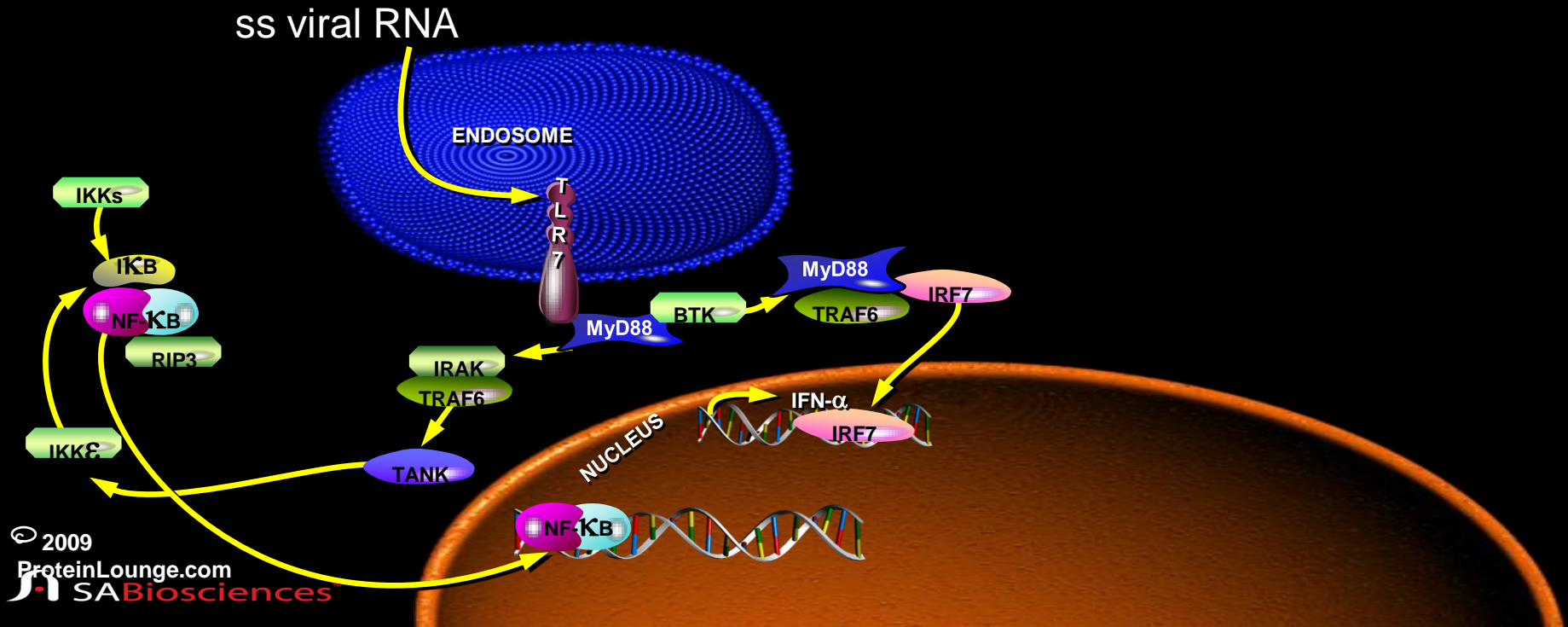
**Robert E. Lanford**

**Texas Biomedical Research Institute**

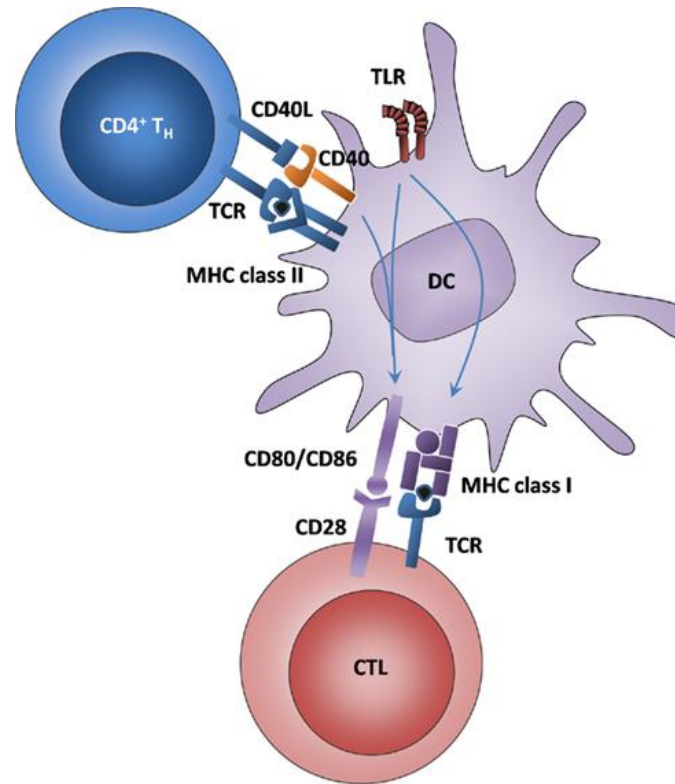
**Southwest National Primate Research Center, San Antonio, TX**

**Gilead sponsored research at Texas Biomedical Research Institute,**  
**No other disclosure.**

# TLR7 Pathway



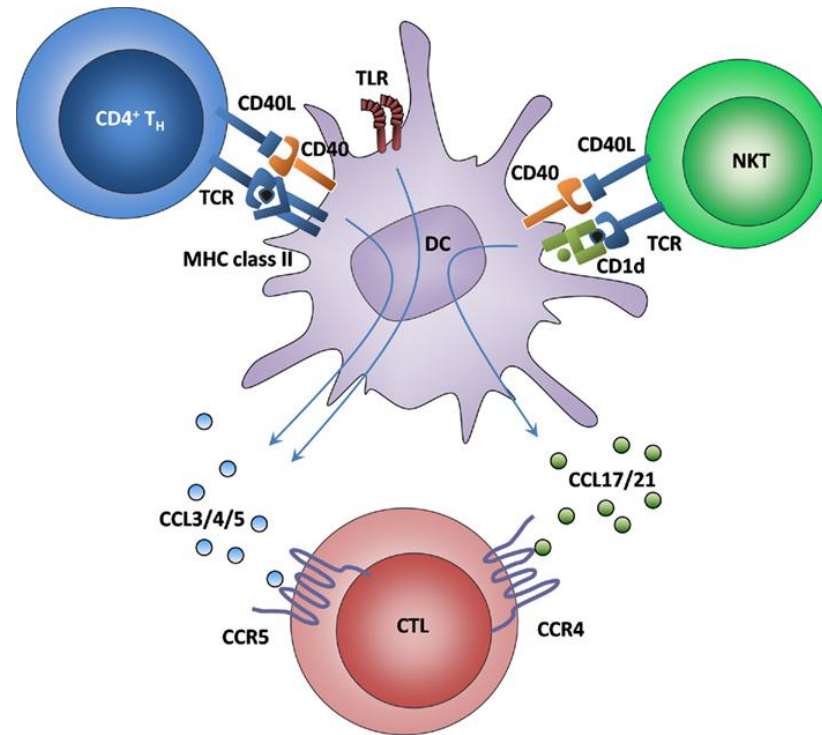
# Classical DC Licensing for Cross Priming of CTL is Enhanced by TLRs



Thaiss et al. *Frontiers in Immunol.* 2011.

