HCV eradication with direct acting antivirals (DAAs)?

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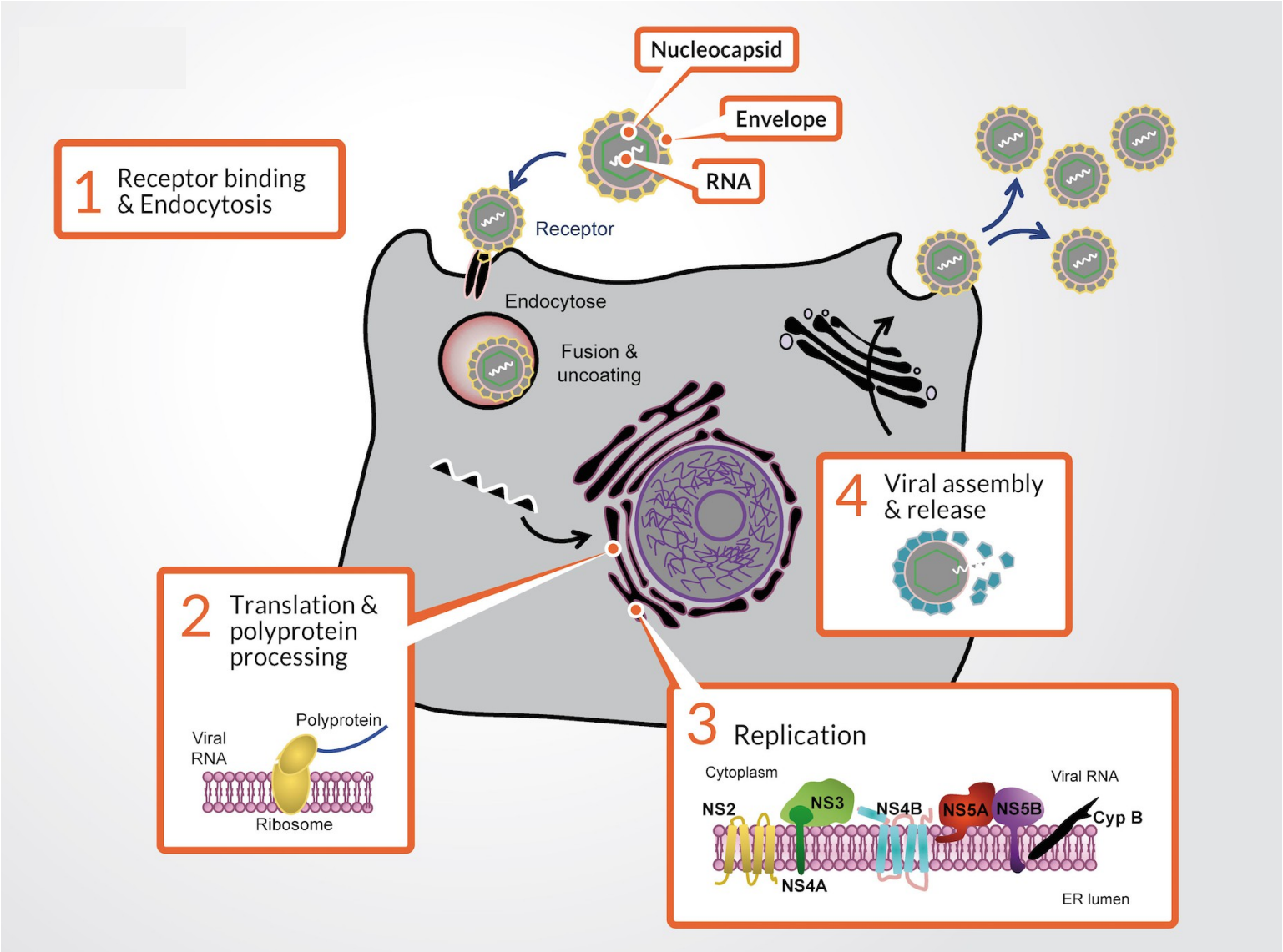
HCV eradication with direct acting antivirals (DAAs)?

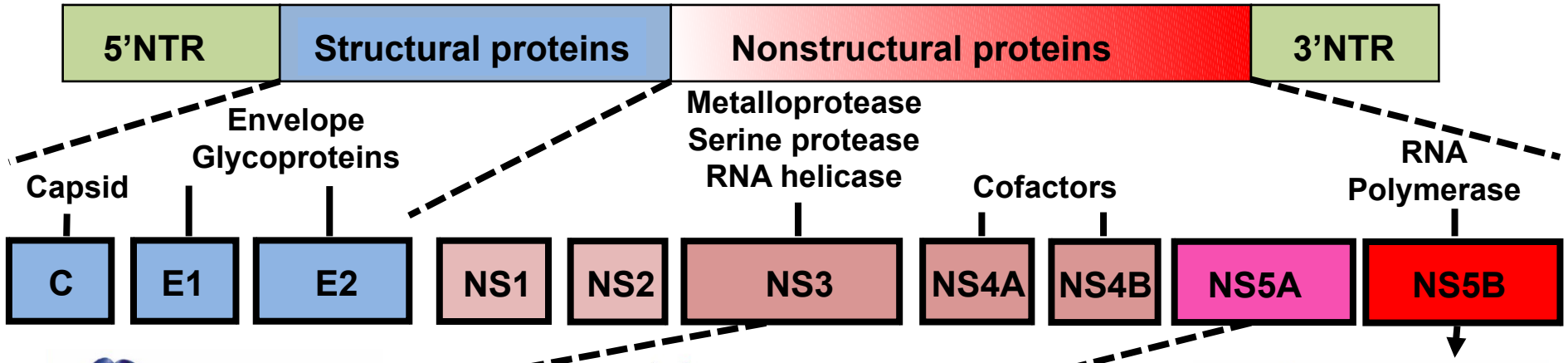
- ✓HCV replication
- ✓HCV genome and DAAs targets
- ✓NS3 inhibitors
- ✓NS5A inhibitors
- ✓NS5B inhibitors
- ✓Take home messages

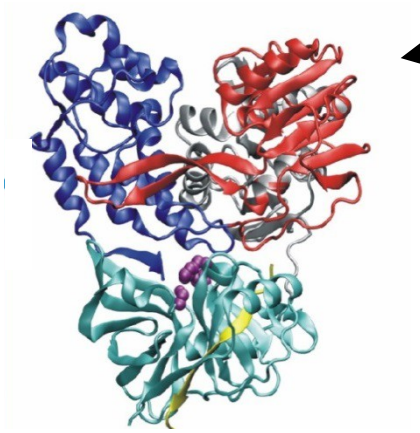
HCV viral cycle

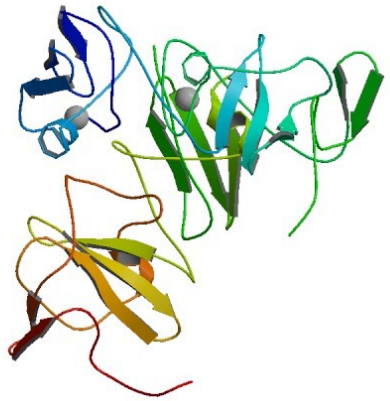


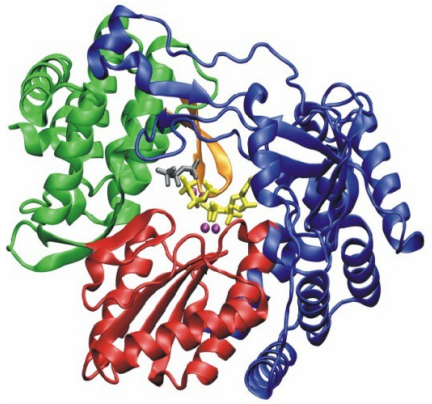
Asselah et al. Liver Int. 2015;35 S1:56-

