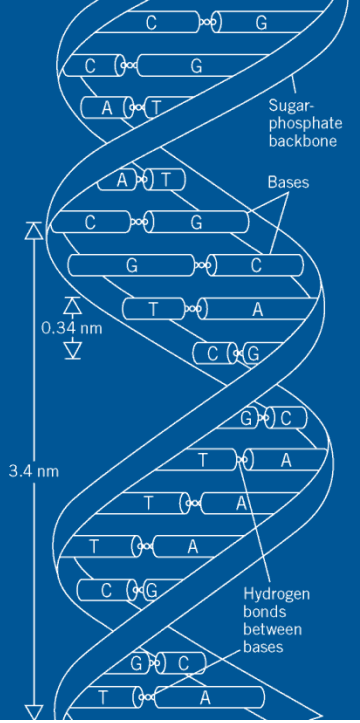

Towards Model-Based Drug Development of New Therapeutics for Hepatitis C Virus

Rong Deng, Brinda Emu, William Capra, Jin Y. Jin

24th Population Approach Group Europe (PAGE) Meeting
2-5 June 2015, Hersonissos, Crete

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Opportunities and Challenges for Application of Quantitative Pharmacology in Infectious Disease Development to Enhance Decision Making

- Quantitative Pharmacology[1] (quantitative drug development sciences):
  - A multidisciplinary approach that integrates the relationships between diseases, drug characteristics, and individual variability
  - Develop quantitative models in order to solve specific, complex, and multivariate problems in drug development

- Opportunities
  - Wealth of viral and bacterial dynamic models and successful implementation in infectious disease
  - Virological data may be both amenable to modeling and approval endpoint

- Challenges
  - No in vivo animal model in preclinical stage
  - Studies in early clinical development are not done in target population
  - Emergence of resistance

Apply HCV disease model to enable early development (ED go) and help Phase I design for an HCV entry inhibitor

[1] Zhang L et al AAPS J 2008, 10 (4)

HCV Life Cycle & Therapeutic Targets

Ribavirin

-- ***Render fraction of new virions non-infectious***

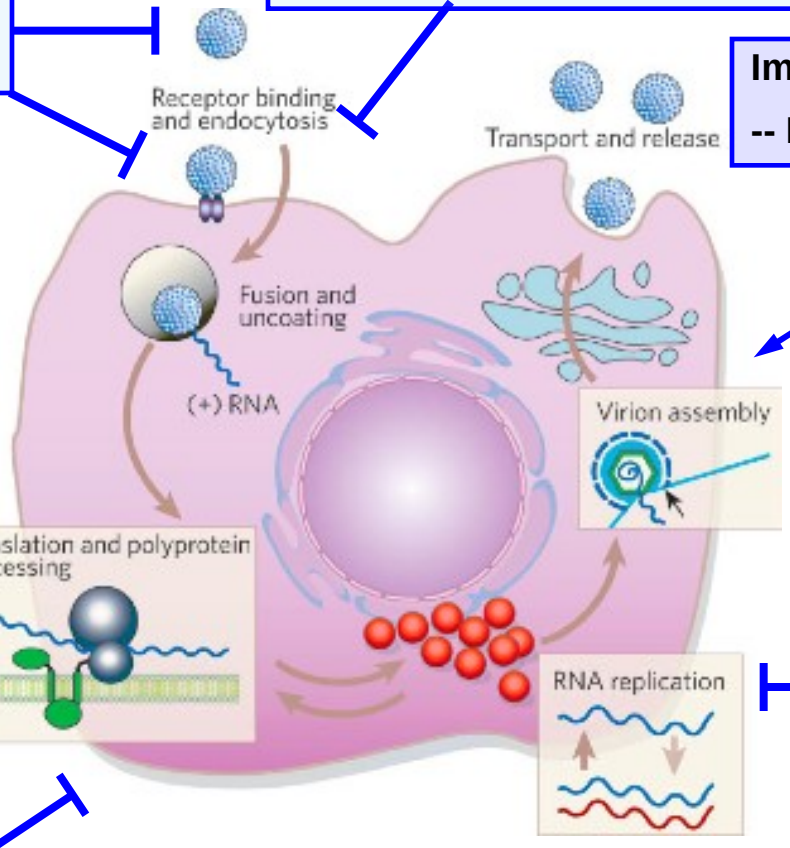
Entrance Inhibitor

-- Increase FcR-mediated clearance

-- Inhibit entrance

Immuno-Modulator

-- Increase kill of infected cells



Protease Inhibitor (e.g. TVR)

