Forum for Collaborative HIV Research

#1 - HCV Lifecycle, Drug Targets, and Mechanisms of Action

Slide set prepared by the
Forum for Collaborative HIV Research and
HCV Drug Development Advisory Group

The Slide Deck

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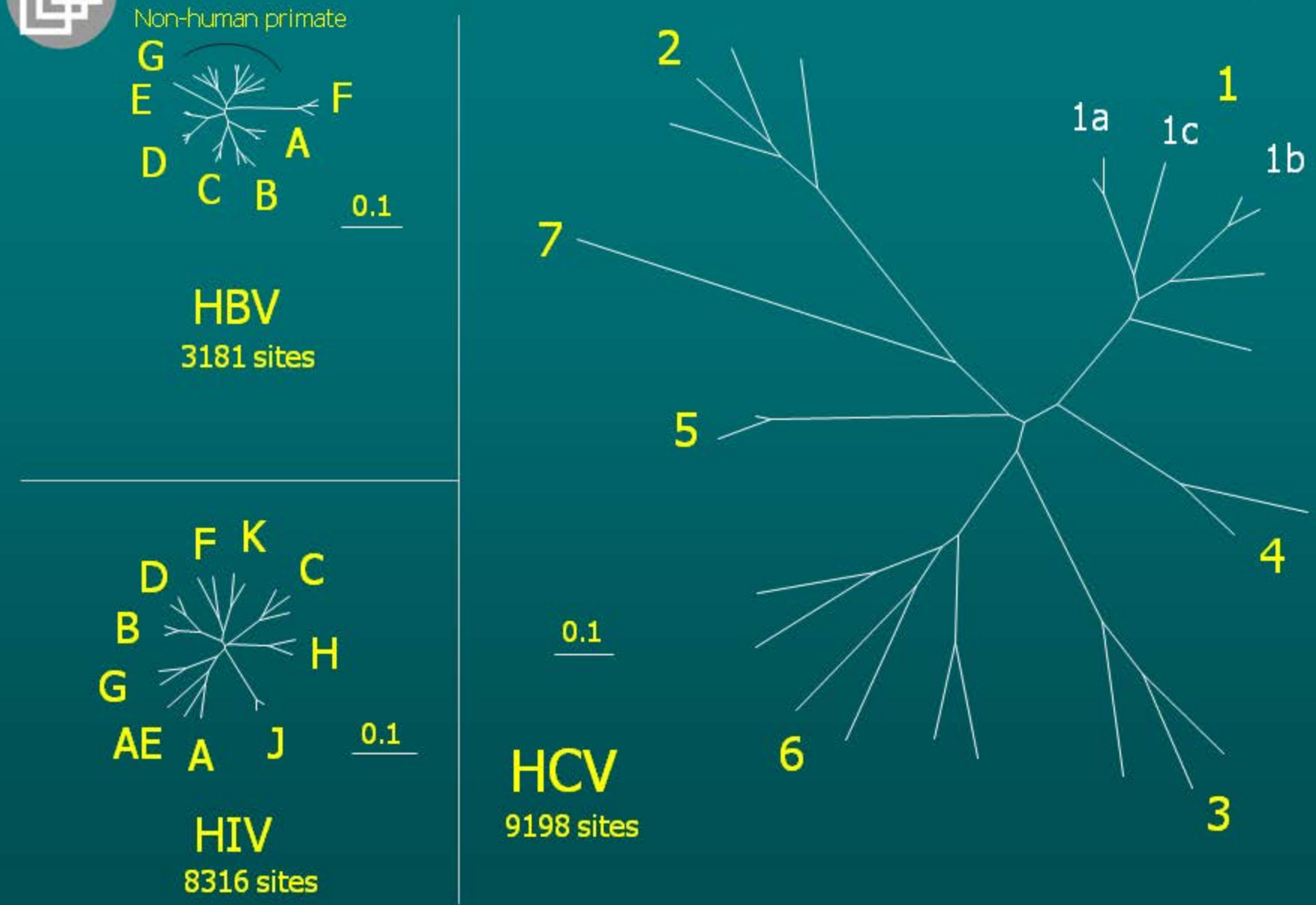
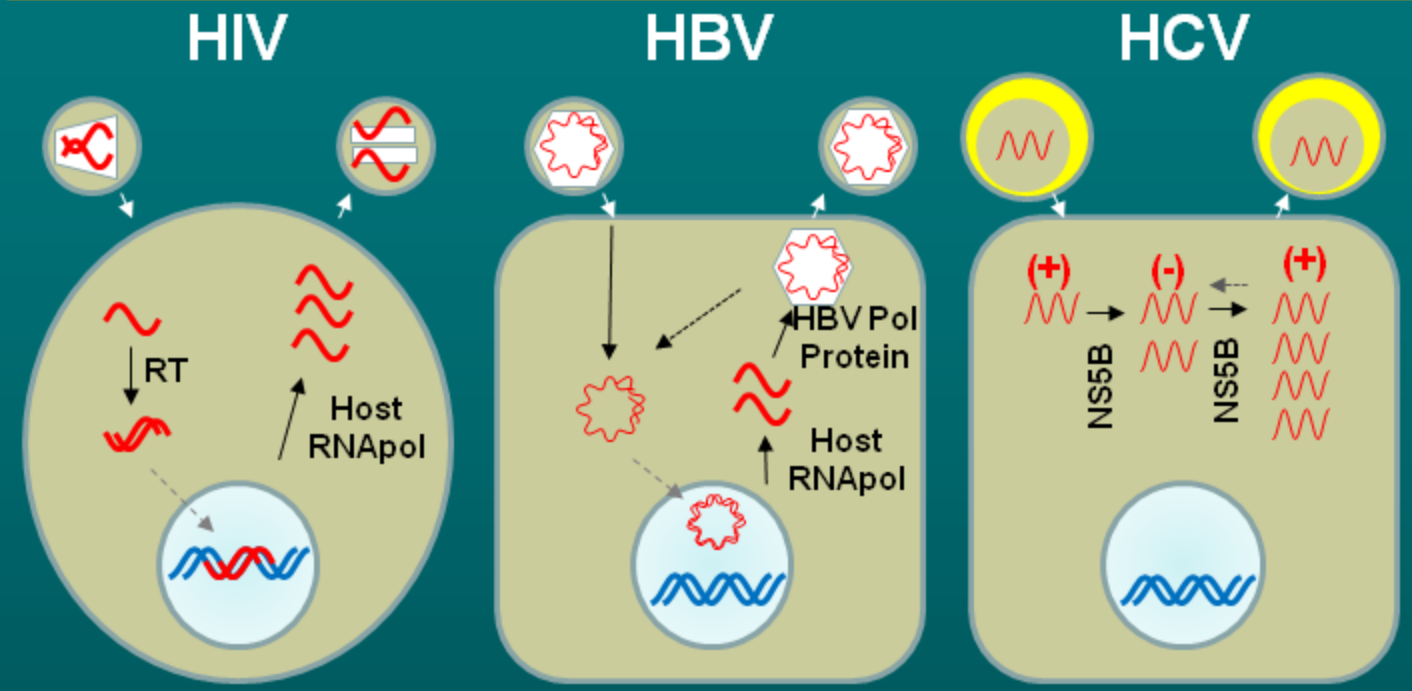
Slide Set #1 Key points