Direct acting antivirals









Protease Inhibitors

Telaprevir
Boceprevir
Simeprevir
Faldaprevir
Asunaprevir

NS5A Inhibitors

Daclatasvir
Ledipasvir
ABT-267
GS-5816

Polymerase Inhibitors

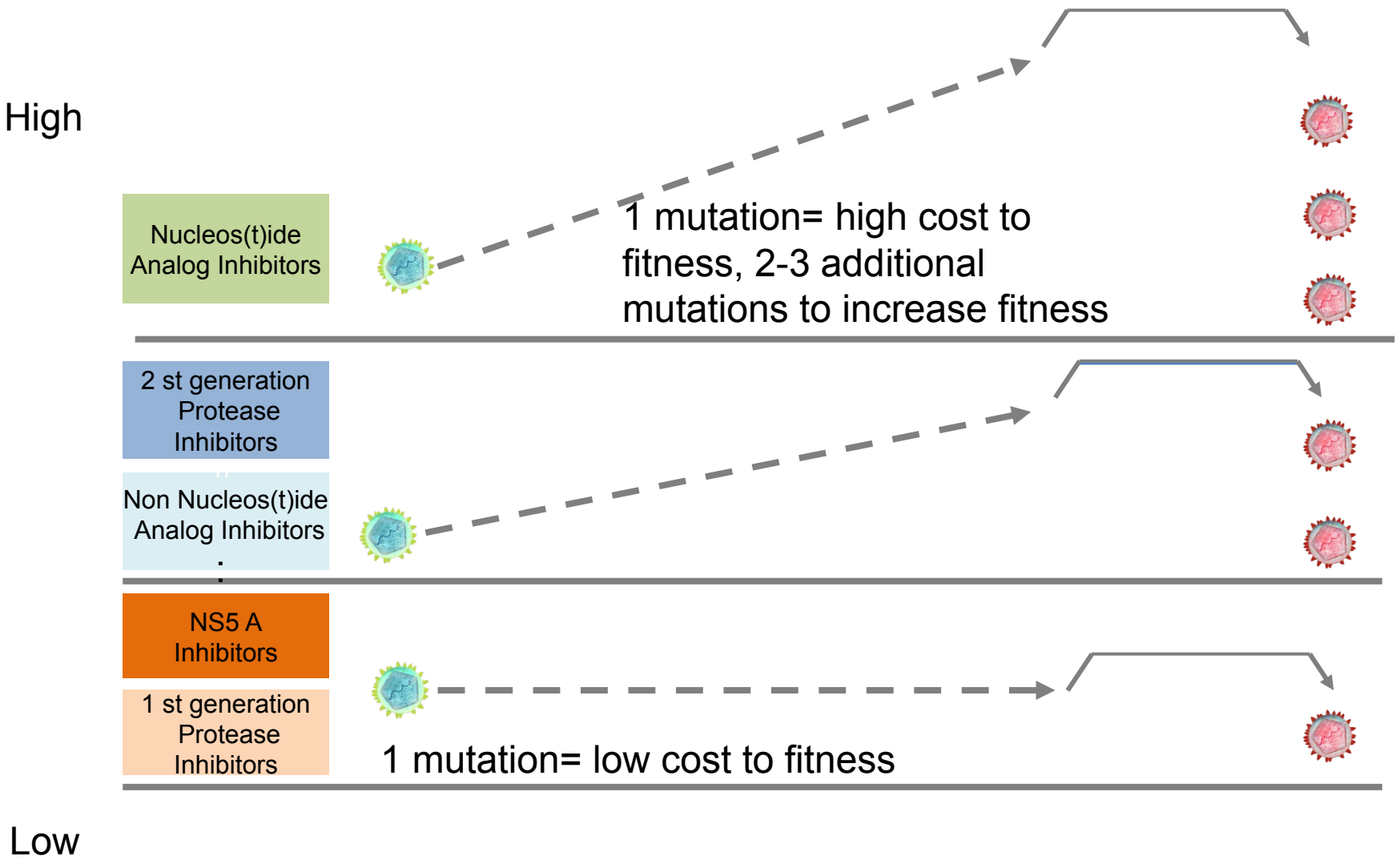
Nucs	Non-Nucs
Sofosbuvir	ABT-333
VX-135	Deleobuvir

Direct Acting Antivirals: 2015

	Nucleotide NS5B inhibitors	Non-nucleoside NS5B inhibitors	NS5A Replication complex inhibitors	Protease inhibitors
Gilead	Sofosbuvir	GS-9669	Ledipasvir GS 5816	GS-9451 GS-9857
Abbvie		Dasabuvir	Ombitasvir ABT-530	Paritaprevir/r ABT-493
Merck (MSD)	MK-3682 IDX-459	MK-8876	Elbasvir MK-8408 Samatasvir	Boceprevir Grazoprevir
BMS		BMS-325	Daclatasvir	Asunaprevir
Janssen (J&J)		TMC-055/r	GSK-2336805	Simeprevir Telaprevir
Achillion	ACH-3422		ACH-3102	Sovaprevir

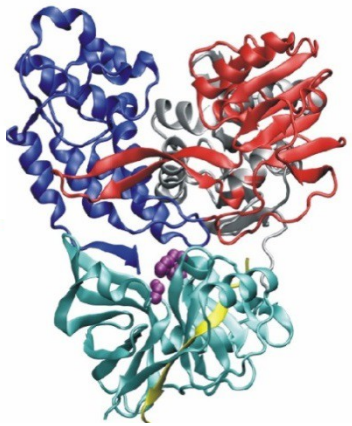
Asselah et al. Liver Int. 2015;35 S1:56-64.

Genetic barrier for HCV direct acting antivirals



Halfon et al. J Hepatol 2011. Vol 55(1):192-206.