-- inhibit production

Polymerase Inhibitor

(e.g. nucleotide analogue)

-- inhibit production

Interferon

-- *inhibit production*

Lindenbach BD et al., Nature, 2005

Text in italic: MOA derived from mathematical modeling rather than experimental data

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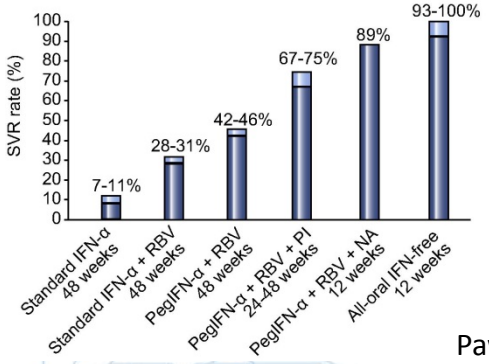
HCV Treatment Overview in 2011

- **Goal of HCV treatment is an effective viral "cure"**
  - Sustained Virologic Response (SVR), is absence of viremia 24 weeks after stopping anti-HCV treatment

- **SOC has been interferon α (IFN, SC weekly) plus ribavirin (RBV, oral twice daily)**
  - The overall cure rate is ~ 50% for pts with HCV genotype 1
  - Treatment duration: 48 wks
  - Frequent and sometimes serious side effects including neuropsychiatric events, flu-like symptoms and hematological toxicities

- **First generation Direct Acting Antivirals (DAA) approved May 2011**
  - Telaprevir (TVP) or boceprevir + IFN/RBV increase cure rates to~ 70% → New SOC
  - However, additive toxicities due to IFN/ribavirin in regimens



Unmet medical Need: Provide an IFN-free regimen with comparable or better efficacy to new standard of care

Pawlotsky JM et al, Journal of Hepatology 2015

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HCV Entry Inhibitor X Proof-of-Activity in Preclinical Stage

- Strategic context :“First and Best” in class HCV entry inhibitor in combination with direct acting antiviral, for the IFN-free treatment of HCV
- *In vitro* data suggest that HCV entry Inhibitor X could replace IFN from SOC
- *In vivo* animal study is not feasible
  - Besides humans, chimpanzees are the only species that is naturally susceptible to HCV infection
  - Ethical considerations, limited availability, genetic heterogeneity, and cost limit their utility
- HCV disease model was used to increase confidence on the PTS on ED GO
  - Removal of IFN and/or RBV from SOC
  - Decreased duration of treatment with SOC

Establish HCV disease model → Validate model based on observed clinical data for SOC → Apply to HCV entry inhibitor X program

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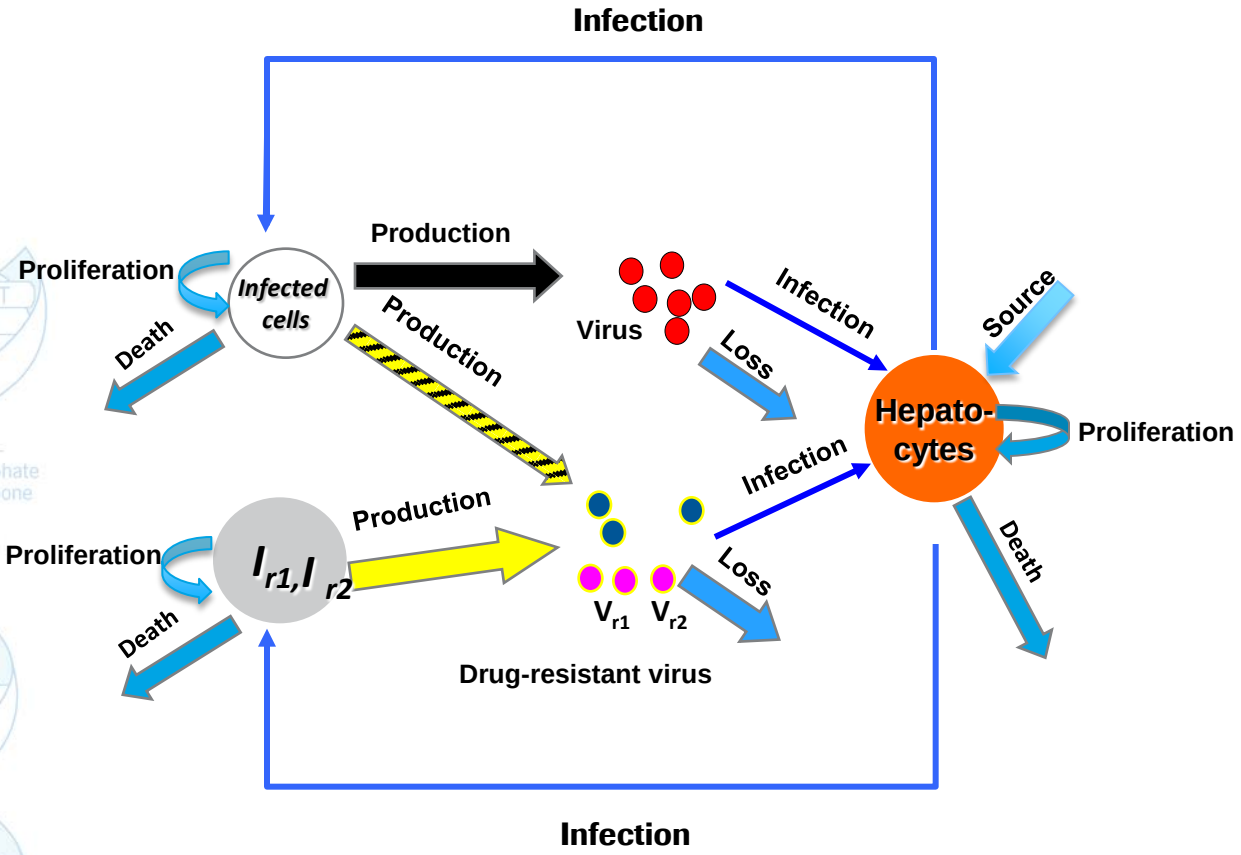
HCV Viral Dynamic Model with Resistance: Three-strain virus

