3-V BIOSCIENCES™

Potent HCV Antiviral Activity by Inhibiting Fatty Acid Synthase

November 11, 2012

AASLD

George Kemble, PhD
CSO

Transforming Therapeutics for Infectious Diseases

Drug Profile: Rationale & Approach

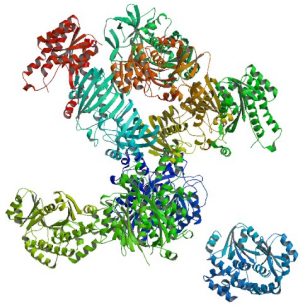
- Unique mechanism of action to enable the following:
  - Pan genotype antiviral activity
  - Activity against other classes of drug resistant HCV mutants
  - Well tolerated
  - High barrier to resistance

- Approach
  - Identify a cellular protein that is:
    - required for HCV replication
    - not critical for day to day function of the host
  - Develop proprietary compounds that fit with the evolving SOC

Fatty Acid Synthase (FASN)

FASN: Large, homodimer
Multiple enzymatic domains

Acetyl-CoA
+
7 Malonyl-CoA
+
ATP, NADPH



Palmitate

- Other fatty acids & complex lipids
- Post-translational modifications (eg NS4b)
- Diglycerides & Triglycerides

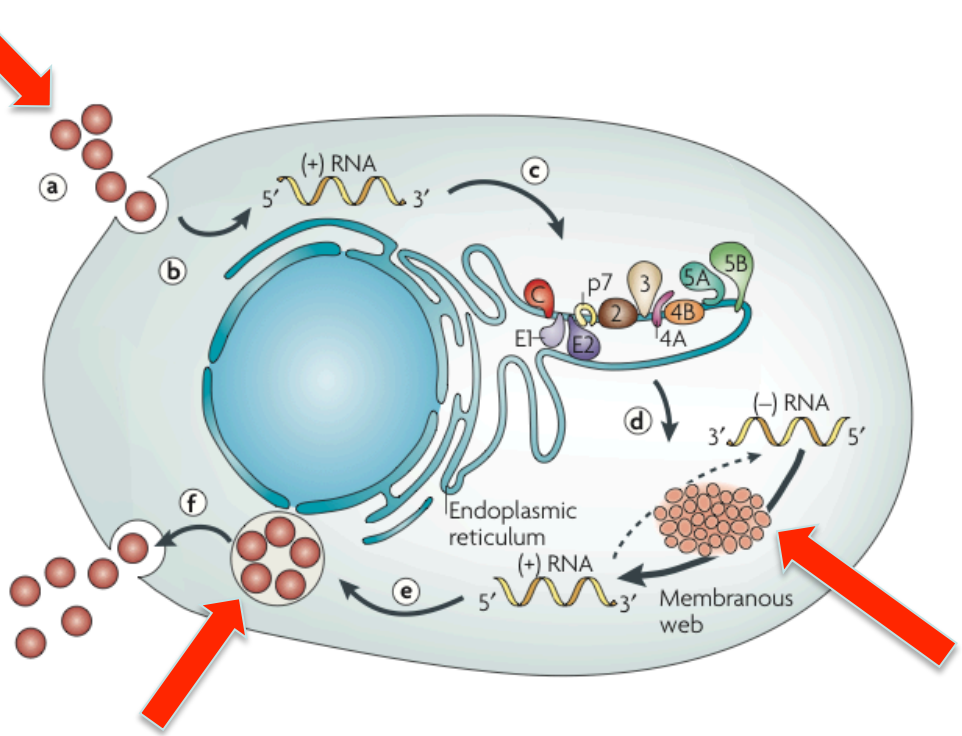
Adult mice lacking liver FASN are normal

Maier, et al. Science, 2002 PDB ID: 2CF2
Chakravarthy, et al, Cell Metabolism, 2005

HCV Depends on the FASN Pathway

FASN and/or its product interact with HCV at multiple points of the viral replication cycle