# Cross Priming of CTL

## Classical and Alternative DC Licensing

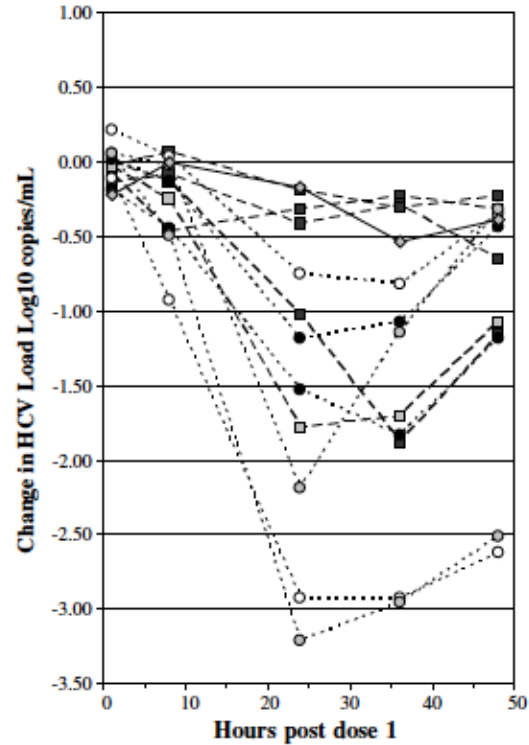


Thaiss et al. *Frontiers in Immunol.* 2011.

# TLR7 Agonist

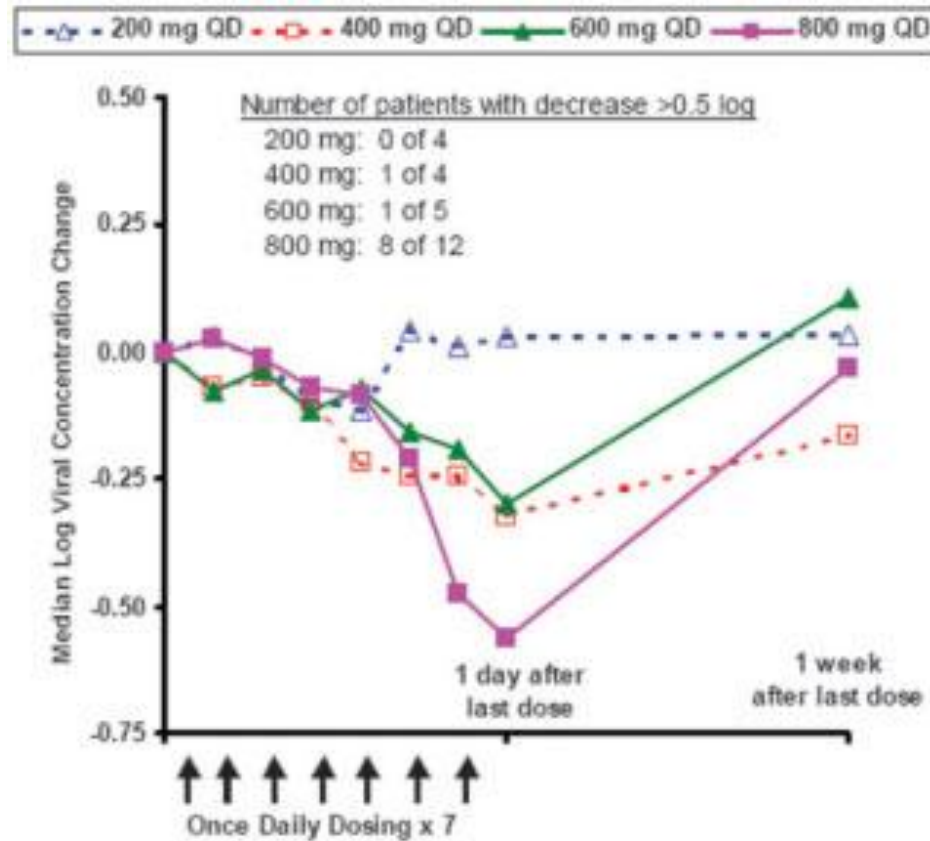
- R837 Imiquimod TLR7/ Aldara papilloma
- R848 Resiquimod TLR7/8 HSV, cancer, vaccines, HCV
- Isatoribine (7-thia-8-oxoguanosine) ANA245→ ANA975
- ANA773
- SM276001-36032 (9-sub-hydroxyadenine)
- PF-04878691 (852A; 3M-001) imidazoquinoline
- GS-9620 Hepatitis B in chimpanzees

# Oral Dosing of Resiquimod in HCV Patients



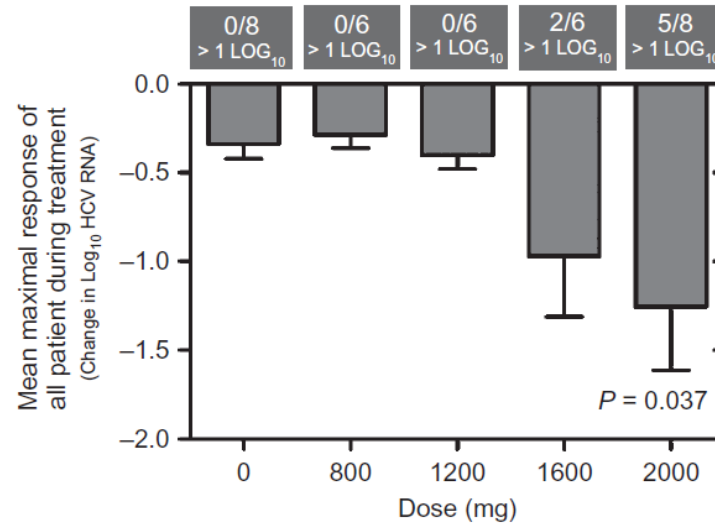
Pockros et al J Hepatol 2007  
HCV 2x/wk for 4 wks; >50% ~1-3 log  
AE similar to IFN