HCV disease

Resistance



Resistance emergence primarily due to pre-existing resistant strain(s)

No overlapping resistance. For example:Vr1, only resistant to SOC such as TVP
Vr2, only resistant to HCV entry inhibitor X

Dahari & Perelson Hepatology, 2007
Rong L et al , Sci Transl Med, 2010
Snoeck,Clin Pharmacol Ther, 2010

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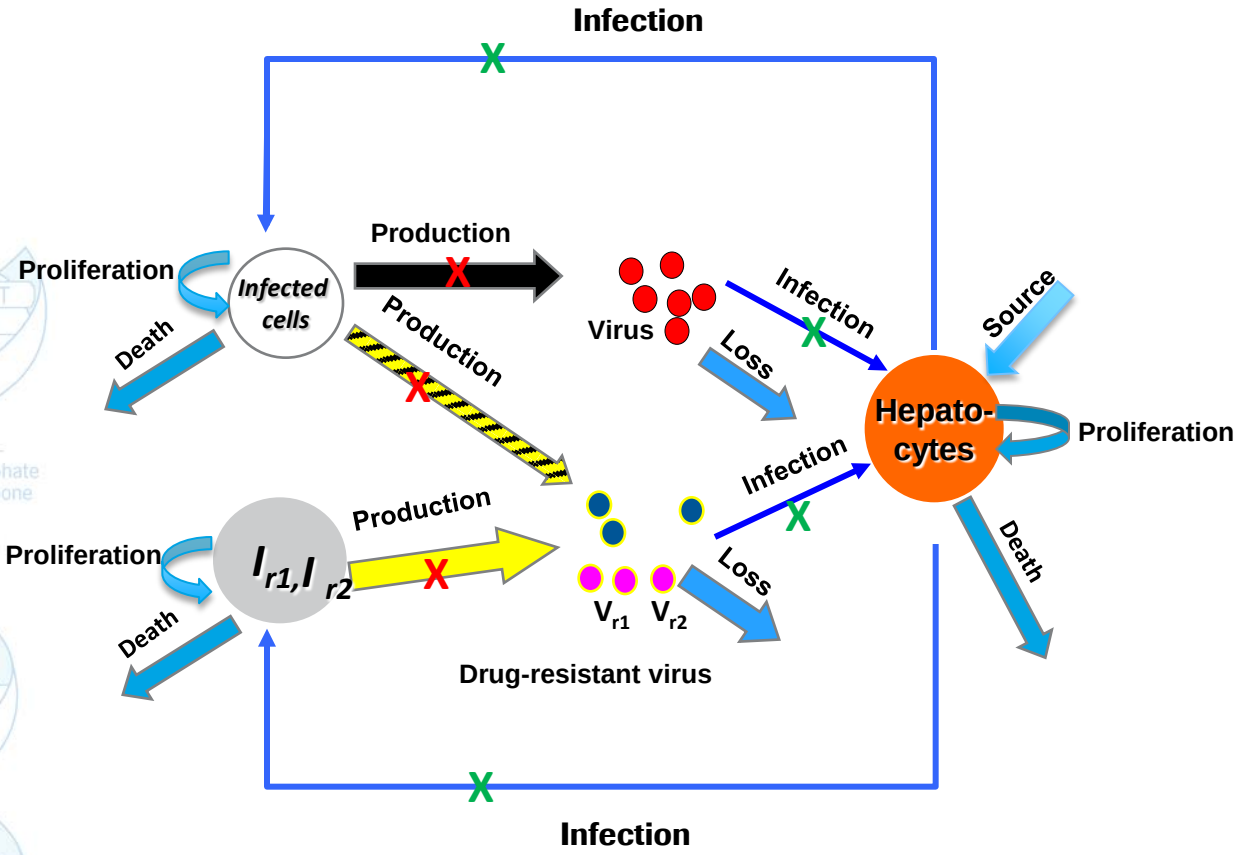
HCV Viral Dynamic Model with Resistance: Drug Effects