Viral Entry



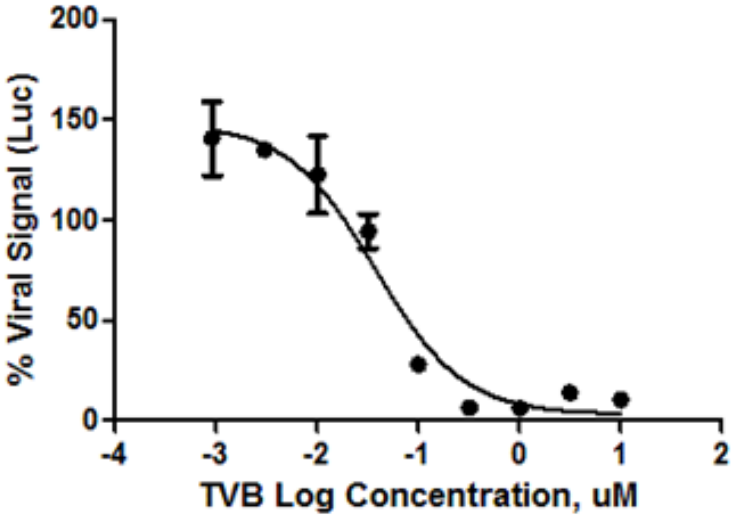
RNA Replication

Virus Assembly and Exit

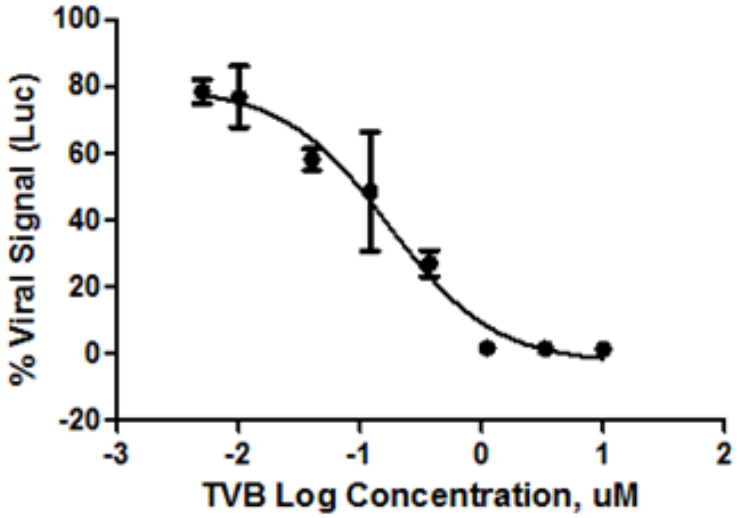
Yang, et al, Hepatol. (2008)
Yu, et al, J. Virol (2006)
Sakamoto, et al. Nat. Chem Biol (2005)
Umehara, et al., Biochem & Biophys Res. Comm (2006)
Majeau, et al, J. Biol. Chem (2009)
Moradpour et al. Nature Reviews Microbiology (2007)

