

Robust antiviral efficacy of a “finger-loop” allosteric inhibitor of the HCV polymerase in HCV infected chimpanzees

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At least 4 distinct non-nucleoside inhibitor-binding sites on the HCV polymerase

NNI site A (FINGER-LOOP)

- Benzimidazoles (*JTK-103*)
- Indoles (*MK-3281*)

NNI site C (PALM)

- Benzothiadiazine (*A-848837*)
- Acyl-Pyrrolidine
- Proline sulfonamides
- Acrylic acid derivatives

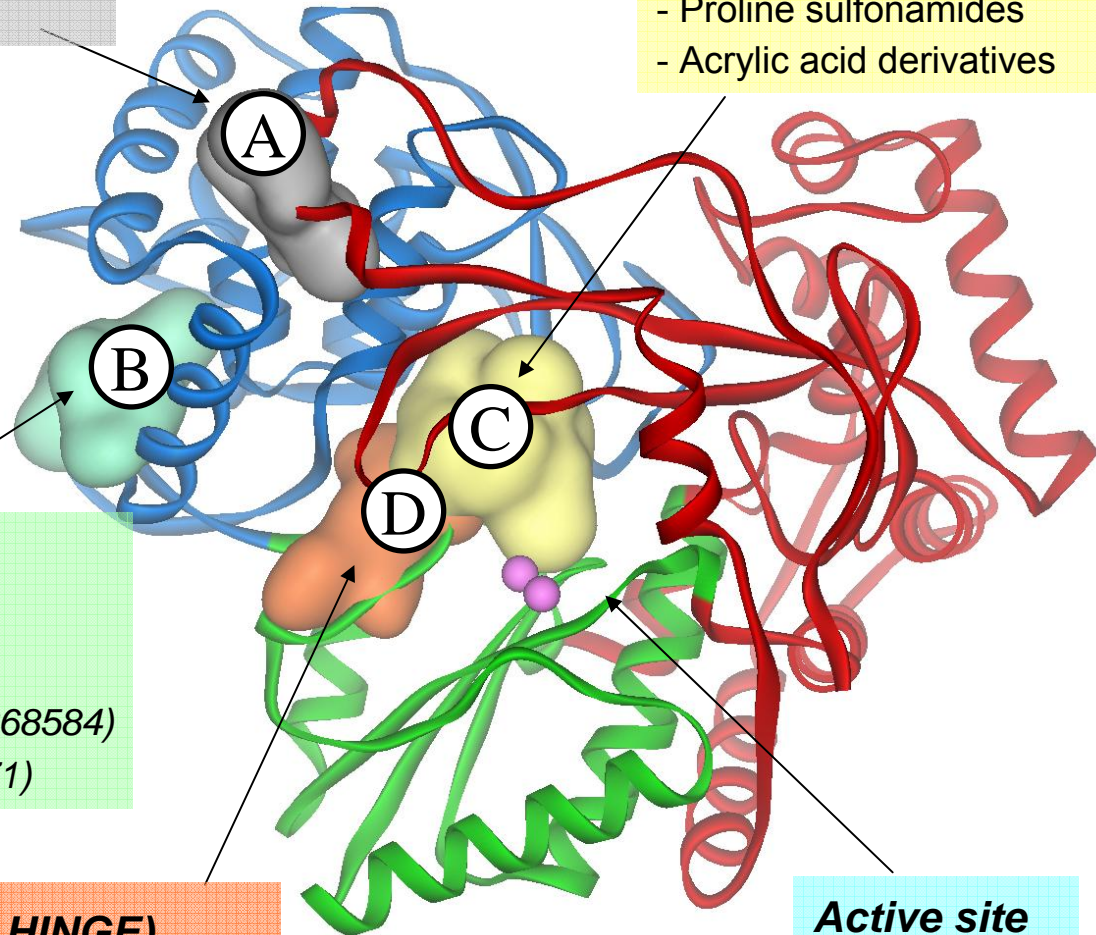
NNI site B (THUMB)

- Phe Derivatives
- Thiophene-COOH
- Dihydroxyprones (*PF-868584*)
- Pyranoindoles (*HCV-371*)