HCV disease

Resistance



X: SOC, ε

X: HCV entry inhibitor X,η

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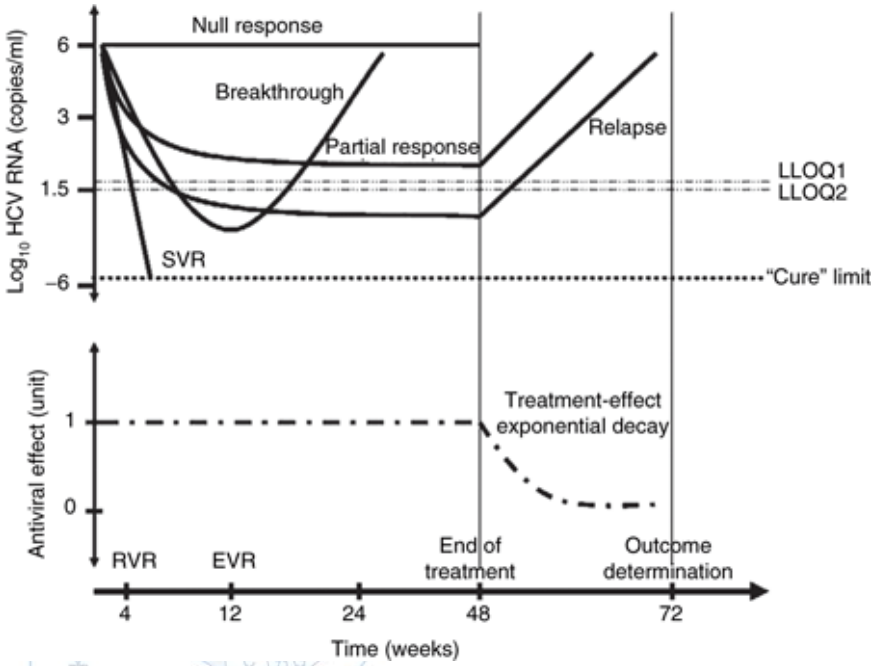
Simulation Method



- Simulation was done using either NONMEM 7.0 or Berkeley Madonna 8.3. Model parameters (typical value and variability) for SOC were based on literature reports [1,2].
  - Combination of resistance model and cure boundary concept
- Effects of SOC and HCV entry inhibitor were assumed to be constant during treatment duration
- The offset of drug effect after stopping treatment was described assuming an exponential decay in function of time (e^{-kt})

[1] Rong L et al , Sci Transl Med, 2010
[2] Snoeck E et al, Clin Pharmacol Ther, 2010