1. HCV is more genetically diverse than HBV and HIV
2. HCV infection can be cured
3. Multiple HCV and host proteins serve as drug targets
4. There are several classes of antivirals and drugs in development, with differing mechanisms of action

HCV sequences are more genetically diverse than HBV or HIV



Life Cycle of HIV, HBV, and HCV



	HIV	HBV	HCV
Stable genome	Provirus	cccDNA	(none)
Virion RNA polymerase	Host RNApol	Host RNApol then HBV Pol Protein	HCV NS5B
Error-prone replications	One by HIV RT, host factors	HBV pol protein, host factors	HCV pol protein, host factors
Plasticity of genome	High	Constrained	Very high
Recombination	Common	Common	Rare

Unlike HIV and HBV, HCV is curable

Virus	HIV	HBV	HCV
Genome	RNA	DNA	RNA
Mutation Rates	Very High	High	Very High
Virions Produced Daily	10^{10}	10^{13}	10^{12}
Long-lived proviral reservoir	YES	YES	NO
Viral Targets of Therapy	Multiple	One	Multiple
Cure With Current Therapy?	NO (Integrated viral DNA)	NO (cccDNA)	YES
Current Therapeutic Goal	Lifelong suppression	Lifelong suppression	**Cure** or eradication of HCV infection

HBV, HIV and HCV have targeted drugs approved or in development

HIV

- Protease
- RT (nucleoside/nucleotide)
- RT (non-nucleoside)
- Co-receptor
- Fusion
- Integrase

HBV

- RT (nucleoside/nucleotide)

