HCV MEDICATIONS & THERAPEUTIC TRIALS

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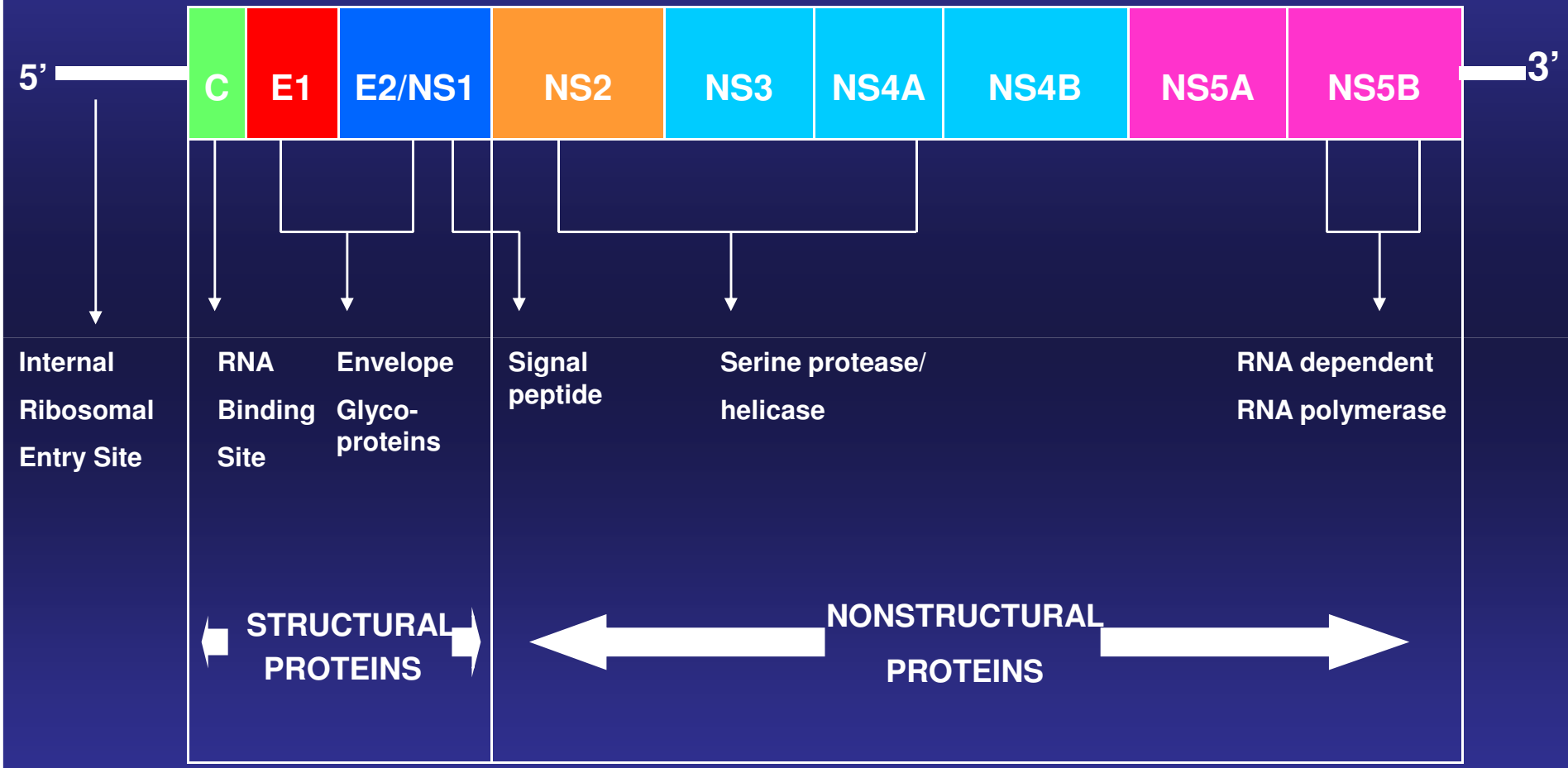
DISCLOSURES
Active or Within 12 Months