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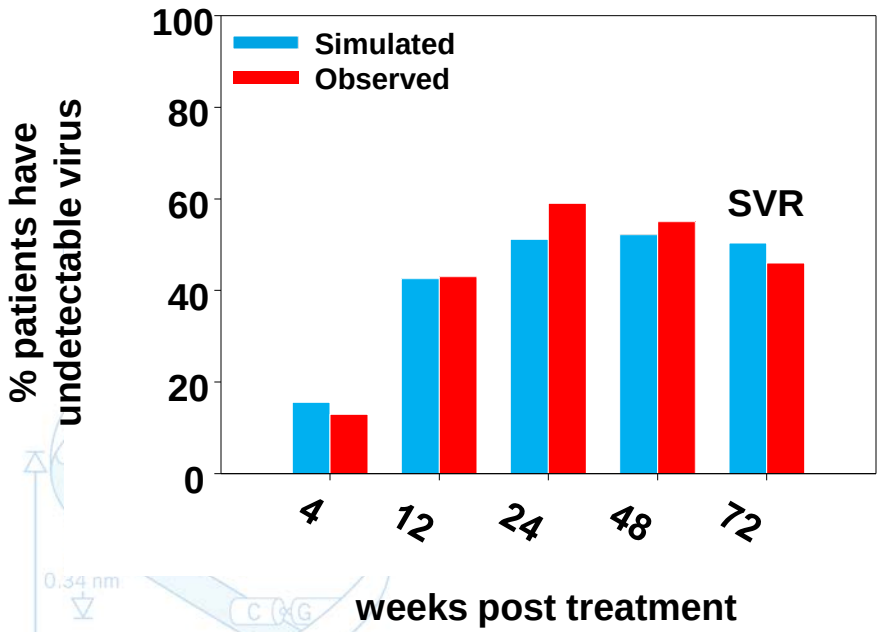
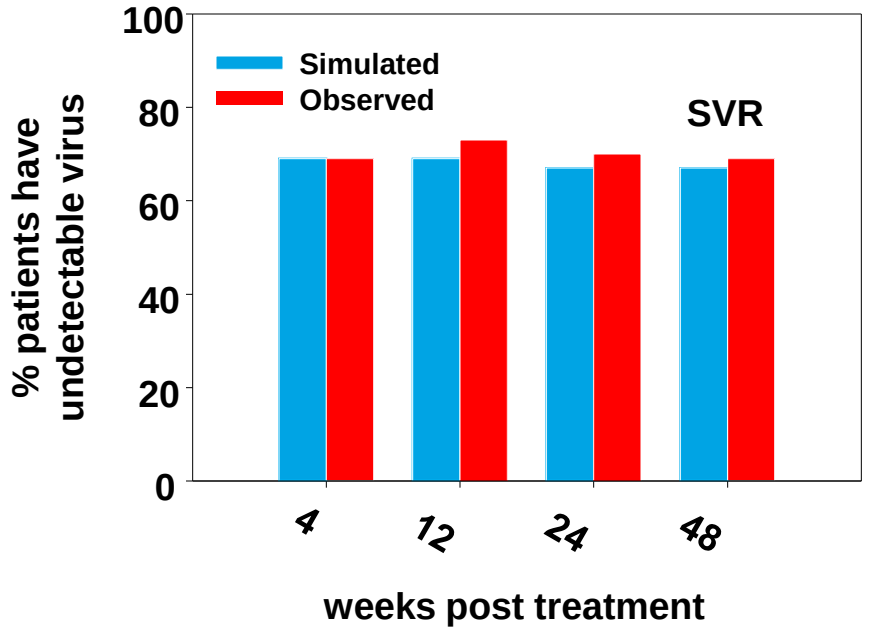
Model Predicts Clinical Outcome with IFN/RBV ± HCV DAA (Telaprevir)

IFN/RBV-48wk



TVR-12wk + IFN/RBV-24wk



Model well predicts viral endpoints for current SOC as well as for Telaprevir-containing new SOC

Sustained Virologic Response (SVR): continued undetectable HCV viral load 24 weeks after completion of therapy.