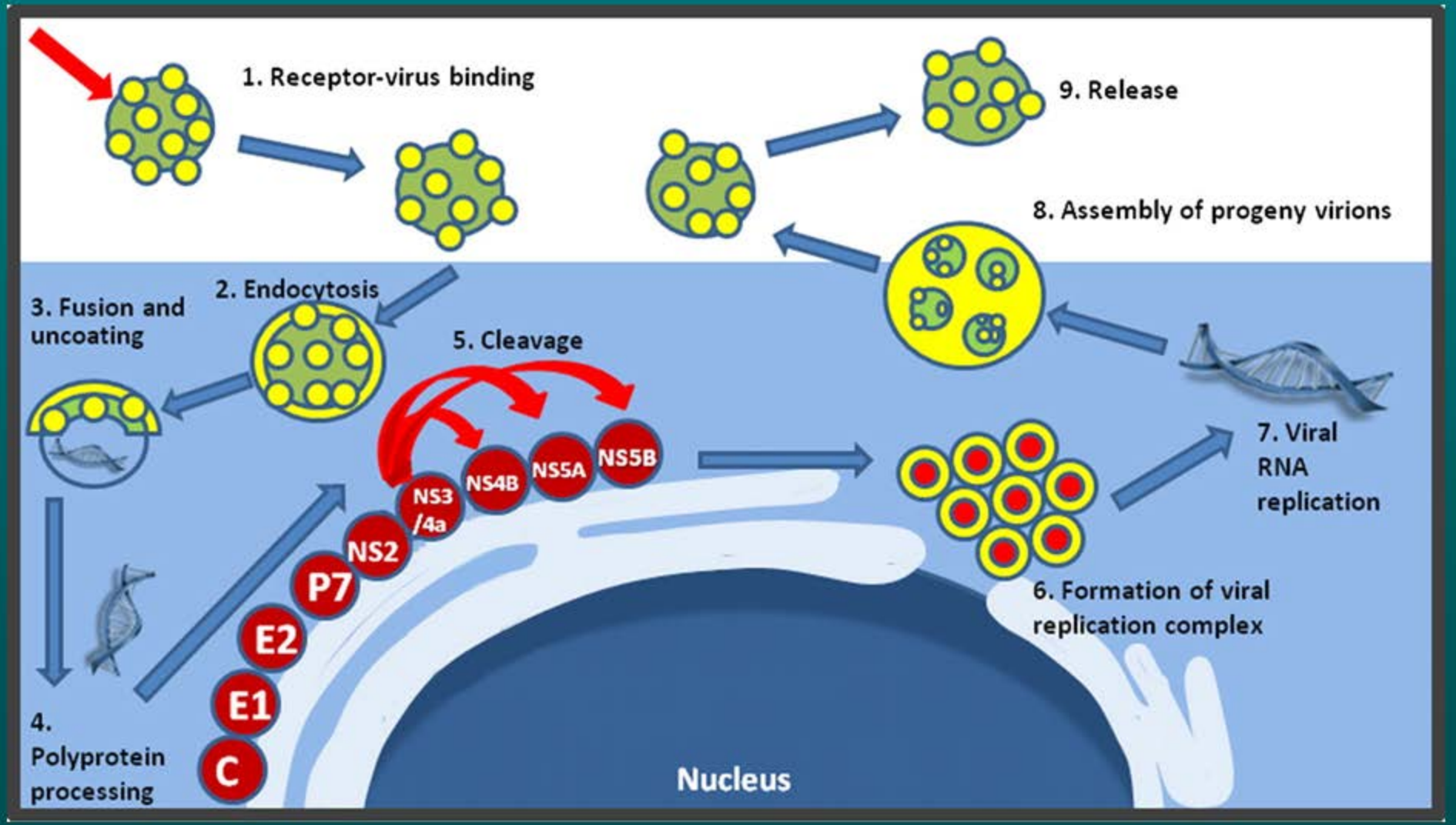
HCV

- NS3-4A Protease*
- NS4B
- NS5A
- NS5B (nucleos(t)ide)
- NS5B (non-nucleoside, multiple classes)
- Cyclophilin
- miR-122
- Entry