# IV dosing Isatorabine ANA245



2 patients > 2 log decline HCV RNA

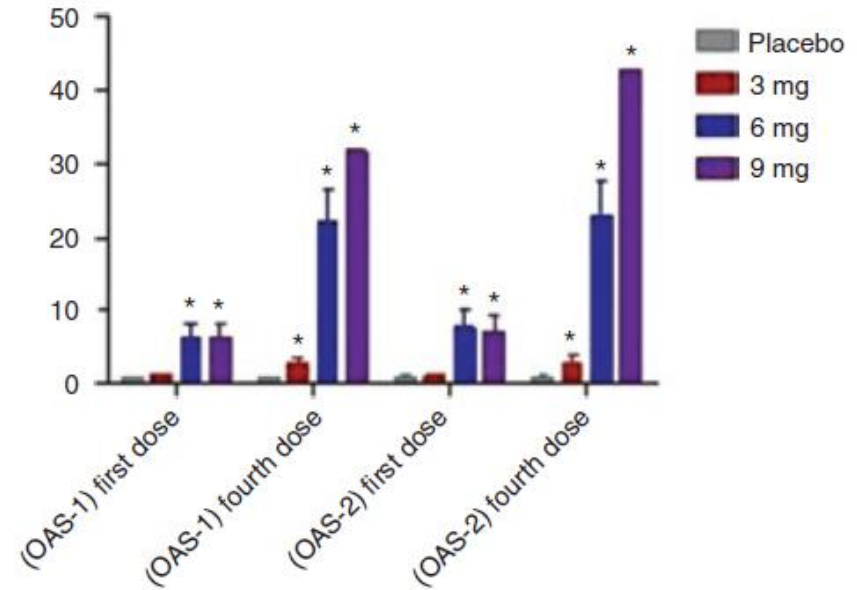
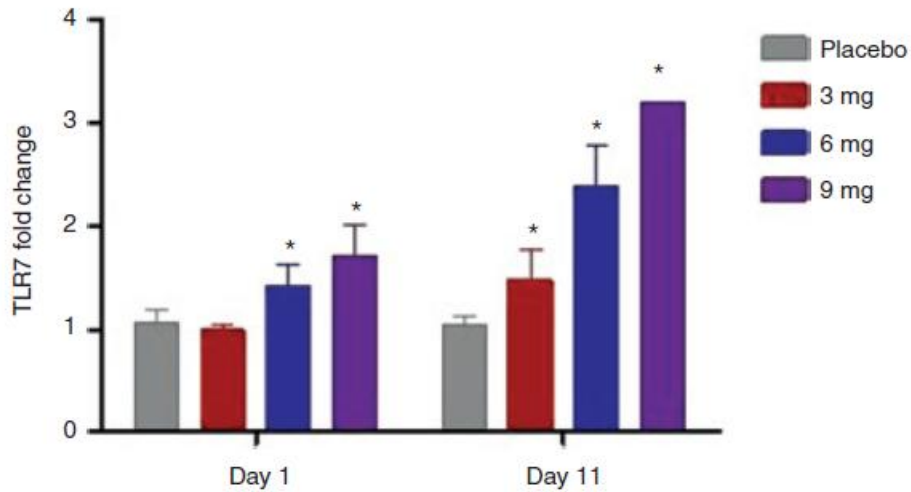
# Oral Dosing of ANA773 in HCV Patients



Every other day for 10 days at 2000 mg > 1 log in > 50% patients

Bergmann et al, Aliment Pharmacol Ther 2011

# Oral Dosing of PF-04878691 in Healthy Adults



Twice per week oral dosing for 2 weeks, 4 total doses  
Discontinued due to AE

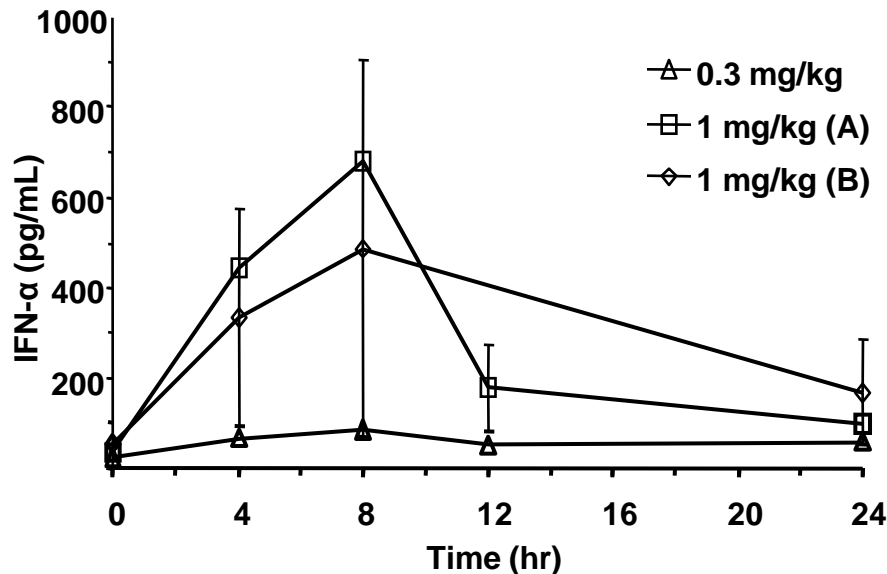
# **GS-9620 Background**

- **GS-9620 is a orally available TLR7 agonist selective for IFN- $\alpha$  and stimulatory cytokines.**
- **Induction of the innate immune response by GS-9620 has been characterized in monkeys, chimpanzees and humans.**
- **Approx. 6-fold less potent in chimpanzees in comparison to man.**
- **HBV infected chimpanzees were selected as the animal model for antiviral efficacy.**

# GS-9620 PK-PD Parameters in Uninfected Chimpanzees

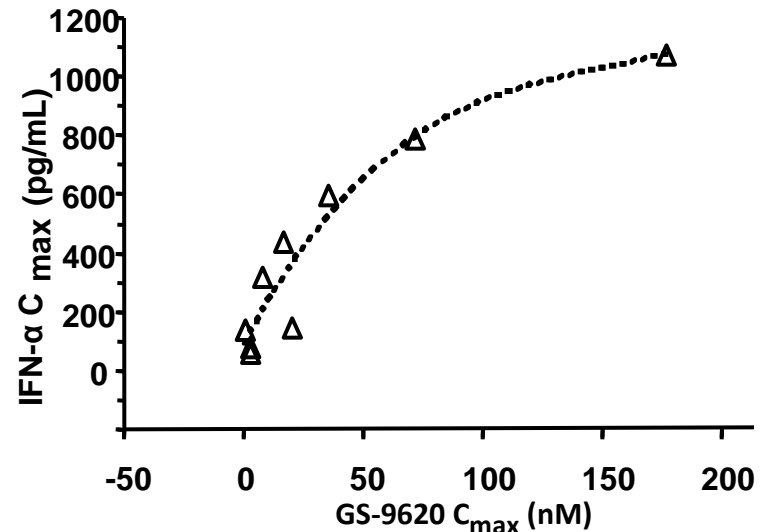
To determine starting dose a pre-study single oral dose evaluation of pharmacokinetics, pharmacodynamics and tolerability was performed in uninfected chimpanzees.