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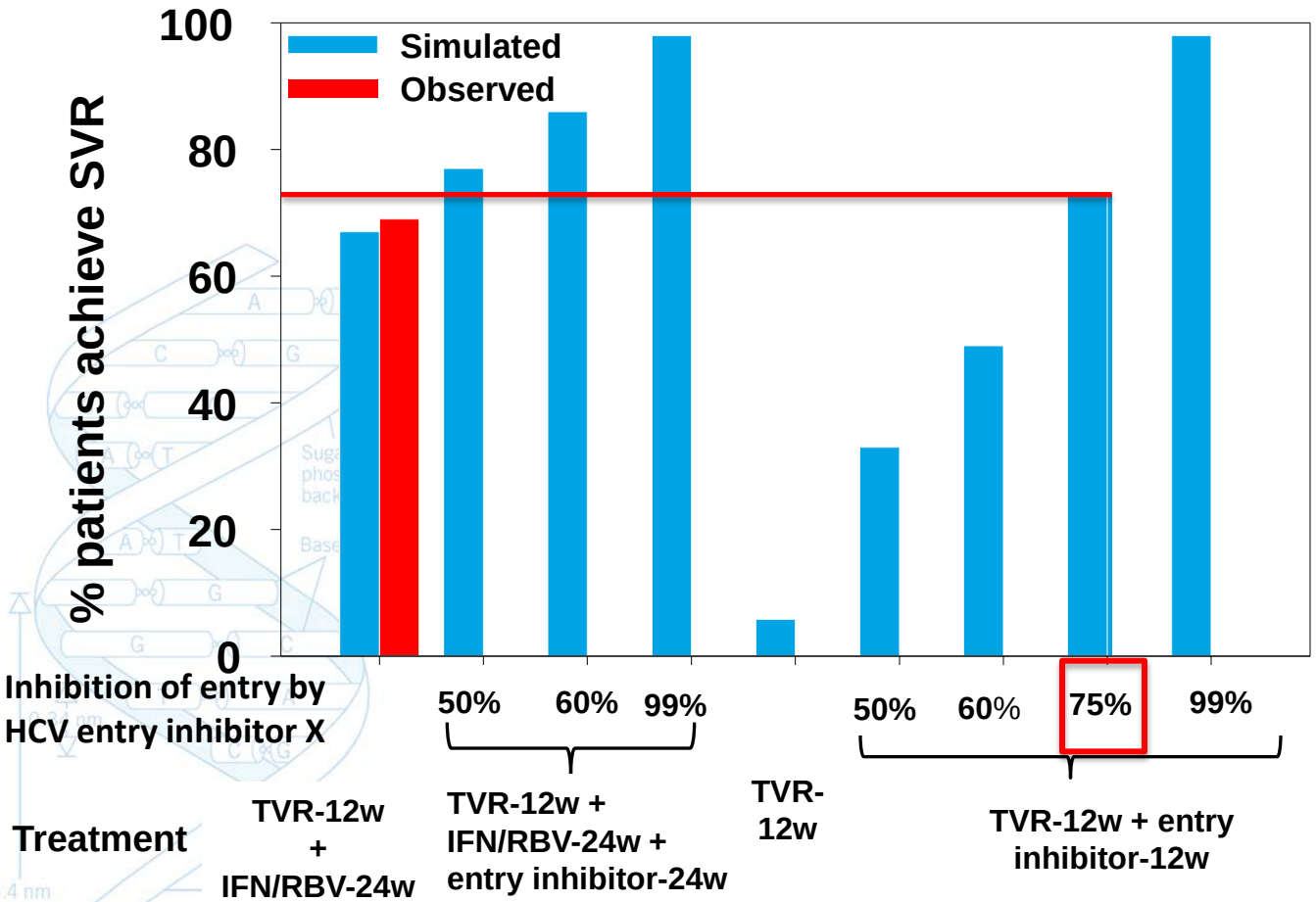
Model Suggests HCV Entry Inhibitor May Increase Cure Rate and Decrease Treatment Duration



- Increase cure rate √
- Remove interferon α (IFN) and/or ribavirin (RBV) from SOC √
- Decrease duration of treatment with SOC √

Simulation results combined with other data enable HCV entry inhibitor X GO decision

Model assumptions:

- **Efficacy of entry inhibitor is constant for the dosing period (model 50%, 60% and 99% inhibition of infection)**
- **No cross-resistance between Telaprevir (TVR) and entry inhibitor**
- **Similar mutation rates for TVR- and entry inhibitor-resistant virus (resistant variants pre-exist)**