3-V Inhibitors Are Potent & Specific

GT1b Replicon



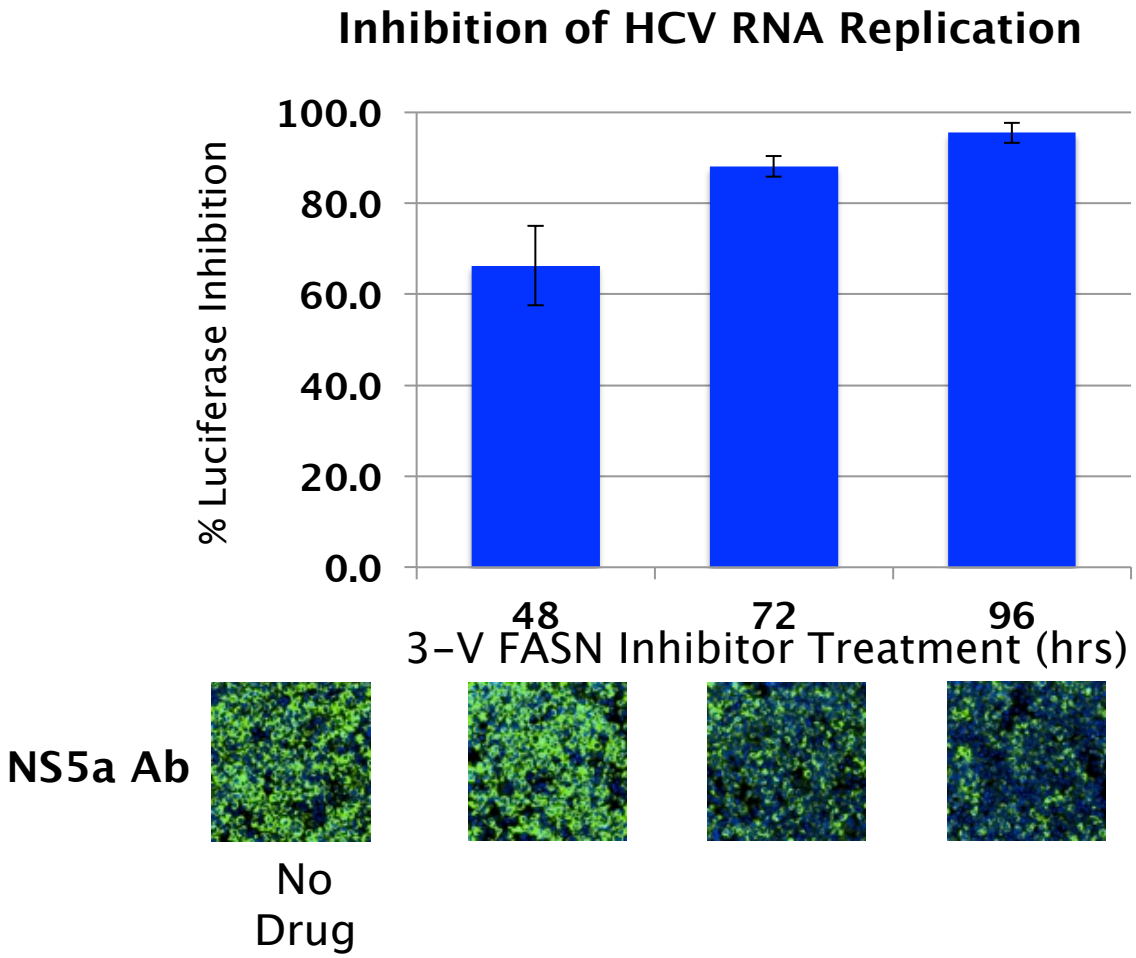
Infectious HCV (Gt2a)



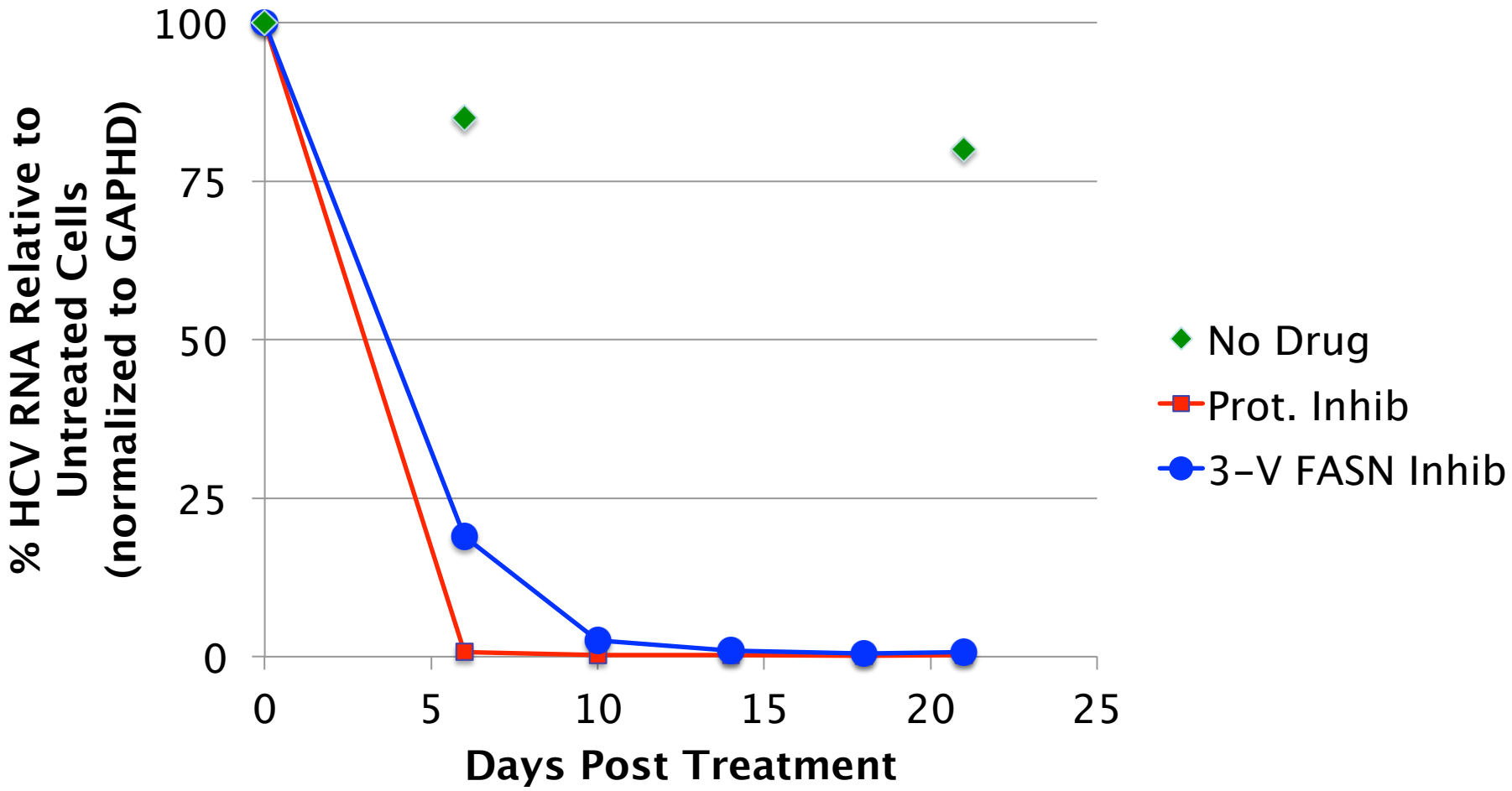
Inhibitory (50%) Concentration			
FASN Enzyme *in vitro*	FASN Enzyme in cells	GT1b Replicon*	GT2a Virus*
50 nM	40 nM	60 nM	41 nM