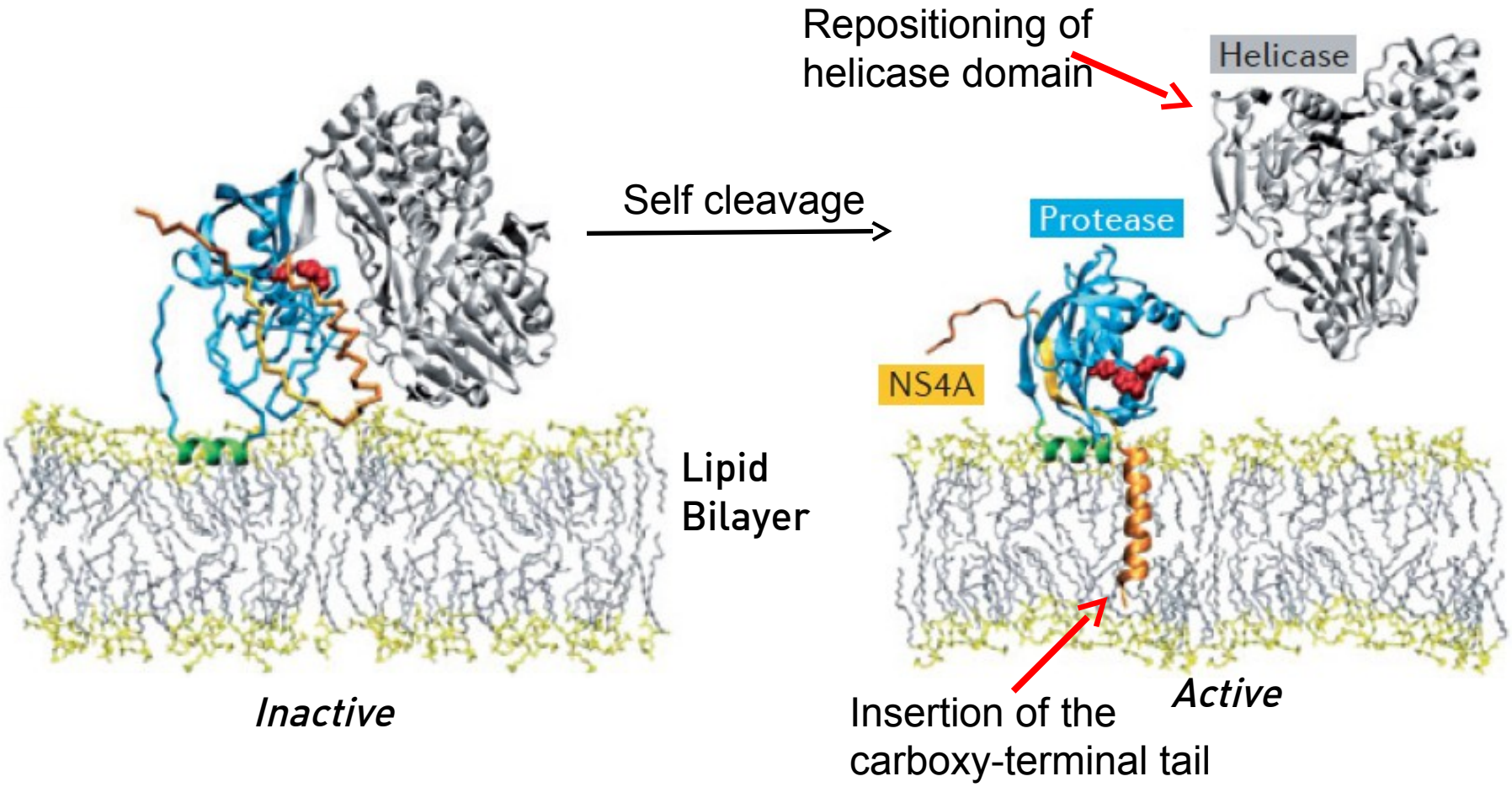
HCV protease inhibitors (PI)



- ✓ Inhibit NS3/NS4A serine protease responsible for the processing of the polyprotein

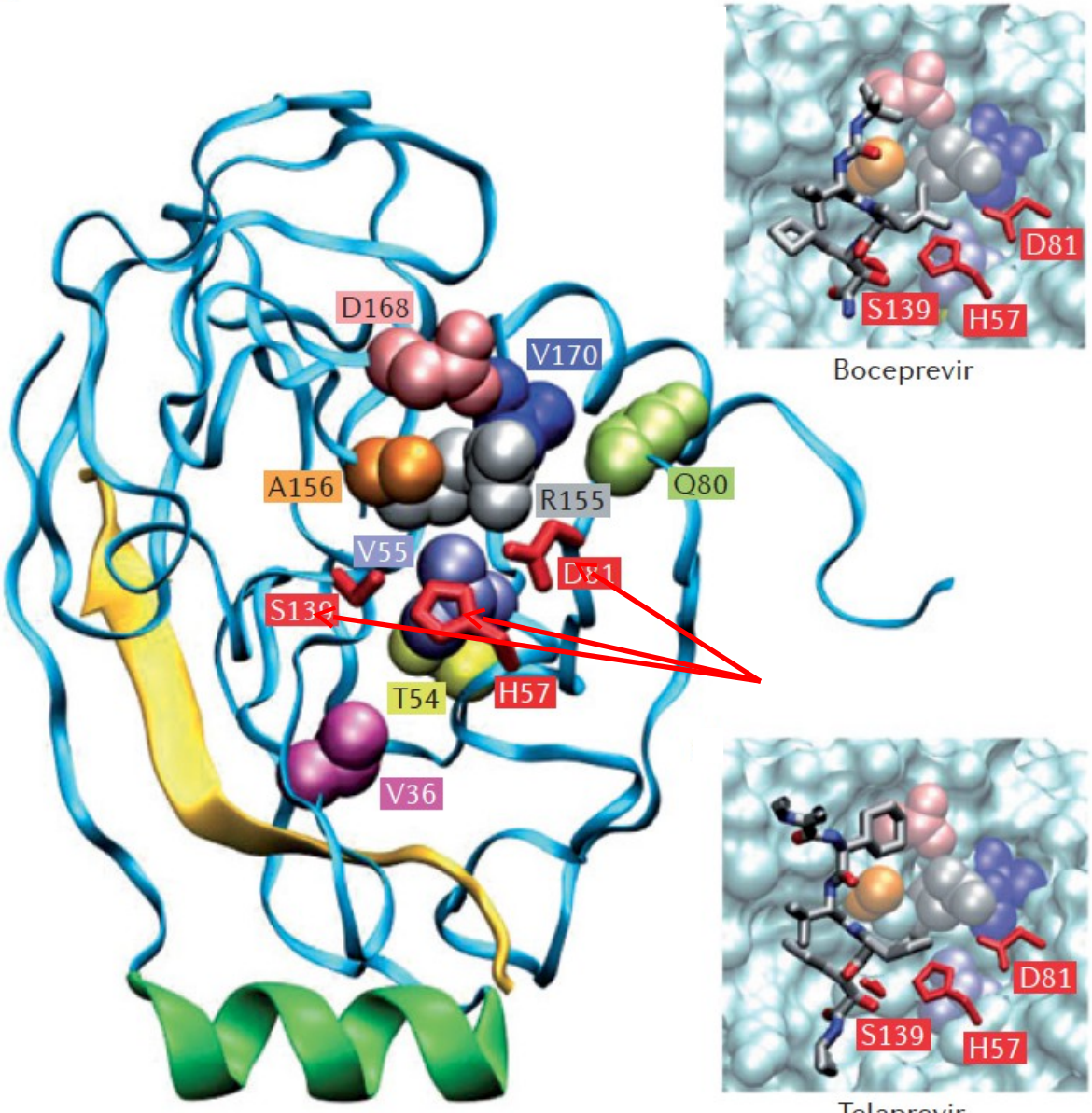
	1st generation	1st generation, 2nd wave	2nd generation
Resistance barrier	low	low	high
Genotype activity	1: 1 a↓ 1b	All except 3	all
Drug drug interaction	Important	Less	Less
Drugs	Boceprevir Telaprevir	Simeprevir (Janssen) Faldaprevir (BI) Paritaprevir (ABT-450)/r (AbbVie) Vedroprevir (Gilead) Vaniprevir (Merck) Sovaprevir (Achillion) Asunaprevir (BMS)	MK-5172 ACH-2684

NS3/NS4A structure



Bartenschlager et al. Nature Reviews Microbiology 2013 11, 482–496

How inhibitors interact with NS3/NS4A



Boceprevir

Telaprevir

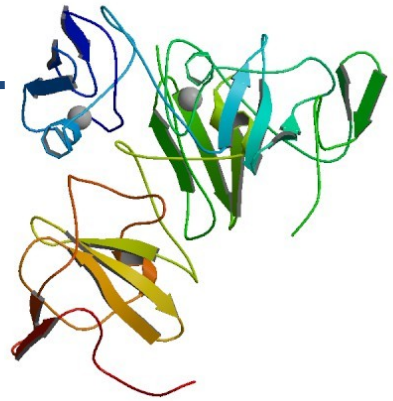
Residues from the catalytic triad:
D81
H57
S139