Host Factors

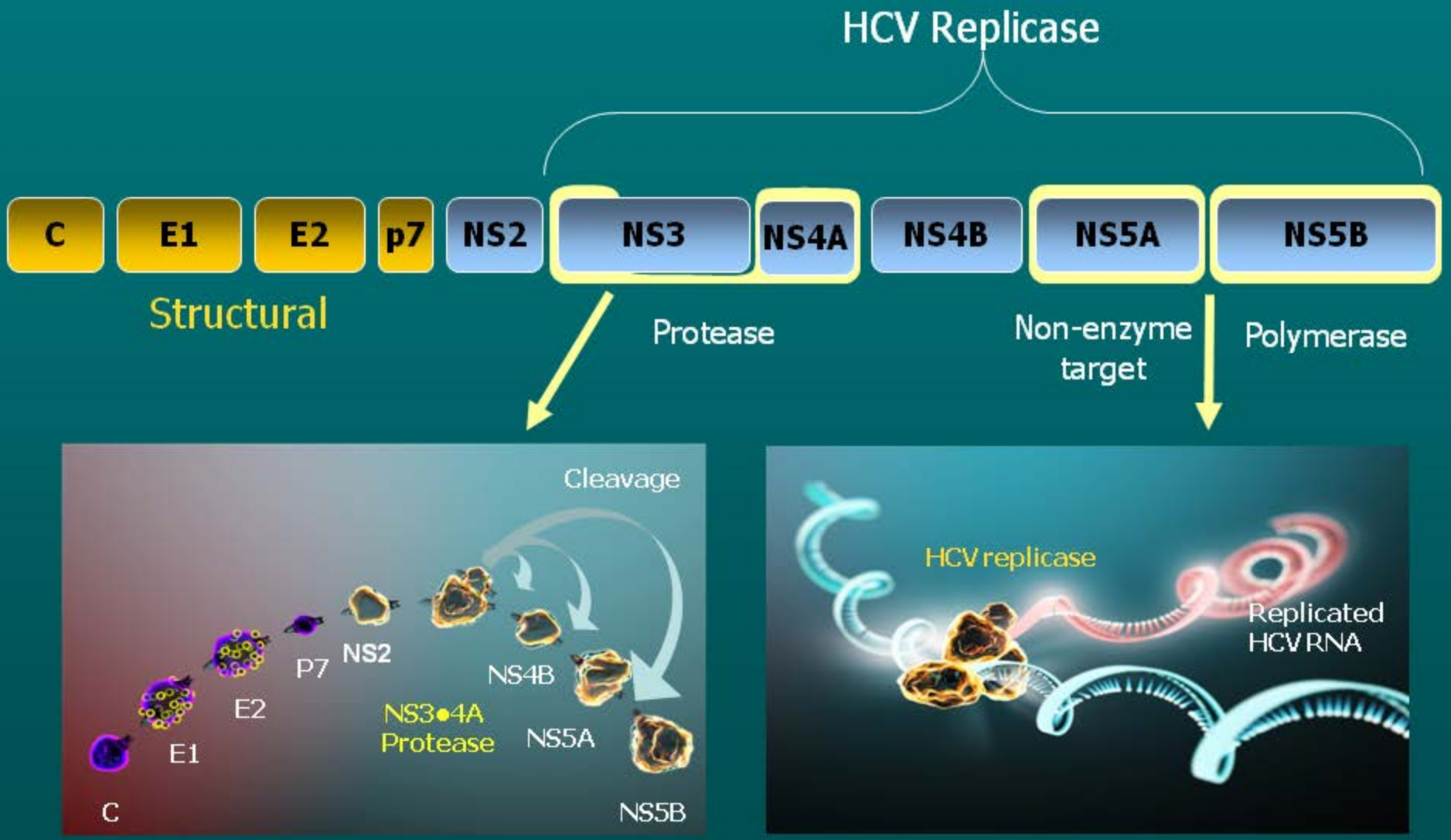
* Approved in 2011

HCV Lifecycle



Modified from Butt A A , Kanwal F Clin Infect Dis. 2012;54:96-104

HCV proteins provide good targets for drug development



Adapted from Kwong AD, et al. *Curr Opin Pharmacol.* 2008; 8(5): 522-31

HCV drug classification and development phase

NS5B inhibitors (nucleos/tide)	Phase
sofosbuvir (GS-7977)	3
mericitabine (RG-7128)	2
VX-135	2
IDX-184	2 (hold)
GS-0938	2 (hold)
GS-6620	1
TMC-649128	1 (hold)

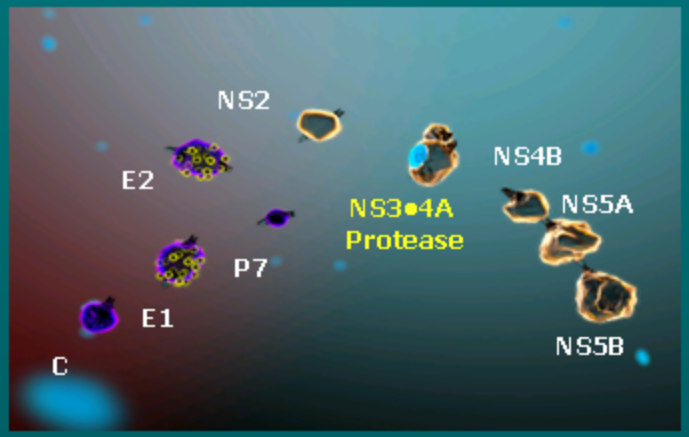
NS5B inhibitors (non-nuc)	Phase
deleobuvir (BI207127)	3
ABT-333	3
setrobuvir (ANA598)	2b
tegobuvir (GS-9190)	2
filibuvir (PF-868554)	2
ABT-072	2
VX-222	2
BMS-791325	2a
TMC-647055	2
VCH-759	2
GS-9669	2

NS3-4A Inhibitors	Phase
telaprevir	Approved
boceprevir	Approved
simeprevir (TMC435)	3
faldaprevir (BI201335)	3
asunaprevir (BMS-650032)	3
vaniprevir (MK-7009)	3
ABT-450/r	3
GS-9256	2b
GS-9451	2
danoprevir/r (RG-7227)	2
sovaprevir (ACH-1625)	2
MK-5172	2
ACH-2684	1b

NS5A inhibitors	Phase
daclatasvir (BMS-790052)	3
ABT-267	3
ledipasvir (GS-5885)	3
GSK-2336805	2
ACH-3102	2a
ACH-2928	1b
PPI-461	1b

Host-targeting antivirals	Phase
alisporivir (DEB025, cyclophilin)	3 (hold)
SCY-465 (cyclophilin)	2
ANA-773 (TLR-7)	1

Mechanism of action: NS3-4A protease inhibitors



Lindenbach, BD and Rice, C, *Nature* 436 933-938 (2005)