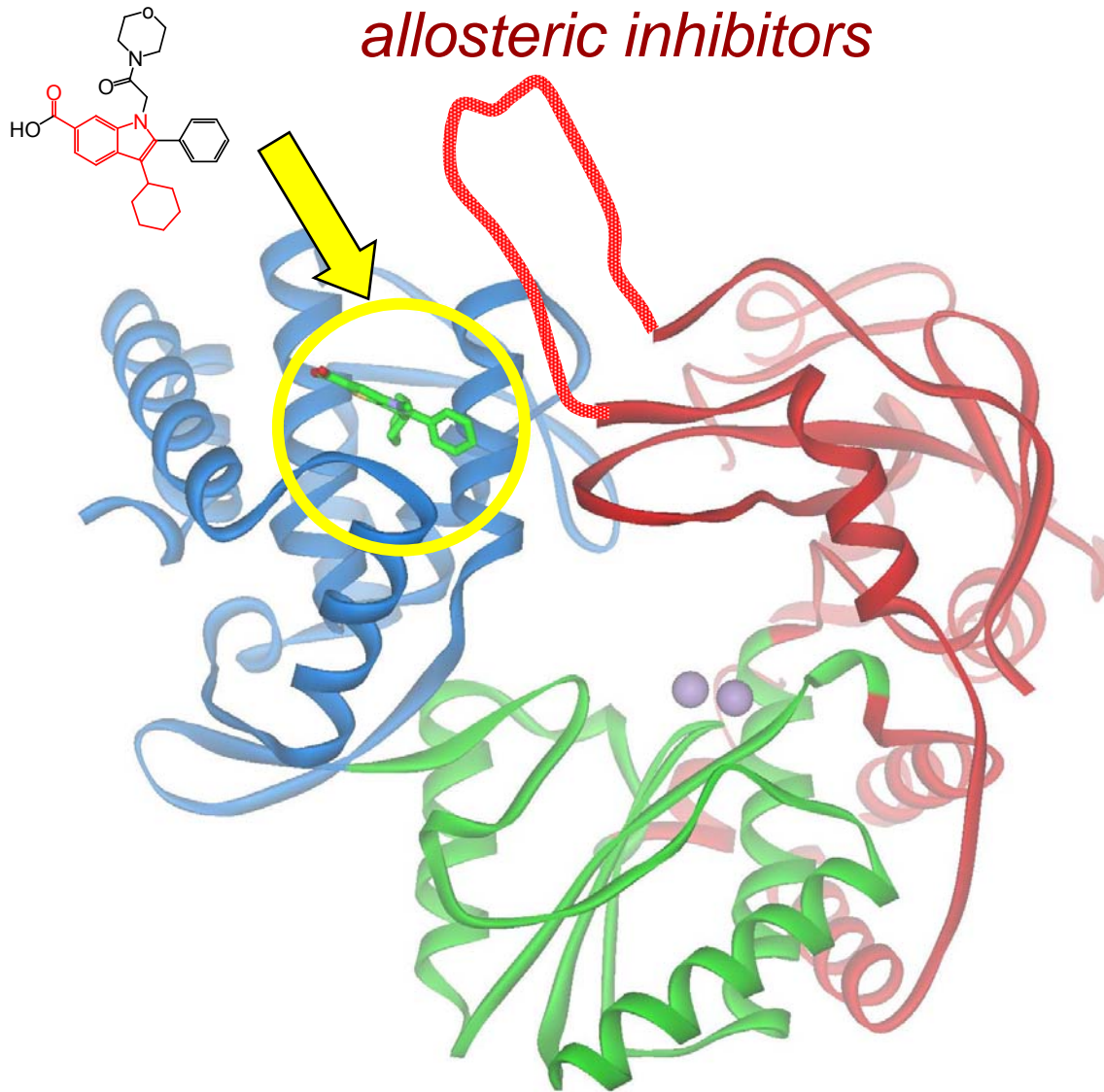
NNI site D (R200 HINGE)

- Benzofurans (*HCV-086*; *HCV-796*)

Active site



Mechanism of action of “finger-loop” non-nucleoside allosteric inhibitors



- **Indole/benzimidazole NNIs**
 - Disrupt fingers/thumb interaction; freeze the “open” conformation
 - Block processive RNA synthesis