Bartenschlager et al. *Nature Revie*
Microbiology 2013 **11**, 482–496

Problem of Cross-Resistance to protease inhibitors

NS3/4A Protease Inhibitors	V36 M	T54 S	V55 A	Q80 R/K	R155 K/T/ Q	A156 S	A156 T/V	D168 A/E/ G/H/ T/Y	V170 A/T
Telaprevir	●	●			●	●	●		
Boceprevir	●	●	●		●	●	●		●
Narlaprevir	●	●			●	●	●		
Danoprevir					●			●	
Simeprevir				●	●		●	●	
BI201335					●		●	●	
Vaniprevir					●			●	
Asunaprivir				●	●			●	
ABT-450					●			●	
GS-9451					●			●	

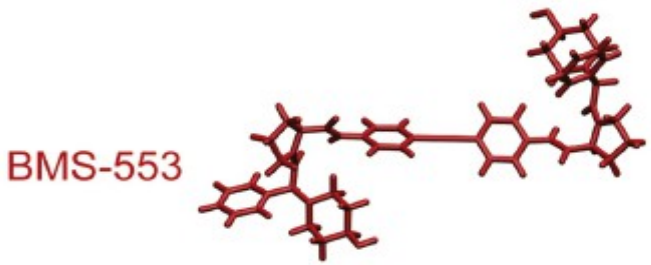
HCV NS5A inhibitors

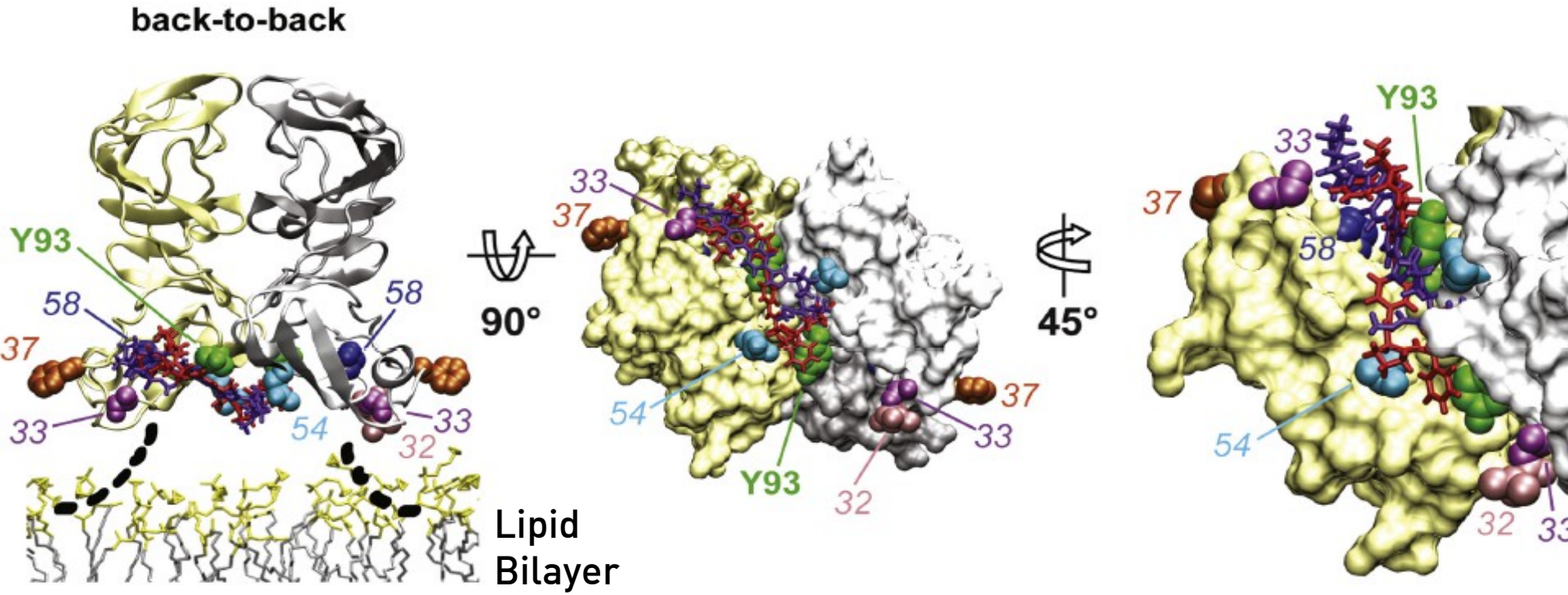


- ✓ Inihibit NS5A, whose funtion is not fully understood.
- ✓ Inhibition of pre-initiation complex
- ✓ Inhibition of assembly
- ✓ Degradation of NS5A?

	1st generation		2nd generation
Resistance barrier	low		intermediate
Genotype activity	1 à 4	all	all
Drugs	Ombitasvir (ABT-267) PPI-461 PPI-668	Daclatasvir Ledipasvir	Elbasvir (MK-8742) ACH-3102 GS-5816