Protease Inhibitors (blue) block NS3-4A mediated cleavage, and subsequent release of NS4B, NS5A, and NS5B

Protease interaction and drug type:

Covalent

- Slow reversible: telaprevir, boceprevir*
- Irreversible: AVL-192†

Non-covalent, Linear

- ABT-450/r
- asunaprevir
- faldaprevir
- GS-9451
- sovaprevir

Non-covalent, Macrocyclic

- simeprevir
- vaniprevir
- danoprevir/r
- GS-9256
- MK-5172
- ACH-2684

* Approved 2011; † Preclinical

Mechanism of action: NS5A replication complex inhibitors

- Role of NS5A in HCV replication is currently under investigation
- NS5A inhibitors and similar chemotypes:
  - bind to HCV NS5A protein in cell culture[1]
  - interact with the NS5A N-terminus of Domain 1[2]
  - block both cis- and trans-acting functions of NS5A, thereby interfering with HCV replication [3,4]
  - redirect NS5A away from endoplasmic reticulum replication complexes lipid droplets via an unknown mechanism[5]
- Current drugs under development:
  - ABT-267, daclatasvir, ledipasvir, GSK-2336805, PPI-461, ACH-2928, ACH-3102

[1]Gao, M. *Nature*, 2010; **465:** 96-100; [2]Lemm, J.A. *J Virol*, 2010; 84 (**1**)**:** 482-491; [3]Fridell, R.A. *J Virol* 2011; 85(14): 7312-20; [4]Lee, C. *Virol* 2011; 414(1):10-8, [5]Targett-Adams, P. *J Virol* 2011; 85(13):6353-6

Mechanism of action: NS5B polymerase inhibitors

NS5B site

Active

Active Site
- sofosbuvir
- GS-6620
- TMC-649128
- IDX-184
- GS-0938
- mericitabine
- VX-135

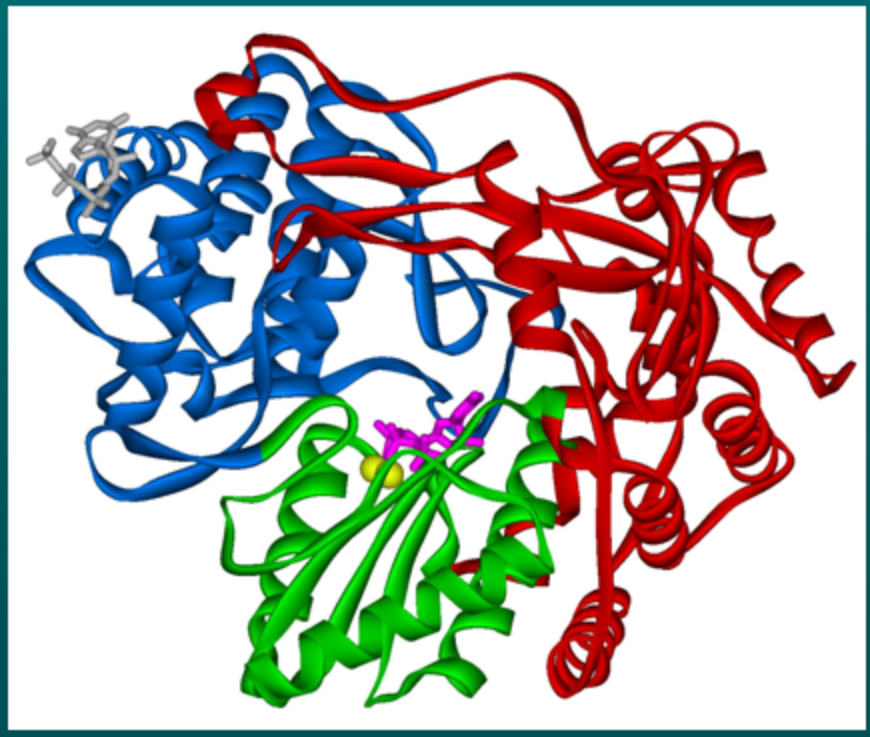
Polymerase active site inhibitors bind and interfere with viral synthesis, while allosteric inhibitors bind at different sites and interfere with initiation of viral RNA synthesis