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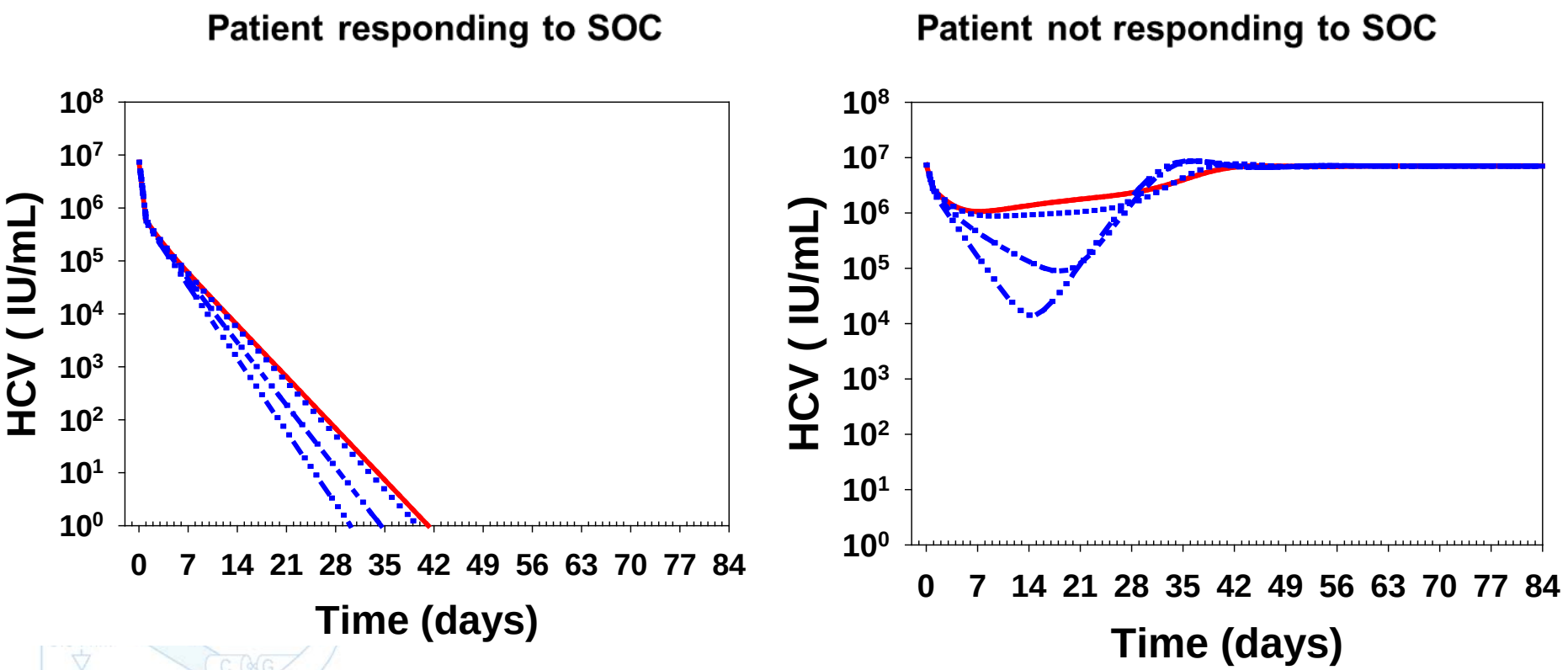
Model Suggests that HCV Entry Inhibitor is Likely to Show Larger Added Benefits in Patients not Responding Well to SOC



1. Patient responding to SOC: ε=0.9; Patient not responding to SOC: ε=0.55
2. Resistance to HCV entry inhibitor ηr =0.01 and change ηs

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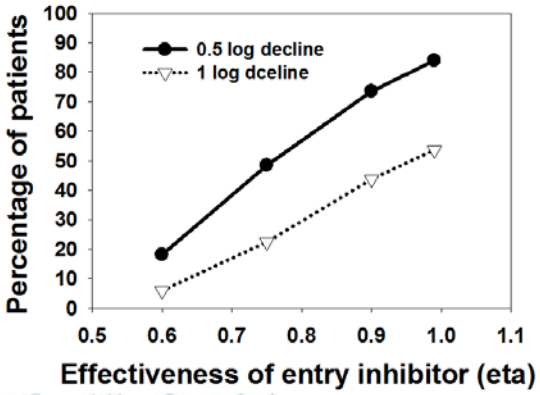
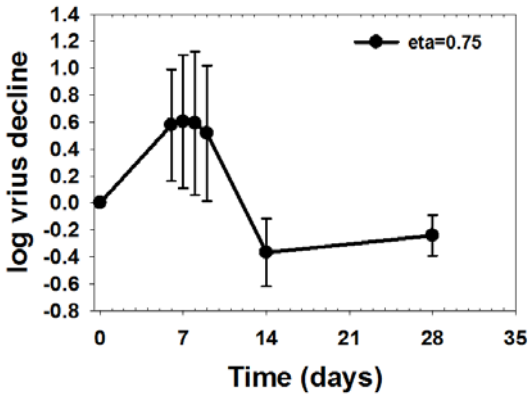
Model Provides Critical Information for Phase I Study Design





Probability of seeing patients with >1.0 log viral load (VL) [a] decline with HCV entry inhibitor monotherapy [b]	Number of patients with >1.0 log VL decline	
	Sample Size N=15	Sample Size N=30
70%	3+	6+

[a] **1.0 log viral load decline is clinical meaningful for efficacy**

[b] **Assuming HCV entry inhibitor is 75% effective in blocking virus entry**

- Limited ability to see patients with >1.0 log viral load decline with reasonable sample size
- Phase I study in healthy + HCV patients with main objectives being safety and PK, regardless of baseline viral load, designed to show evidence of viral load decline, and the PKPD relationship of a novel HCV entry inhibitor.