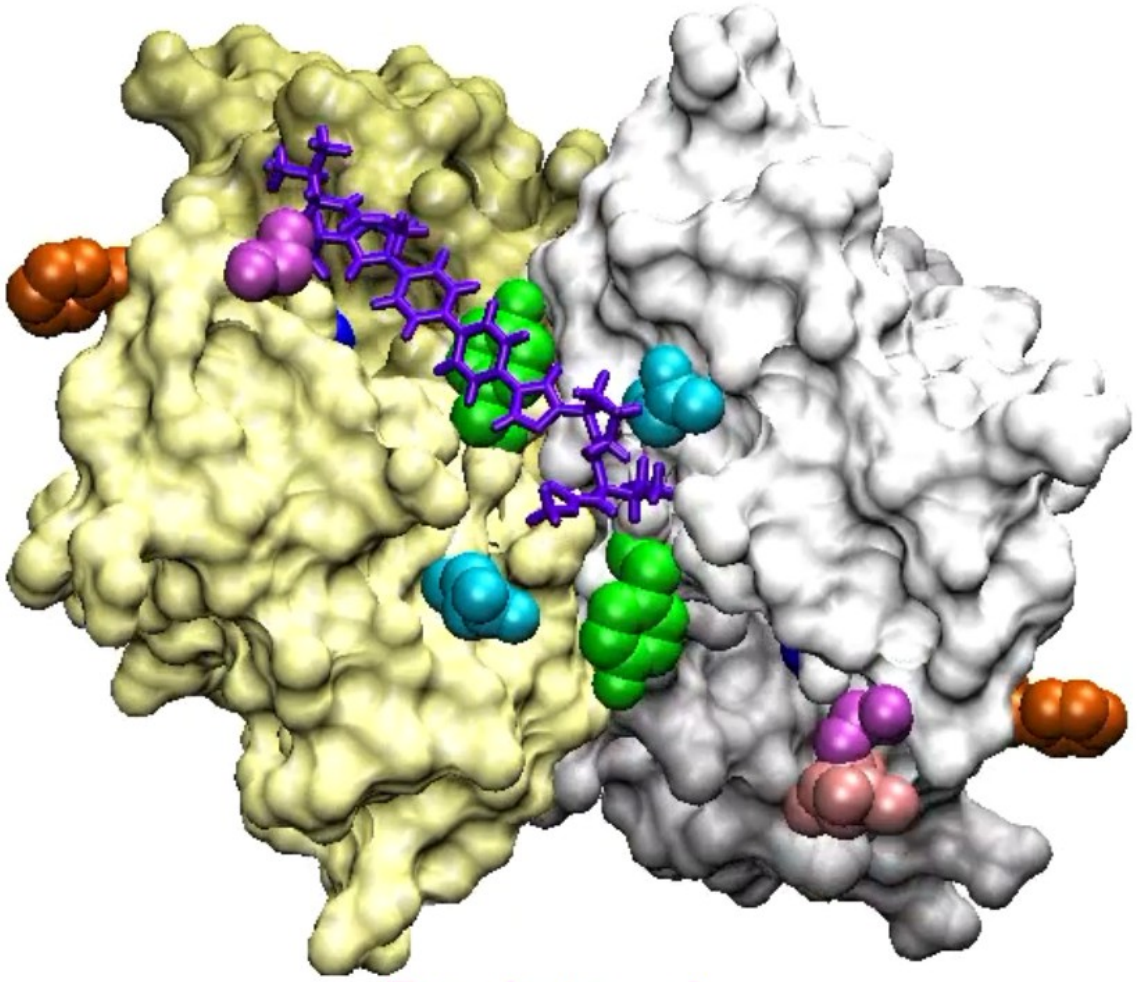
HCV NS5A inhibitors



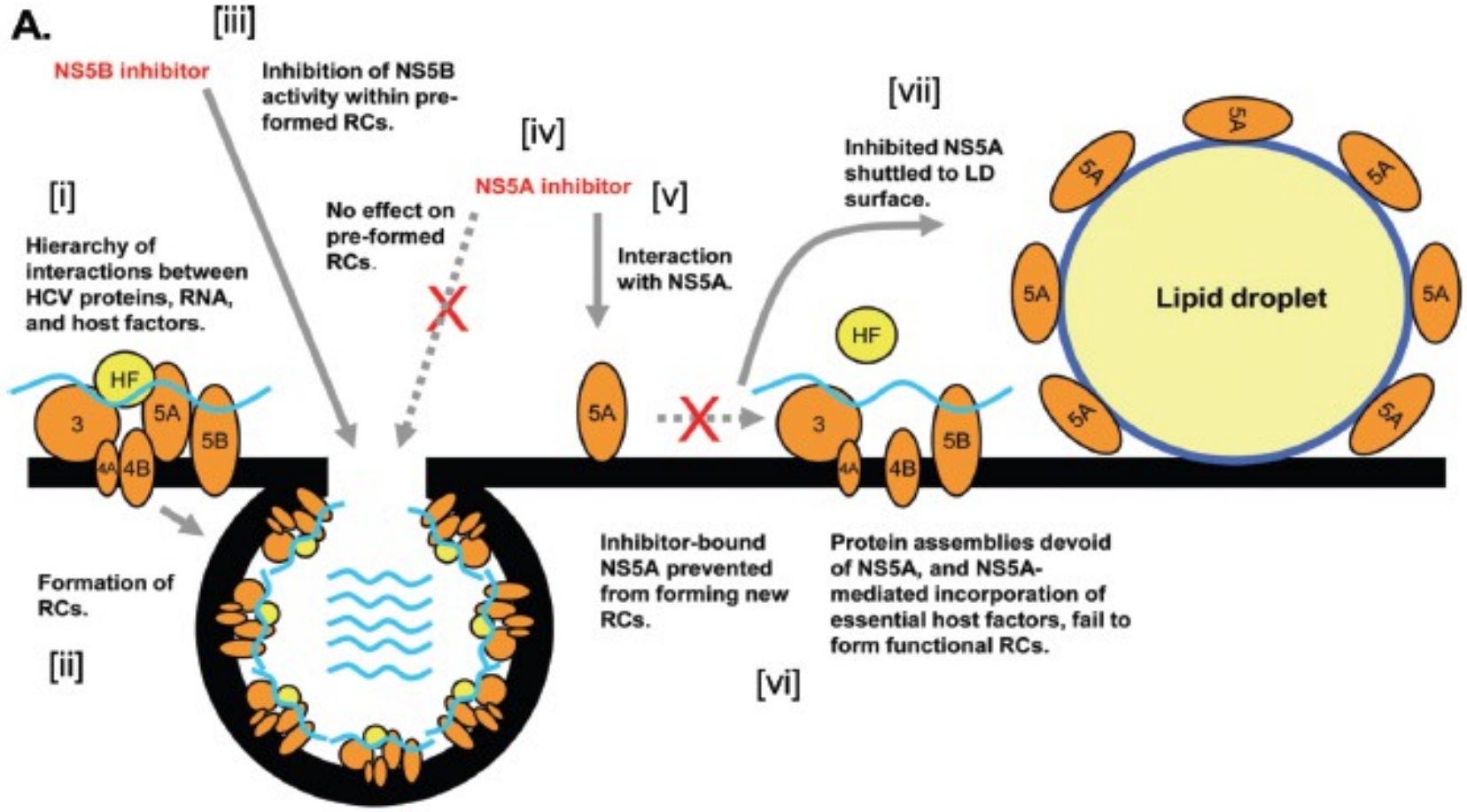


Berger et al. Gastro 2014. Vol 147 (5): 1094-1105.

Interaction of daclatasvir with NS5A



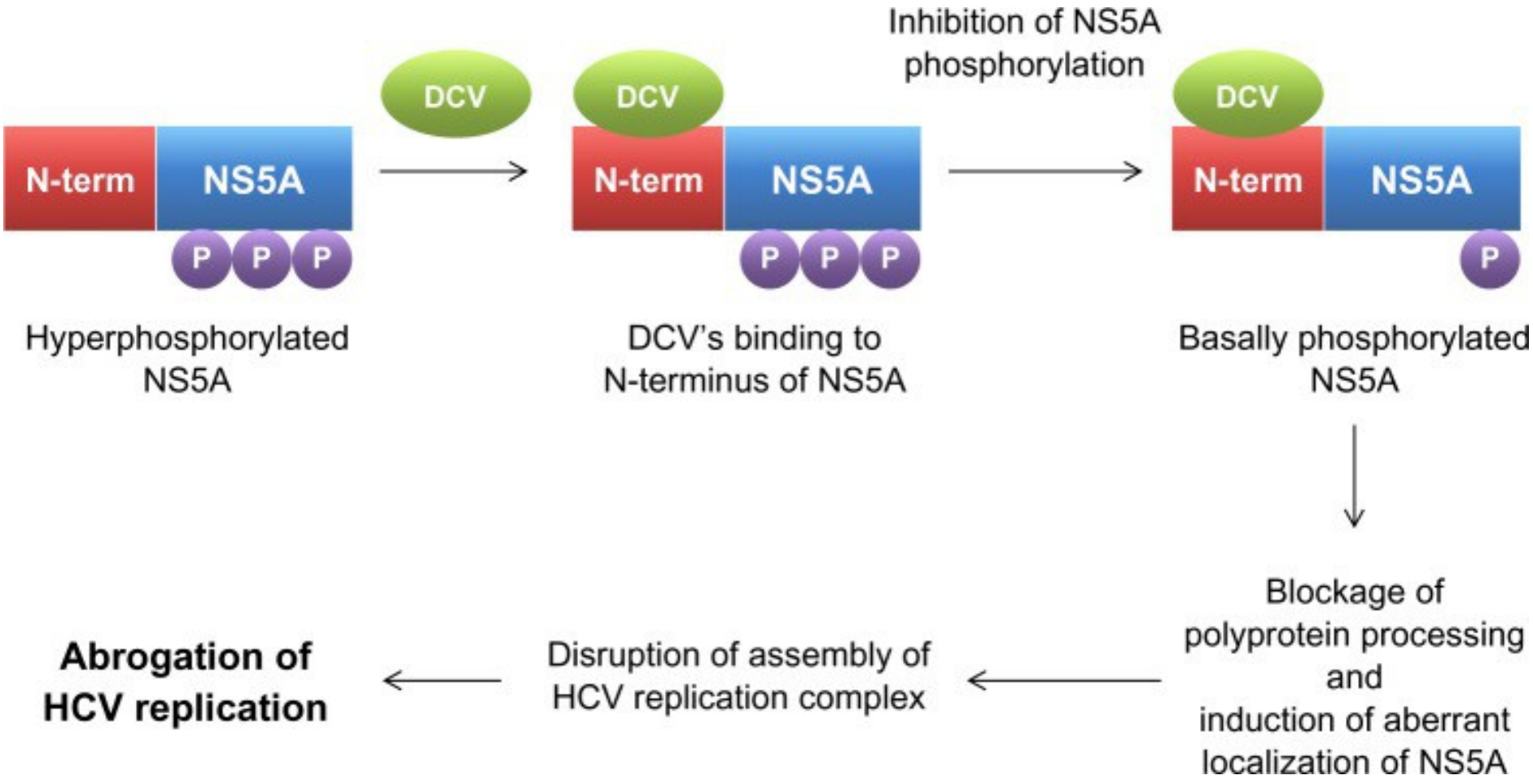
The inhibition of NS5A limits the formation of replication complex