### IFN $\alpha$ Induction @ 0.3 and 1 mg/kg



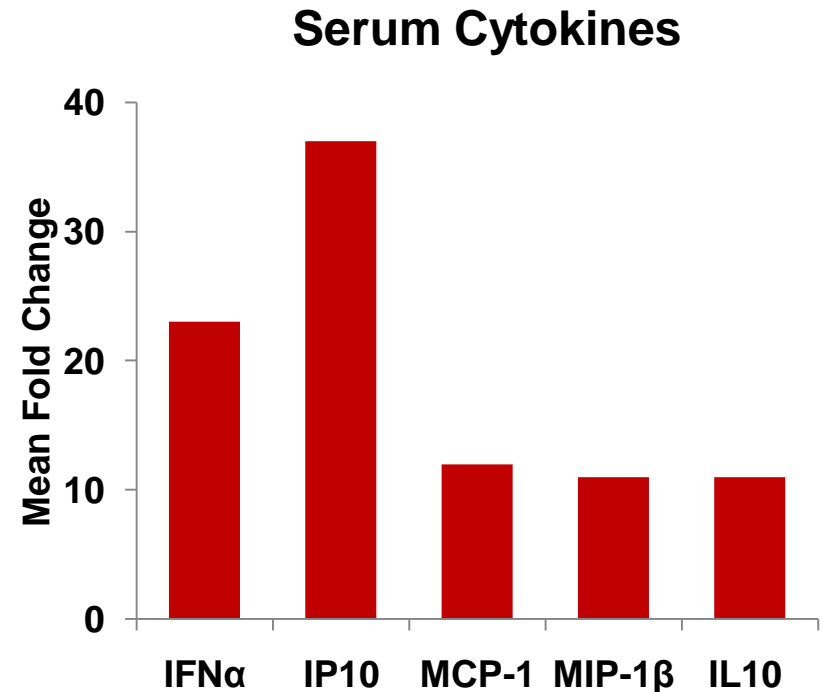
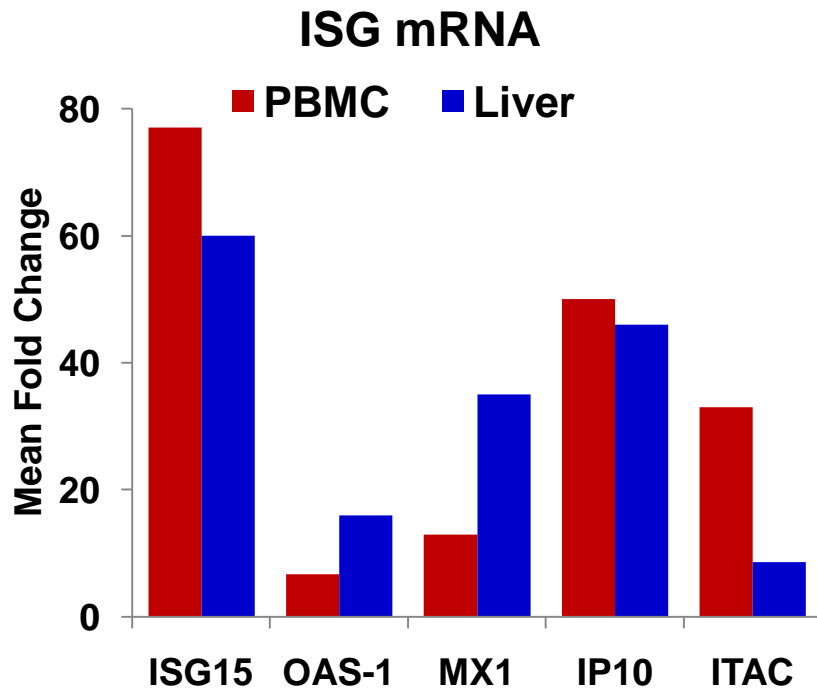
N = 3 animals at 0.3 mg/kg, n =3 at 1 mg/kg (A), and n =4 1mg/kg (B).

### C<sub>max</sub> GS-9620 vs IFN $\alpha$



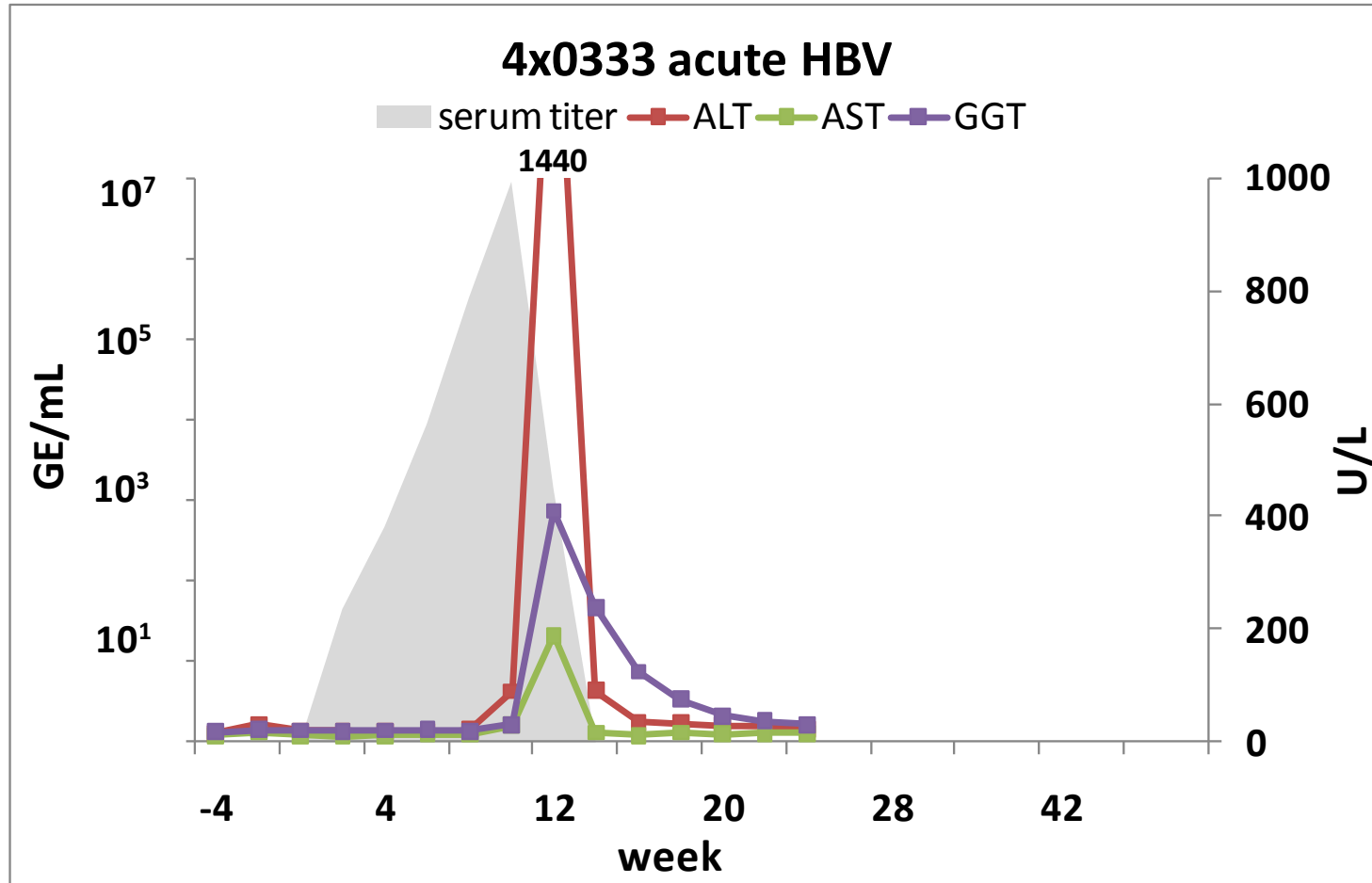
# ISG and Serum Cytokine Induction in Uninfected Chimpanzees

Pharmacodynamic responses in uninfected animals after a single oral GS-9620 dose of 1 mg/kg.