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Additional Questions has been addressed by M&S

- Early introduction of entry inhibitor treatment before virus breakthrough may bring more benefits to HCV patients receiving Telaprevir + HCV entry inhibitor X
  - delay drug resistance and short treatment duration

- The initial small drop on viral load following HCV entry inhibitor X monotherapy treatment is unlikely able to predict the viral load reduction for combo therapy

- The minimal duration of entry inhibition necessary to achieve a clinically meaningful benefit in the setting of the evolving standard of care

Summary

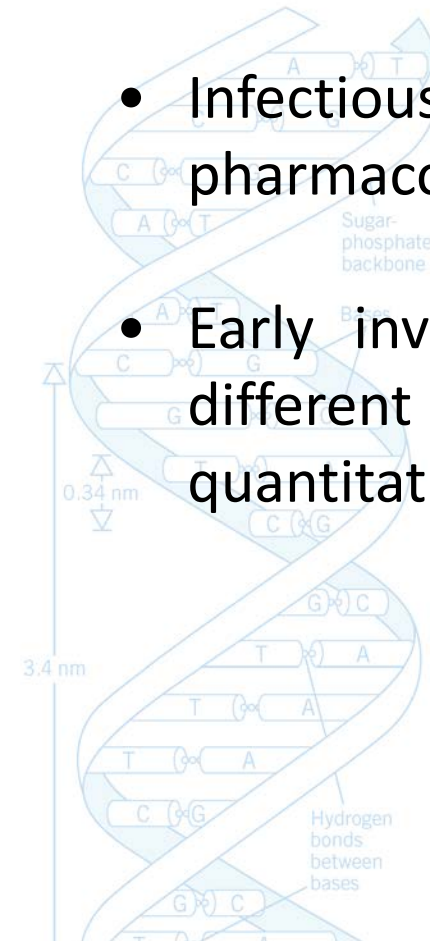
- A novel HCV disease model with resistance was successfully developed based on literature data

- Simulation results combined with other data enable a HCV entry inhibitor GO decision
  - Increase confidence on the PTS to achieve efficacy goal

- Provided critical information to assist the design of clinical trials of a HCV entry inhibitor by testing different input clinical parameters (choice of antiviral therapy, viral load, known characteristics of patient population), to inform selection of virologic endpoints, sample size, and patient population.

Conclusions

- One example to demonstrate how quantitative pharmacology can enhance decision making in early drug development (ED to Phase I)
- Infectious disease is a great place to apply quantitative pharmacology with lots of opportunities
- Early involvement into program and collaborations with different functional groups are essential for better applying quantitative pharmacology



Acknowledgments

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Sharookh Kapadia

Suhas Iyer
Paul Fielder

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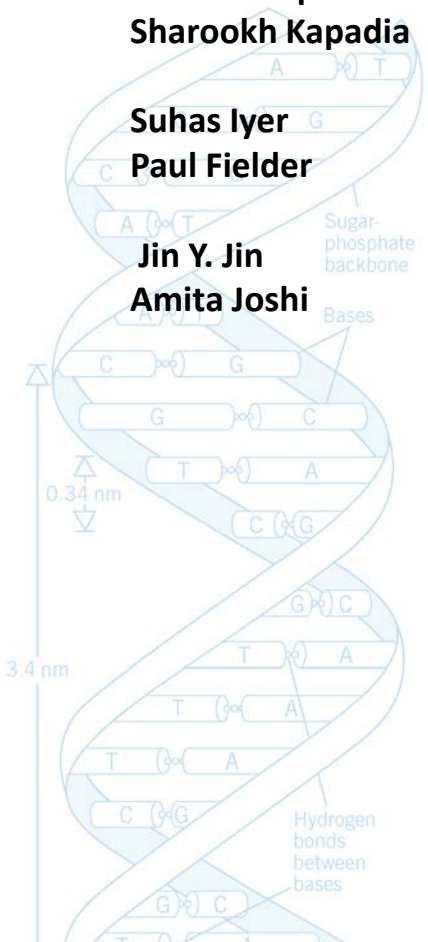
Amita Joshi



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