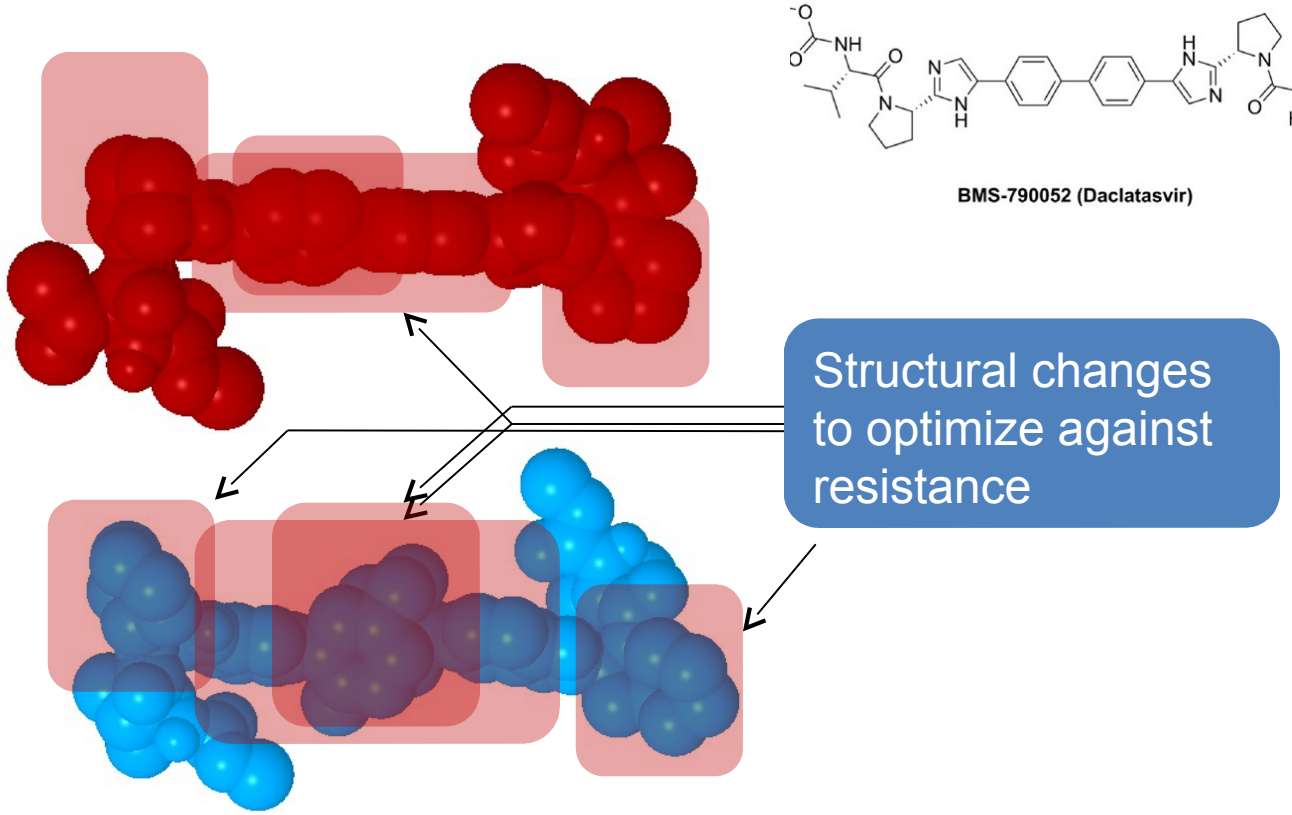
- ✓ NS5A/inhibitor cannot be incorpoated in replication compexs (RCs).
- ✓ NS5A is therefore shuttled at the surface of lipid droplets

Targett-Adams et al. J Virol. 2011 Jul;85(13):6353-68

Inhibition of NS5A activity by Daclatasvir

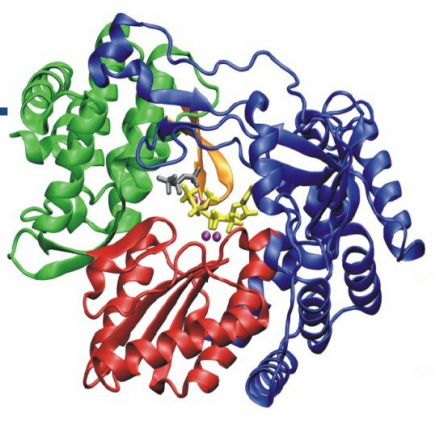


Optimization of NS5A inhibitors structures against resistance variants



- ✓ NS5A inhibitors require a rigid core structure for potent activity.
- ✓ End groups of ACH-3102 were optimized to retain activity against resistant variants