*No toxicity observed at highest concentration tested (10,000 nM)

FASN Inhibition Blocks HCV RNA Replication & Protein Expression



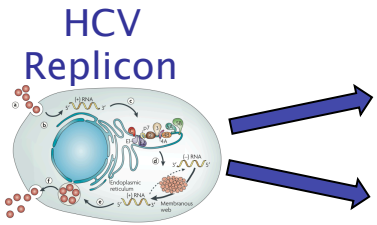
FASN Inhibition Reduces HCV RNA In Passaged Cell Lines



Targeted Inhibition of FASN

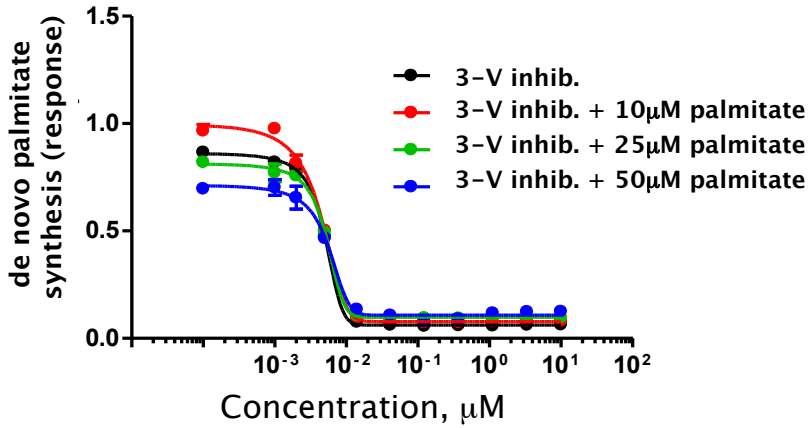
Palmitate add-back demonstrates on-target mechanism

FASN inhibitor
+ / -
Palmitate

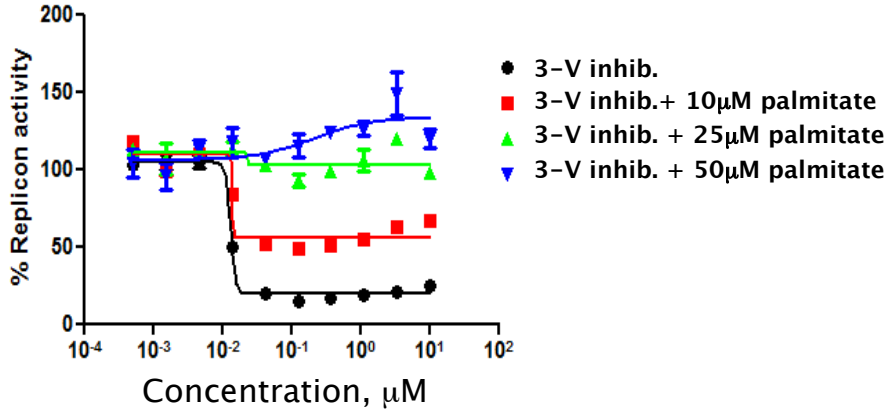


HCV RNA replication (Luciferase)