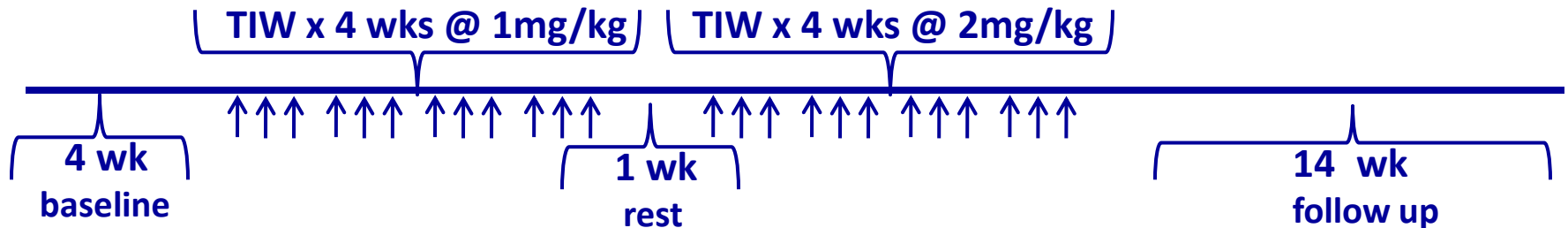
Evaluated at 0, 4, 8 and 24 hrs post dosing at 1mg/kg for n=7 animals.  
Mean of the peak fold increases are shown.

# Acute Resolving HBV Infection in the Chimpanzee



# HBV Efficacy Study Design

3 HBV chronically infected chimpanzees Oral dosing three time per week

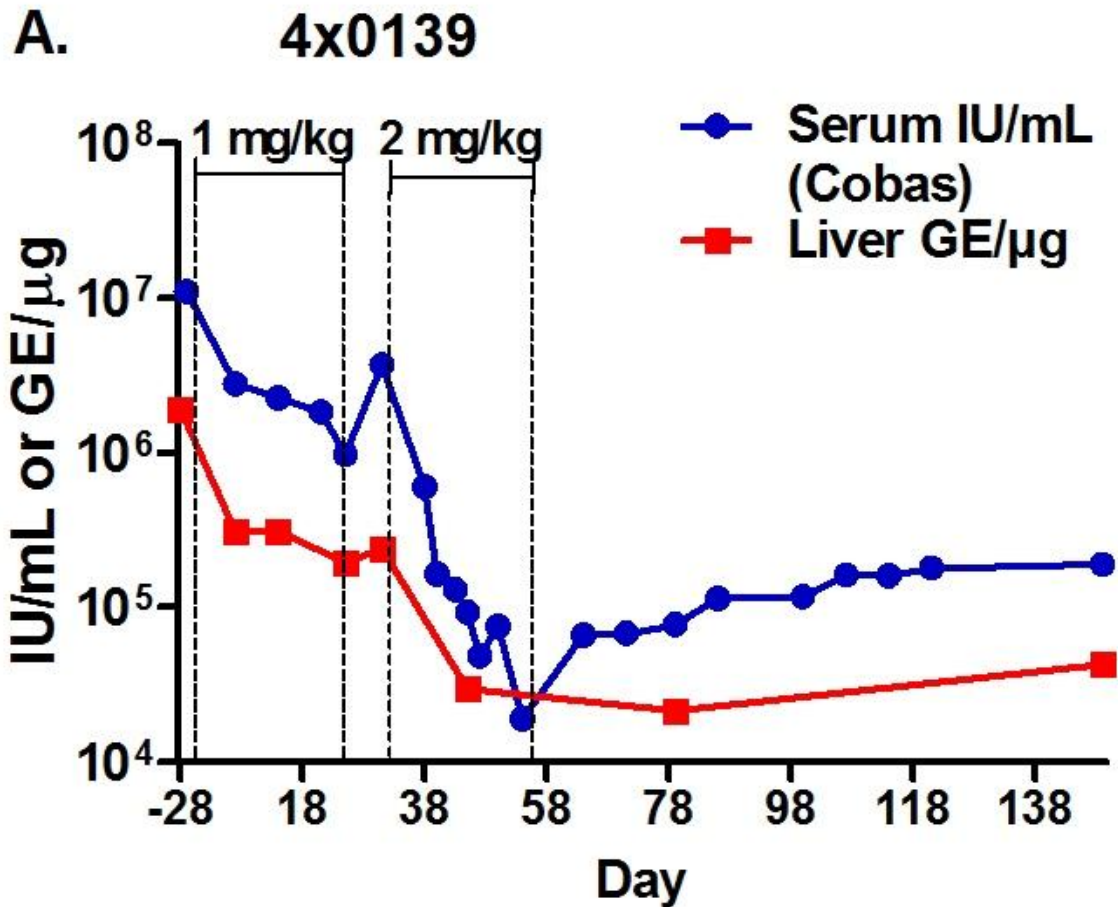


- HBV DNA, HBeAg and HBsAg
- ISGs in PBMC and Liver, Cytokine/Chemokine
- Lymphocyte activation markers,
- Safety parameters: CBC, blood chemistries, observations