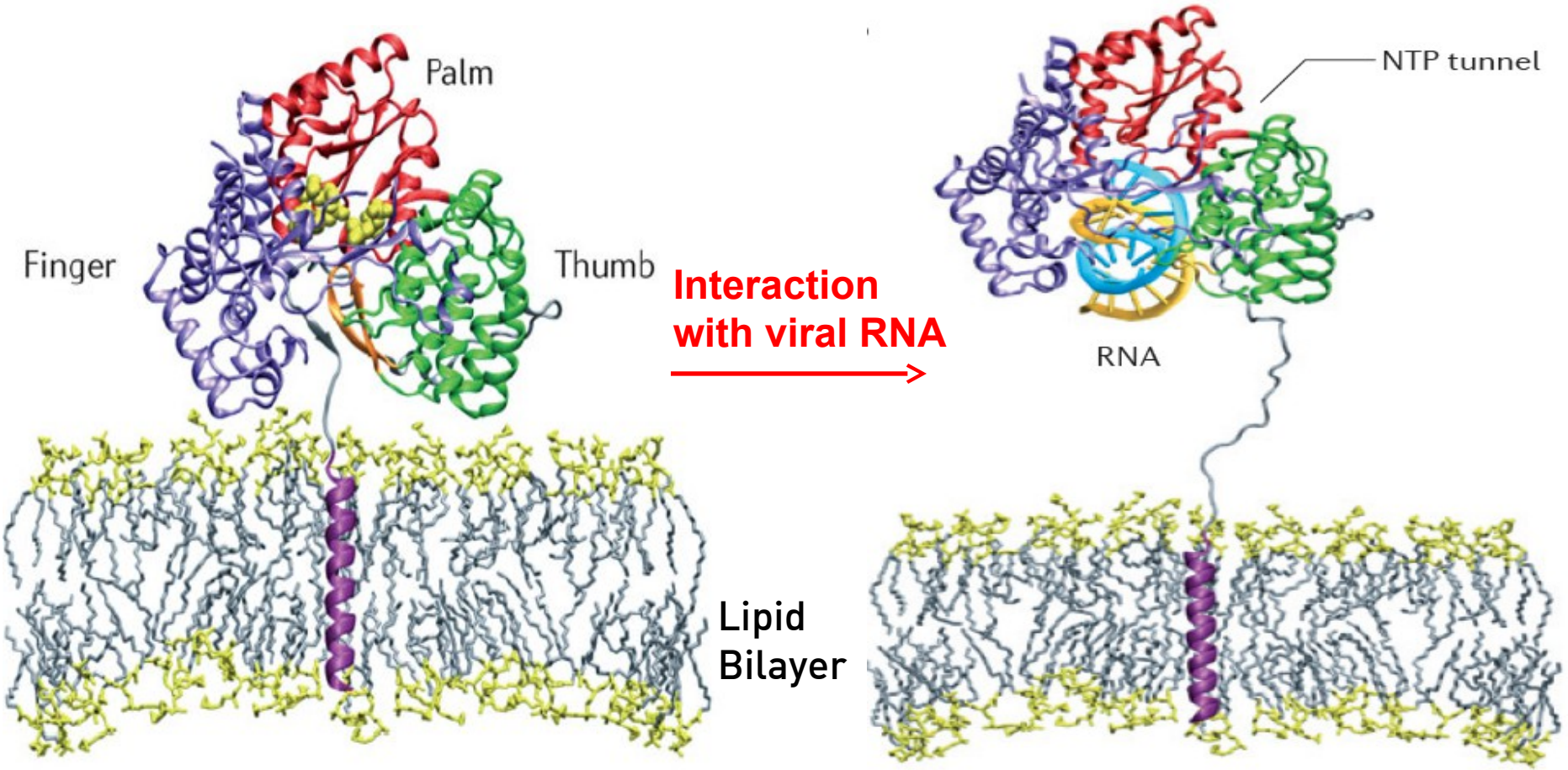
HCV NS5B inhibitors



- ✓ Inihibit NS5B polymerase.
- ✓ Two kind of inhibitors:
  - Nucleot(s)ides analogues: inhibit competively by binding to the catalytic site of NS5B.
  - Non- nucleot(s)ides inhibitors: allosteric inhibition of the binding site of NS5B

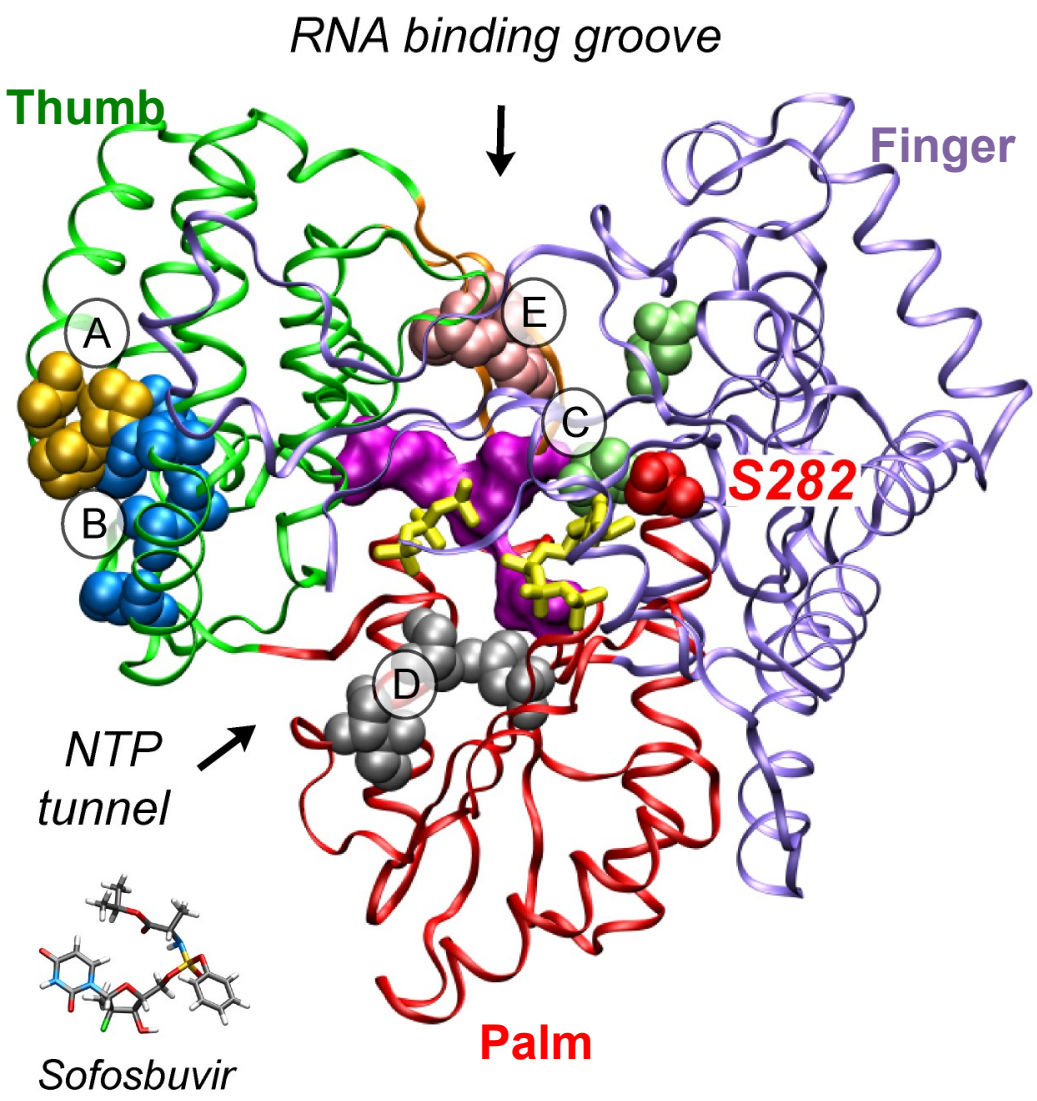
	Nucleos(t)ide analogues	Non-nucleoside inhibitors
Resistance barrier	high	low
Genotype activity	all	G1 (1b ↑ 1a)
Drugs	Sofosbuvir ACH-3422	BMS-791325 (BMS) Dasabuvir (ABT-333) (AbbVie) ABT-072 (AbbVie)

HCV NS5B crystal structure



Bartenschlager et al. Nature Reviews Microbiology 2013 11, 482–496

HCV NS5B inhibitors



- **Nucleos(t)ide inhibitors (NI)**
  - Mericitabine
  - Sofosbuvir
- **Non-nucleoside inhibitors (NNI) = allosteric inhibitors**