FASN enzymatic activity (palmitate synthesis)



FASN is inhibited

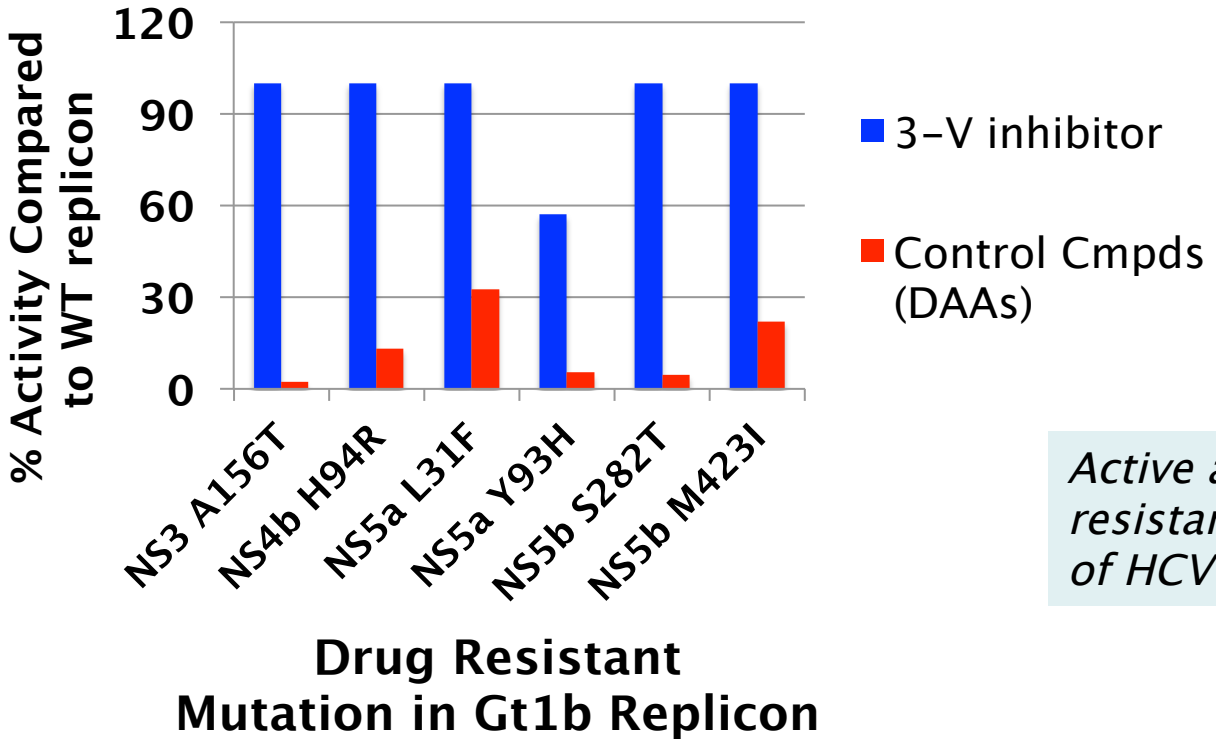


HCV RNA repl is restored

3-V FASN inhibitors active against a range of HCV variants

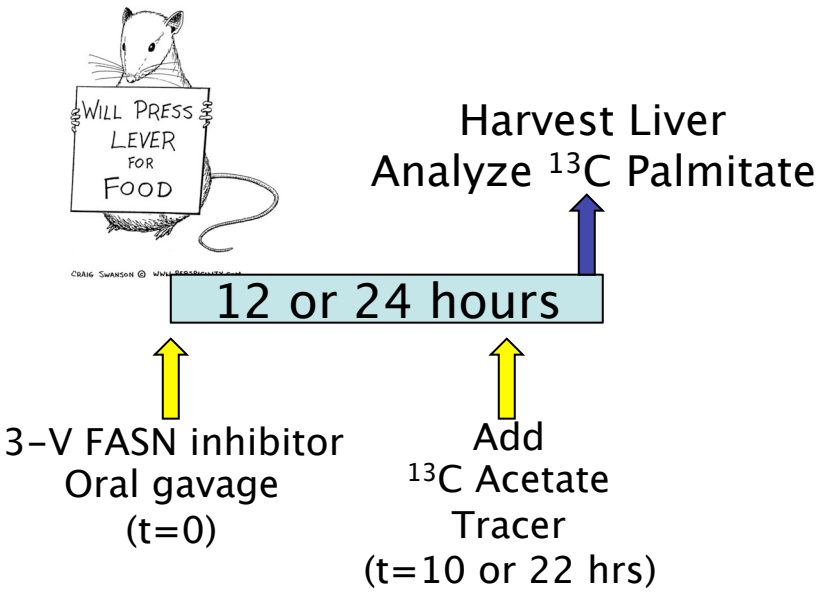
Active across genotypes

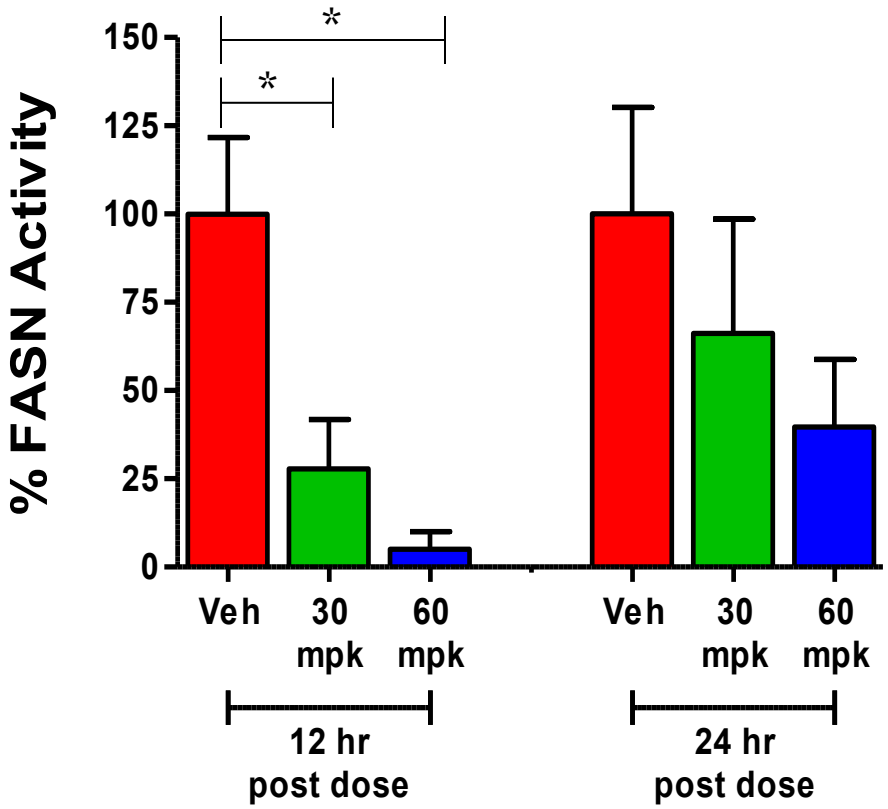
Median Effectiveness Concentration (μM)		
Gt1a	Gt1b	Gt2
0.06	0.06	0.10



Active against replicons resistant to other classes of HCV drugs

FASN inhibited in rats following oral administration





P<0.05 Mann-Whitney

Profile of 3-V's FASN inhibitors

- Attractive compounds with unique mechanism of action
  - On-target activity confirmed
  - Potent (EC_{50}'s < 100nM)
  - Pan genotype antiviral activity
  - Active against HCV mutants resistant to various classes of DAAs
  - Well tolerated following multiple day dosing at levels that suppress liver FASN in rats
- IND enabling studies underway
- Phase 1 and proof of concept in HCV patients in 2013

3-V Biosciences, Inc. Contributors

Doug Buckley
Marc Evanchik
Robert McDowell
Stefan Moese
Yamini Ohol
Johan D. Oslob
Merdad Parsey
Amy K. Patick
Mohan Sivaraja
Sam Tep
Satya Yendluri

Visit Poster #1876
for additional information

3-V BIOSCIENCES™
Transforming Therapeutics for Infectious Diseases