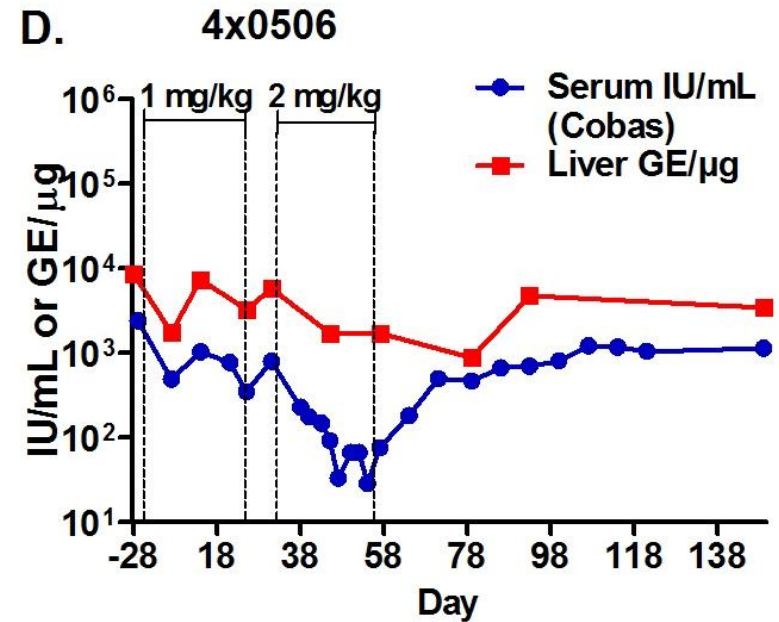
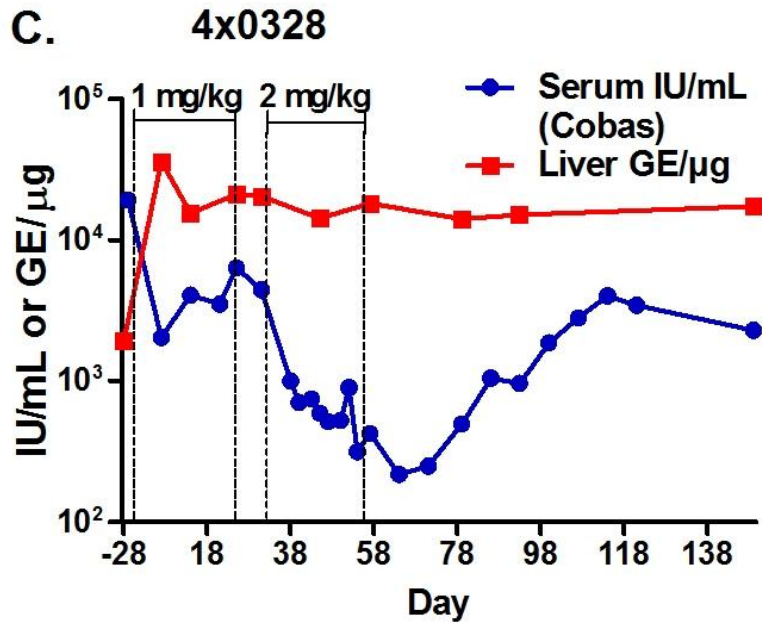
# Baseline Characteristics of HBV Chronically Infected Chimpanzees

Animal ID	Baseline HBV DNA	HBeAg	Anti-HBeAg	Anti-HBcAg	Sex	Duration of HBV Infection
4x0139	$6.5 \times 10^7$	+	-	+	F	30 Years
4x0328	$2.5 \times 10^5$	+	-	+	M	> 24 Years
4x0506	$1.6 \times 10^4$	-	+	+	F	> 27 Years

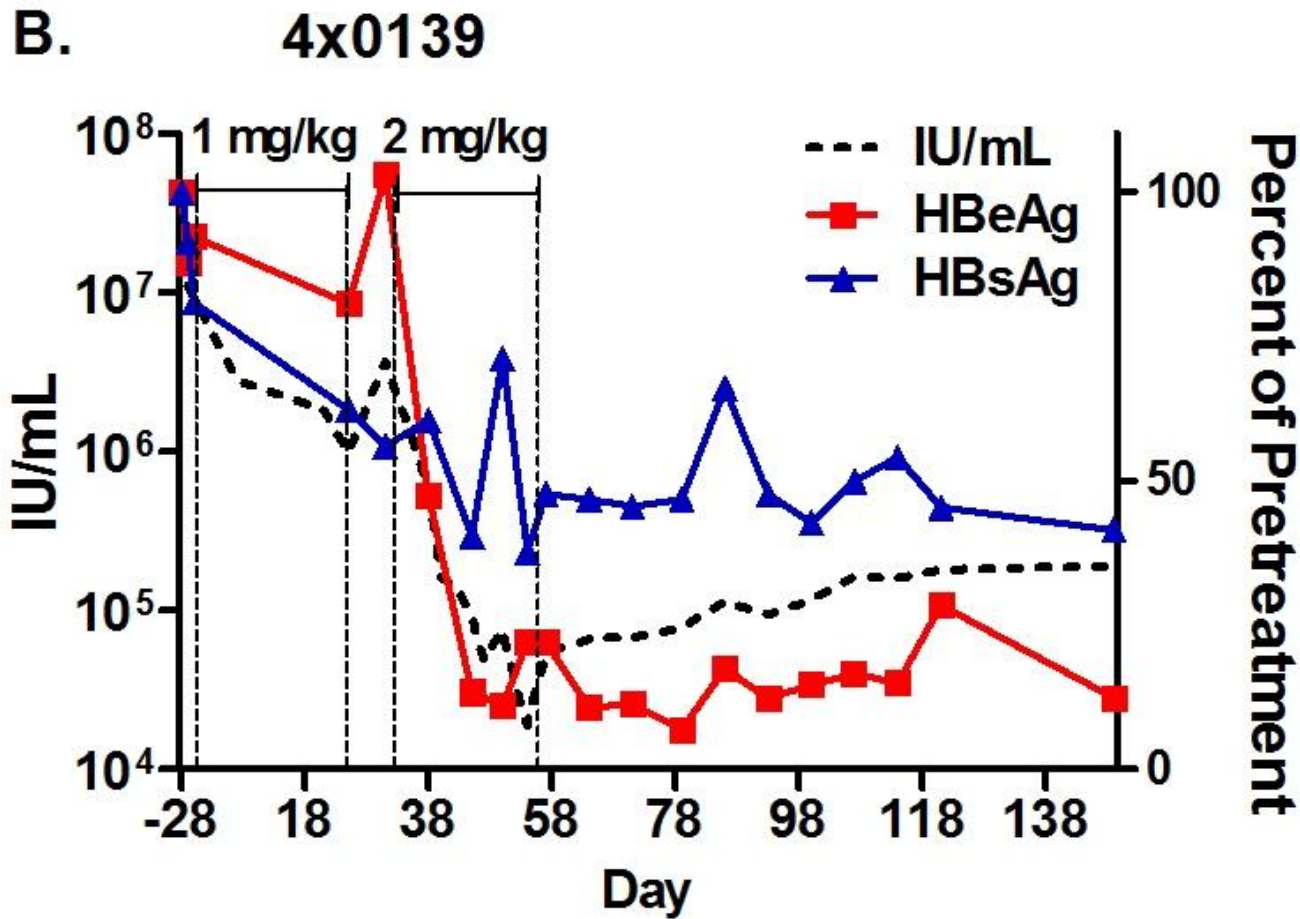
# Antiviral Response in High Titer Chimpanzee