*MK-3281 – an optimized indole-based “finger-loop”
non-nucleoside inhibitor*

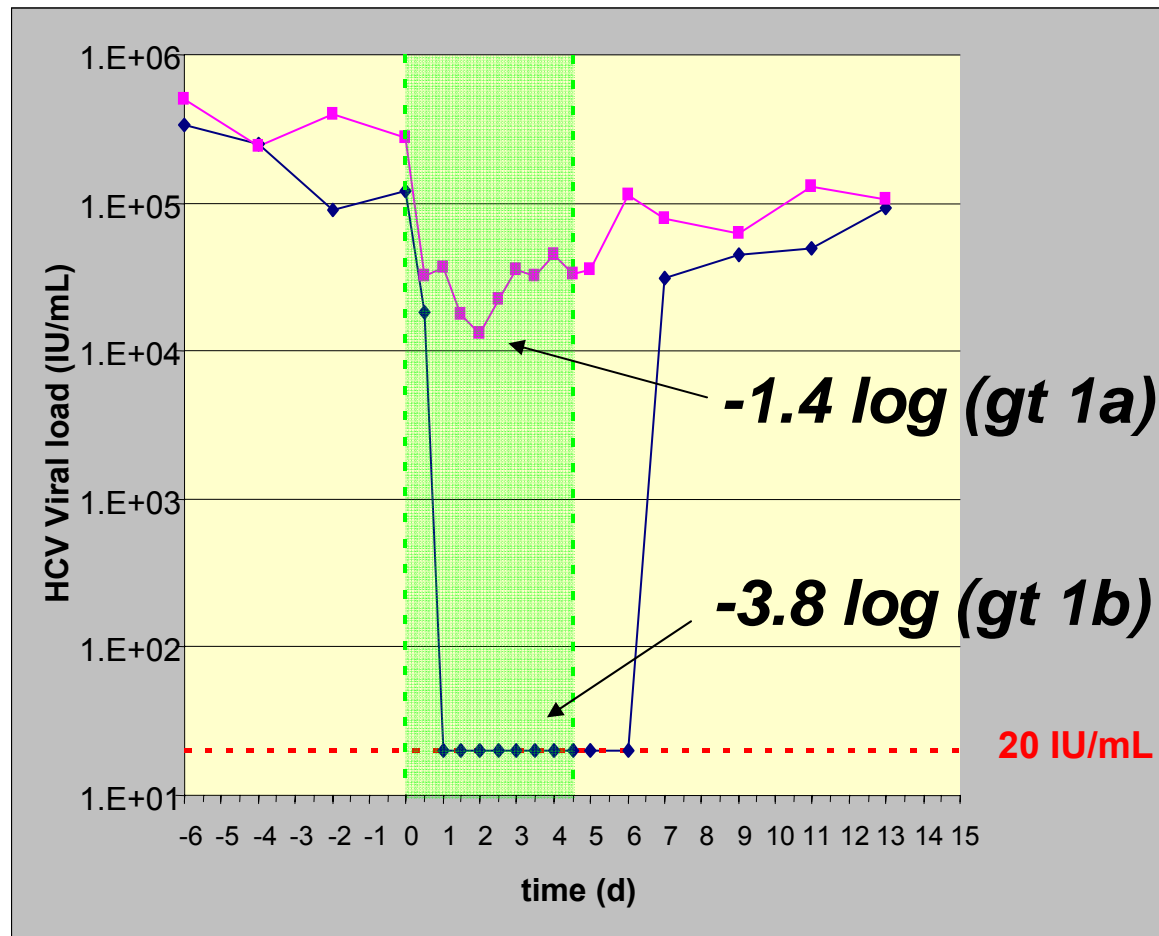
HCV gt 1b RNA polymerase	<	IC ₅₀ 6 nM
Con1 Replicon [10% NHS]		EC ₅₀ 40 nM (EC ₉₀ 116 nM)
Con1 Replicon [50% NHS]		EC ₅₀ 110 nM (EC ₉₀ 260 nM)

- Equipotent on genotypes 1a, 1b and 3a
- Weakly active on genotypes 2a and 2b
- Viral resistance in cell culture is engendered by **P495→L/S/T/A** mutations in NS5B (>100-fold loss of potency)

MK-3281: pre-clinical proof-of-concept

- **Dosed in two chronically-infected chimpanzees**
 - **CAO133 (HCV genotype 1b)**
 - **1492 (HCV genotype 1a)**
 - **10 mg/kg *per os* every 12 hours for 5 days**

Proof-of-concept: MK-3281 dosed in HCV-Infected Chimpanzees CA0133 (—◆—) and 1492 (—■—)



Variable response in CA0133 (HCV gt 1b) and 1492 (HCV gt 1a)

What are the determinants of the different observed antiviral response?