Ⓐ **Thumb I**
e.g. deleobuvir

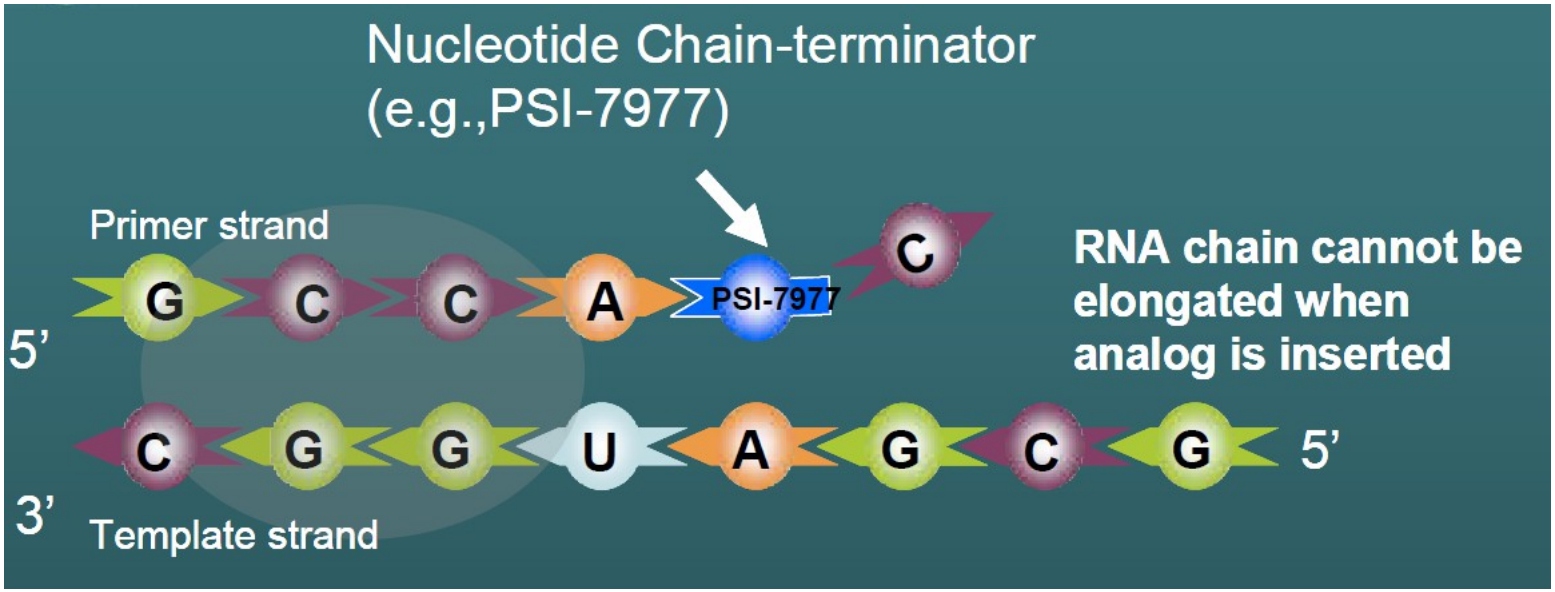
Ⓑ **Thumb II**
e.g. lomibuvir, filibuvir

Ⓒ **Palm I**
e.g. ABT333, setrobuvir

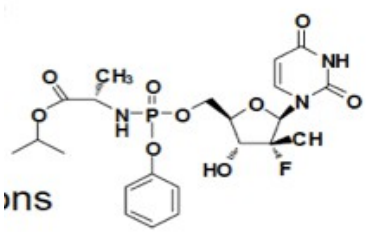
ⒹⒺ **Palm II**
e.g. nesbuvir, tegobuvir

Bartenschlager R *et al*. Nat Rev Microbiol 2013;11:482-496.
Scheel TK and Rice CM. Nat Med 2013;19:837-849.

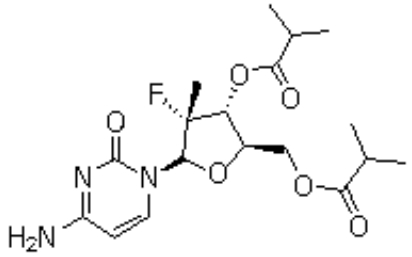
Nucleotide /Nucleoside analogs



Sofosbuvir :
Nucleotide

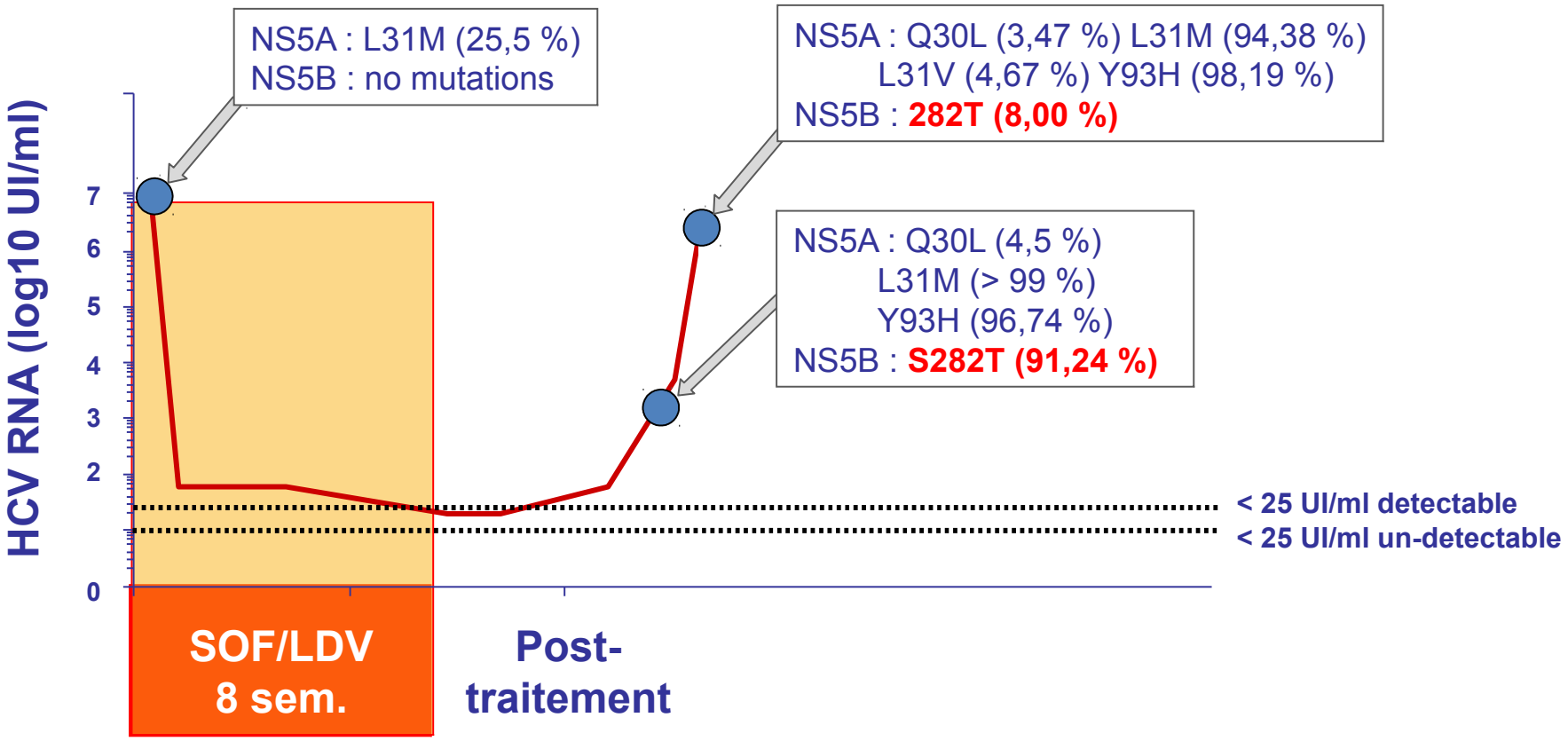


Mericitabine :
Nucleoside



Re-treatment of patients who relapsed after 8 weeks of sofosbuvir + ledipasvir

Patient from LONESTAR study



Lawitz E ,US, AASLD 2013, Abs. 215/1844.

Take home messages

- ✓Knowledge of HCV replication crucial for the development of DAAs
- ✓Importance of genetic barrier
- ✓Cross-resistance to protease inhibitors
- ✓NS5A functions are not fully understood, however blocking NS5A inhibit HCV replication
- ✓The combination of DAAs decreases the risks of resistance

General Characteristics of Direct-Acting Antivirals

	PI, 1st Generation	PI, 2nd Generation	NS5A Inhibitors 1st Generation	NS5A Inhibitors 2nd Generation	NS5B Nucleoside Inhibitors	NS5B Non-Nucleoside Inhibitors
Efficacy						
Resistance Profile						
Pangenotypic Efficacy						
Adverse events						
Drug-drug interactions						

Good profile Average profile Least favorable profile

Schinazi R et al. Liver International 2013