# Antiviral Response in Low Titer Chimpanzees

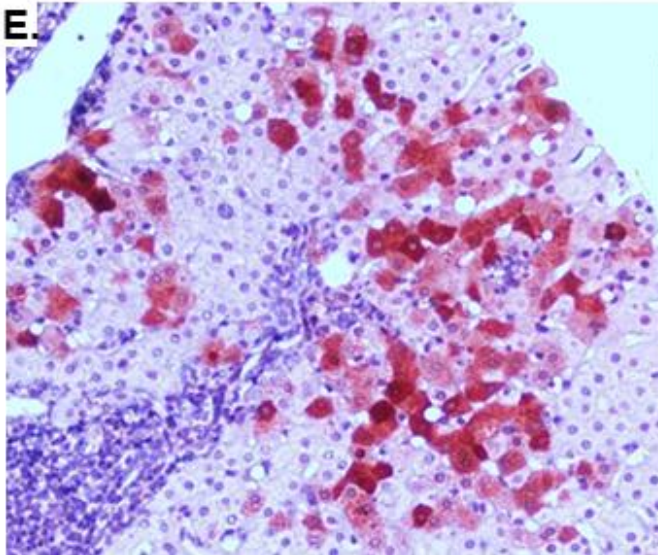


# Reduction in Serum HBsAg and HBeAg in High Titer Chimpanzee

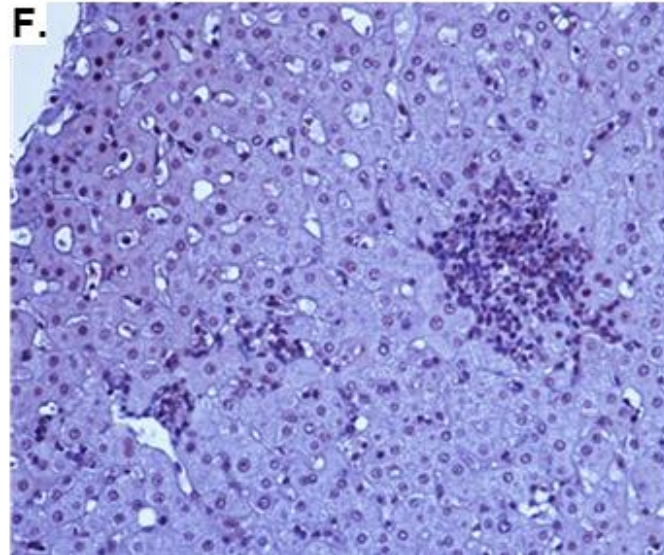


# Reduction in HBcAg Positive Hepatocytes in High Titer Chimpanzee

Prestudy



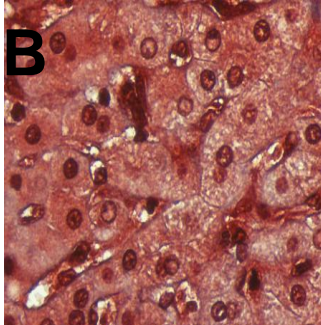
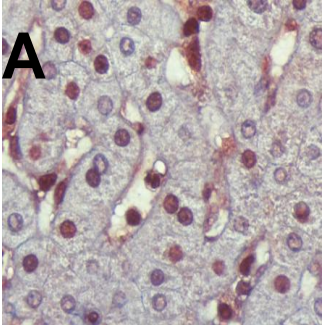
Day 57, last dose



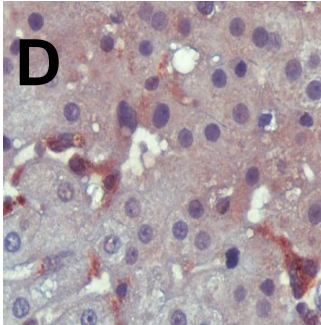
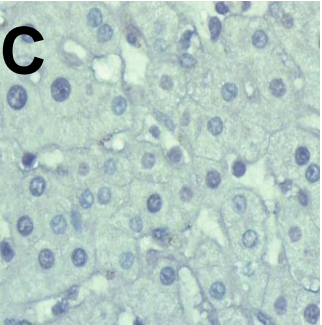
# Immunohistochemistry in Liver of High Titer Chimpanzee

Prestudy

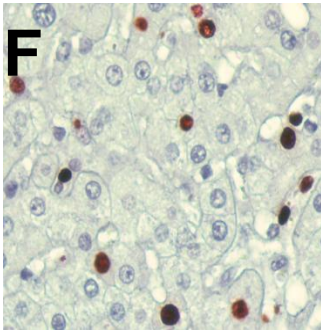
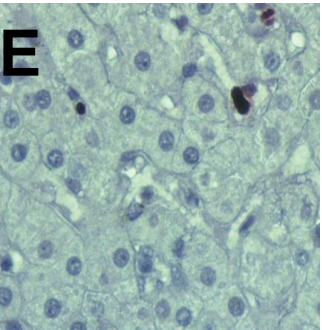
Day 57 - 79



**ISG15**

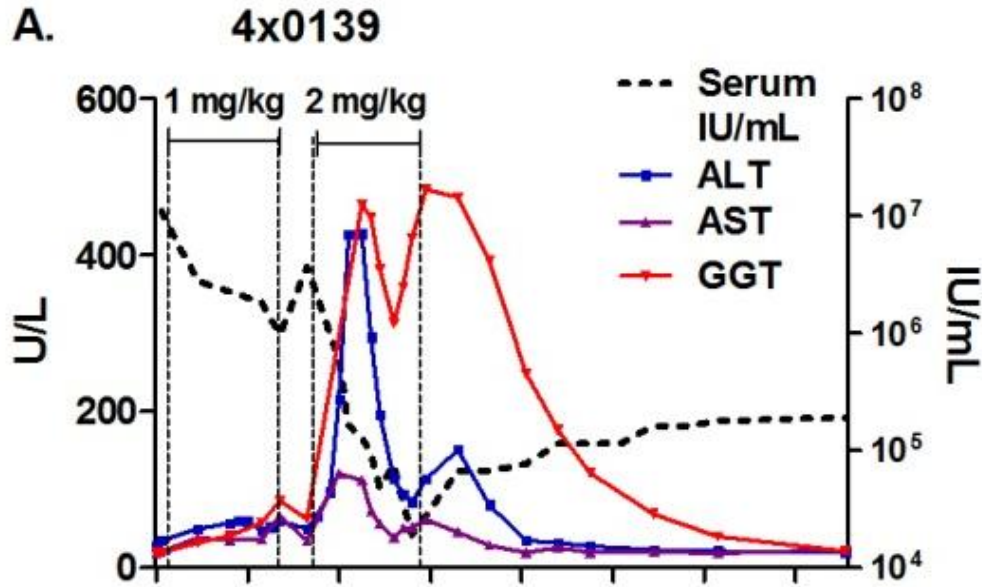


**Caspase 3**

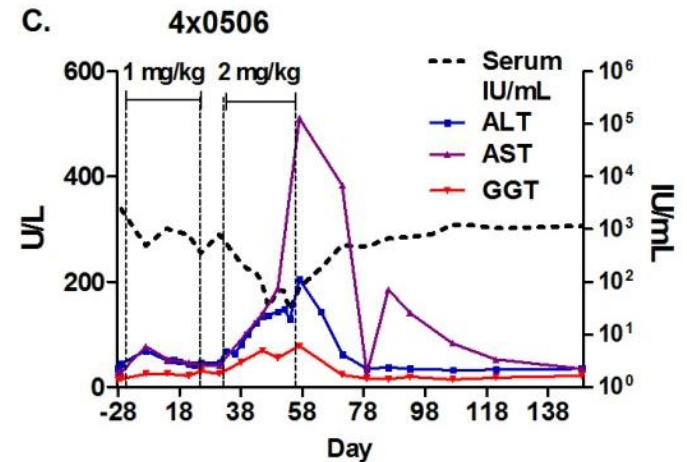
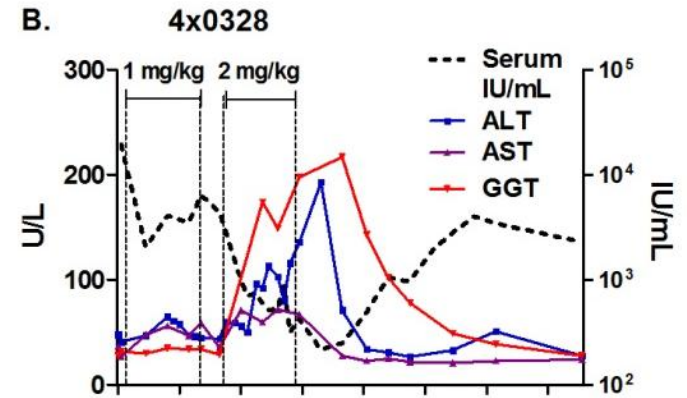