Clone	Max Viremia Drop (Log ₁₀)	Avg Plasma [Drug] _{12h} (μ M)	Replicon EC ₅₀ (nM)
1492 – gt 1a (low responder)	-1.4	2.7	11.3
CAO133 – gt 1b (high responder)	- 3.8	4.4	6.9

- Small difference in MK-3281 plasma levels (~ 2-fold)
- Small difference in intrinsic susceptibility to MK-3281 (~ 2-fold)
- Not due to selection of known or novel resistant virus variants (*see poster*)

→ Could moderate differences in the ratio between plasma drug levels and intrinsic drug sensitivity (~ 4-fold) be responsible for the observed response difference?

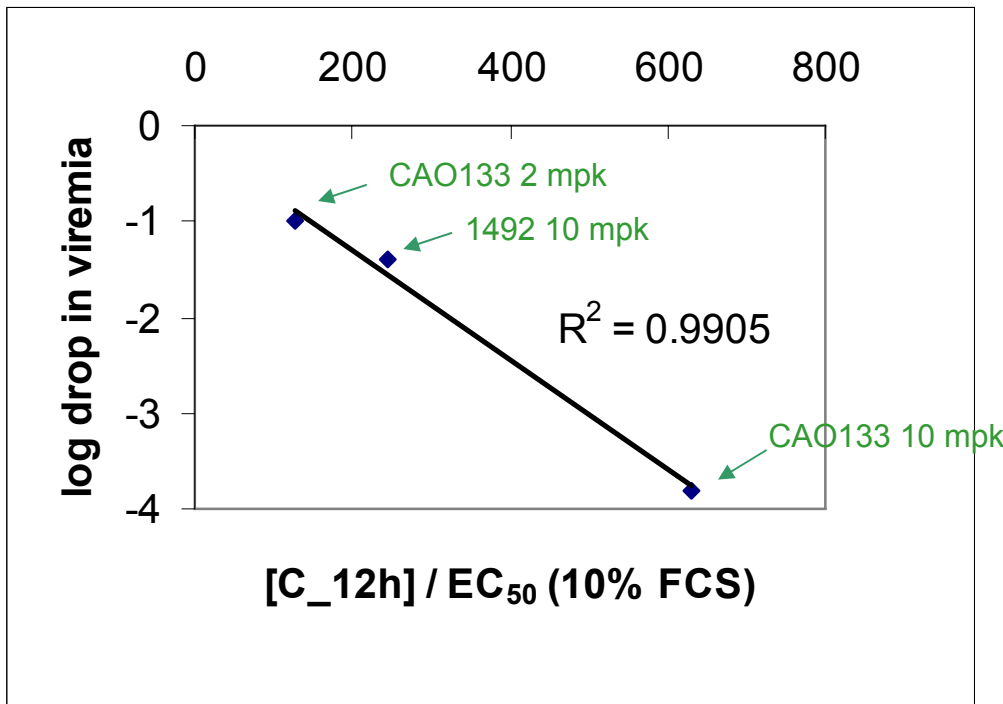
- Steep dose-response curve?

Where are we on the dose response curve?
- Low Dose Antiviral Response in CAO133 (high responder)

- **CAO133 (gt1b) @ 10 mg/kg b.i.d.**
(average plasma [drug]_{12h} = 4.4 μM)
→ **-3.8 log₁₀ max. viremia drop**
- **Dose reduced 5-fold (2 mg/kg b.i.d.)**
(average plasma [drug]_{12h} = 0.8 μM)
→ **-1.1 log₁₀ max. viremia drop**

• 5-fold decrease in dose leads to ~500-fold decrease in viral response

(Tentative) chimp PK-PD relationship



Average C_{12h} (μM):

- CAO133: 4.4 (10 mpk); 0.8 (2 mpk)
- 1492: 2.7 (10 mpk)

➤ Very steep dose response curve

- Approx. 1 additional log in viremia drop for each doubling in dose

Polymerase “finger-loop” non-nucleoside inhibitor MK-3281: Summary and Conclusions

- Proof of concept achieved in HCV infected chimpanzees
 - High Responder (CAO133 – gt 1b)
 - 3.8 log max viremia decrease (10 mg/kg bid)
 - 1.1 log at 5-fold lower dose (2 mg/kg bid)
 - Low Responder (1492 – gt 1a)
 - 1.4 log max viremia decrease (10 mg/kg bid)
 - No phenotyping/genotyping changes associated with low response
 - No emergence of resistance observed (5 day-monotherapy)
 - Moderate differences in intrinsic drug sensitivity and plasma levels may account for observed difference in response
 - Very steep dose-response