Allosteric

Thumb 1
- deleobuvir
- BMS-791325
- TMC-647055

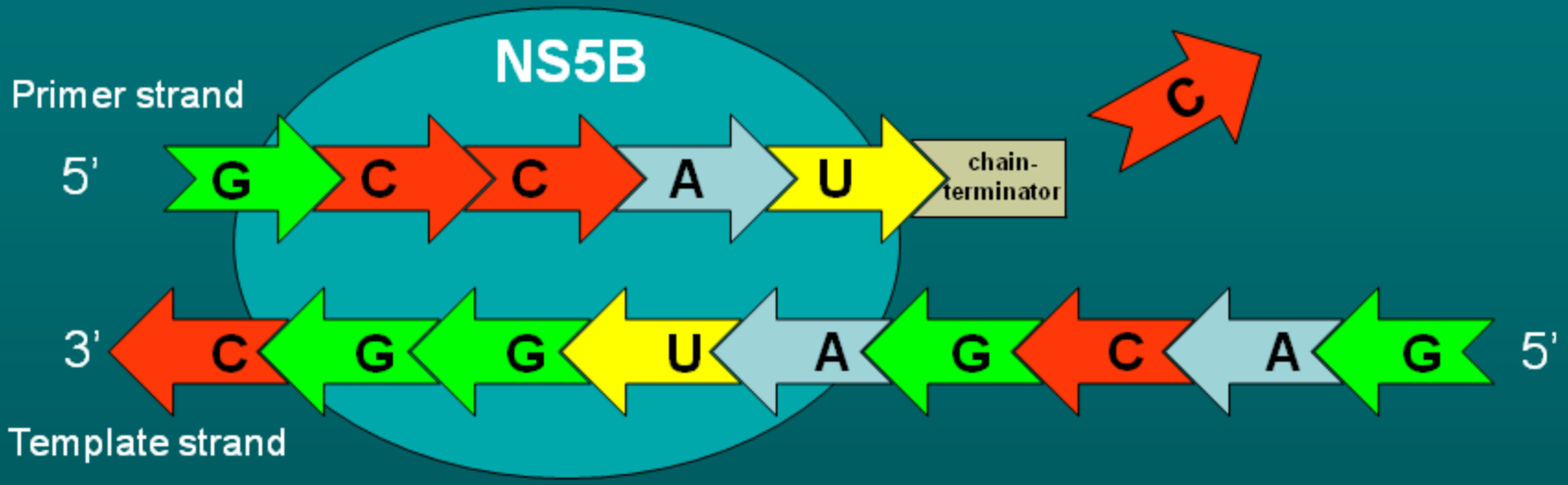
Thumb 2
- VX-222
- filibuvir
- GS-9669
- VCH-759

Palm
- ABT-333
- ABT-072
- setrobuvir
- tegobuvir



Note: drugs interaction sites are color-coded with the NS5B ribbon diagram

NS5B active site inhibitors: nucleos(t)ide analog chain-terminators



- Chain termination results as RNA chain cannot be elongated upon analog insertion
- Both pyrimidine and purine analogs can inhibit NS5B activity

Carroll S.S. *J Biol Chem*, 2003; 278:11979-11984; Deval, J. *Antimicrob Agents Chemother*, 2007; 51:2920-2928; Klumpp, K.G. *J Biol Chem*, 2006; 283: 3793-3799; Klumpp, K.G. *J Biol Chem*, 2008; 283: 2167-21675; Ma, H. *J Biol Chem*, 2007; 282: 29812-29820; Migliaccio, G. *J Biol Chem*, 2003; 278: 49164-49170; Murakami, E. *Antimicrob Agents Chemother*. 2007; 51:503-509

Mechanism of action: host factor inhibitors

Key attributes of host-targeting antiviral (HTA), *e.g.*, cyclophilin inhibitors