**Ki67**

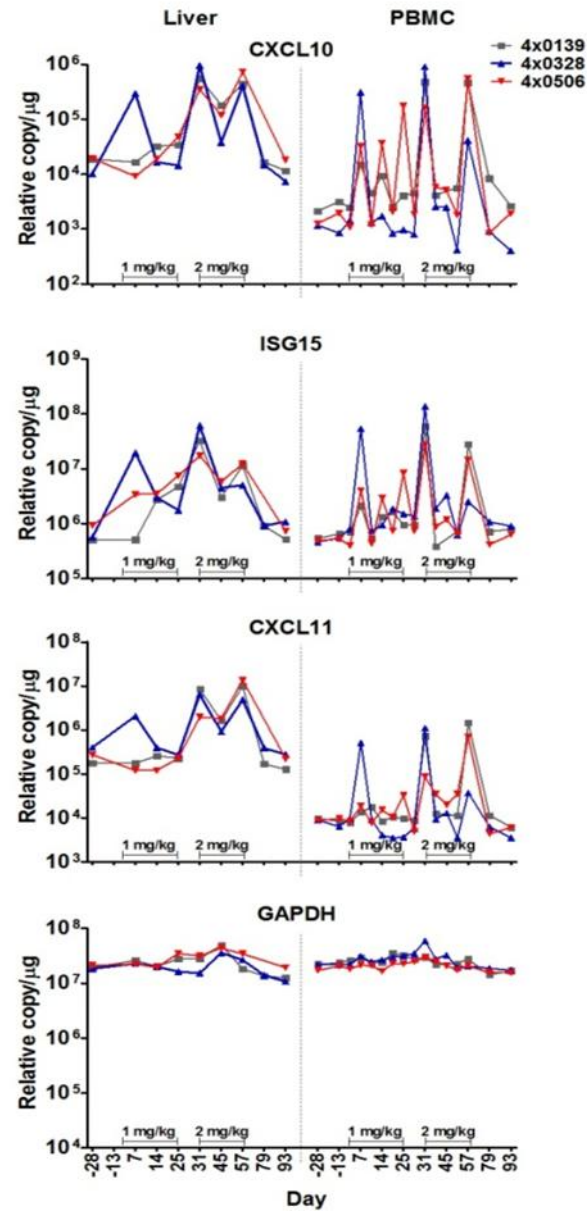
# Serum Levels of Liver Enzymes: ALT, GGT & AST



4x0139 had a dosing holiday on Days 43, 45 and 47.



# Induction of ISG Transcripts in Liver & PBMC



# Activation of Peripheral Blood Cells

<b>Cell Population</b>	<b>Marker</b>	<b>Fold Increase in Percent Positive Cells (Range)</b>
<b>B Lymphocytes</b>	<b>CD69</b>	<b>3-5 fold</b>
<b>CD8 T lymphocytes</b>	<b>CD69</b>	<b>2-5 fold</b>
	<b>CD25</b>	<b>2-5 fold</b>
<b>CD4 T lymphocytes</b>	<b>CD25</b>	<b>2-4 fold</b>
<b>NK and NKT Cells</b>	<b>CD69</b>	<b>2-6 fold</b>

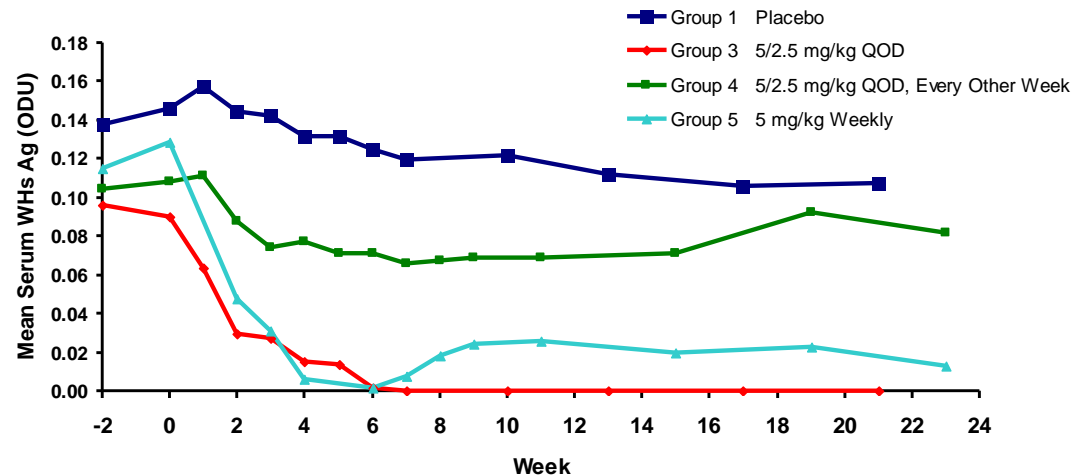
Evaluated on Day -28 and 8 hours post dose on Days 7, 14, 25, 31, 45 and 57 .

# Conclusions

- Oral GS-9620 for 8 weeks reduced serum and liver viral DNA in all three HBV infected chimpanzees.
- The mean maximal reduction in serum viral load was 2.2 logs, with a duration of at least one log reduction from 64 days to >121 days.
- Reductions in viral load correlated with reductions in serum HBsAg in all three animals.
- Dose dependent increases in serum IFN- $\alpha$ , ISGs in PBMCs and liver, and activation of lymphocyte subsets.
- Adverse events were generally tolerated and returned to baseline by the end of the study.
- Data are consistent with immune elimination of infected hepatocytes.

# Woodchuck Efficacy Trial of GS-9620

## Serum WHsAg



- Reduction in serum WHsAg to undetectable levels (<16 ng/ml) occurred in 100% of animals treated every other day for 4 weeks (Group 3).
- Reduction in WHsAg was sustained after cessation of treatment.
- Mean reduction in WHV DNA in Group 3 = 6.1 logs.
- Percent seroconversion for HBsAg in Group 3 = 29%

# Collaborators

## Gilead Sciences

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**Deborah Chavez**

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