- Research Support
  - Idenix
  - Roche
  - GSK
  - Schering
  - Vertex
  - Human Genome Sciences
  - SciClone
- Speakers Bureau
  - SciClone
- Advisory Board
  - BMS
  - SciClone
  - Idenix
  - Vertex

Agents and uses not approved by the FDA will be discussed

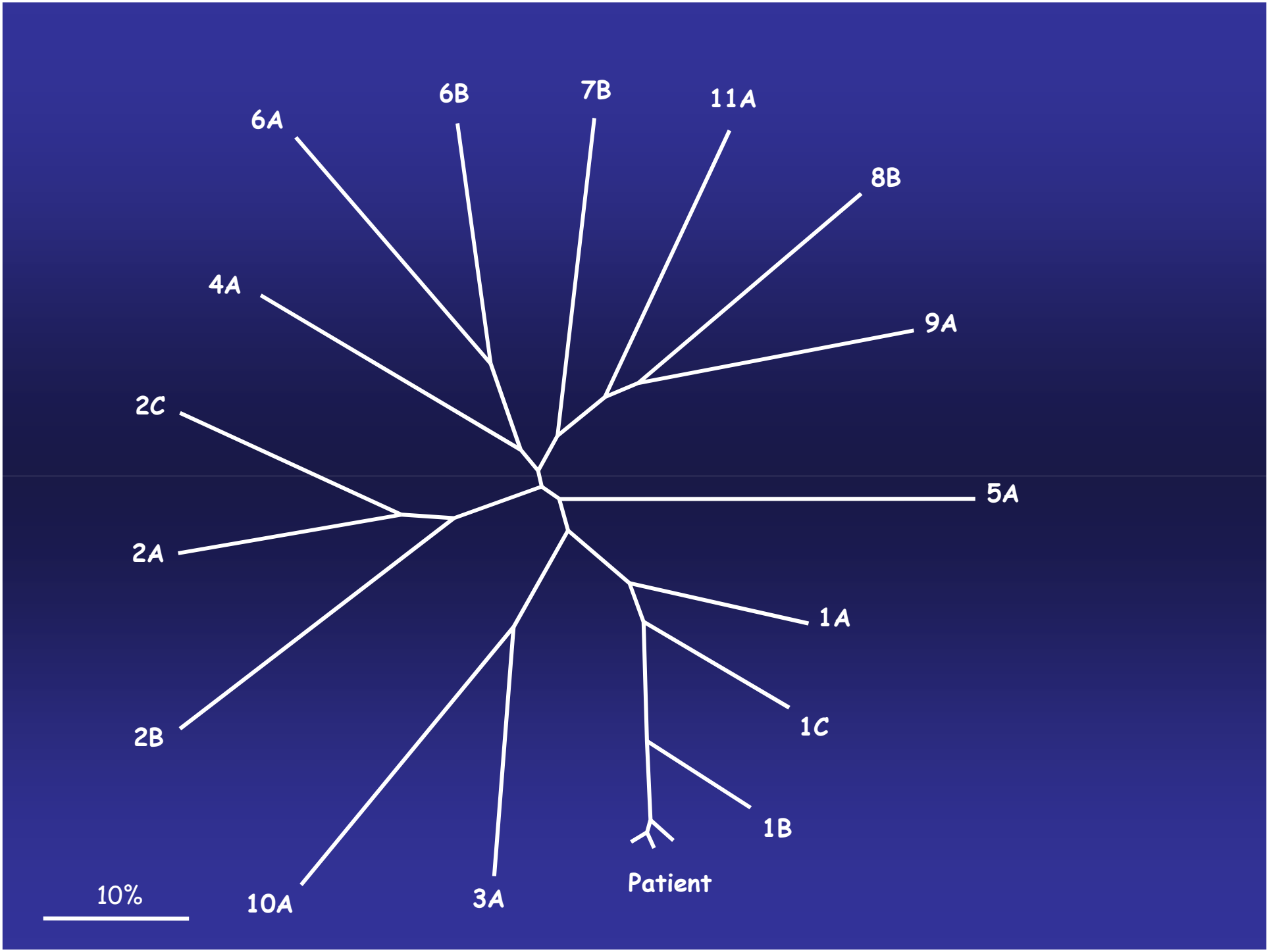
HEPATITIS C VIRUS

Genome



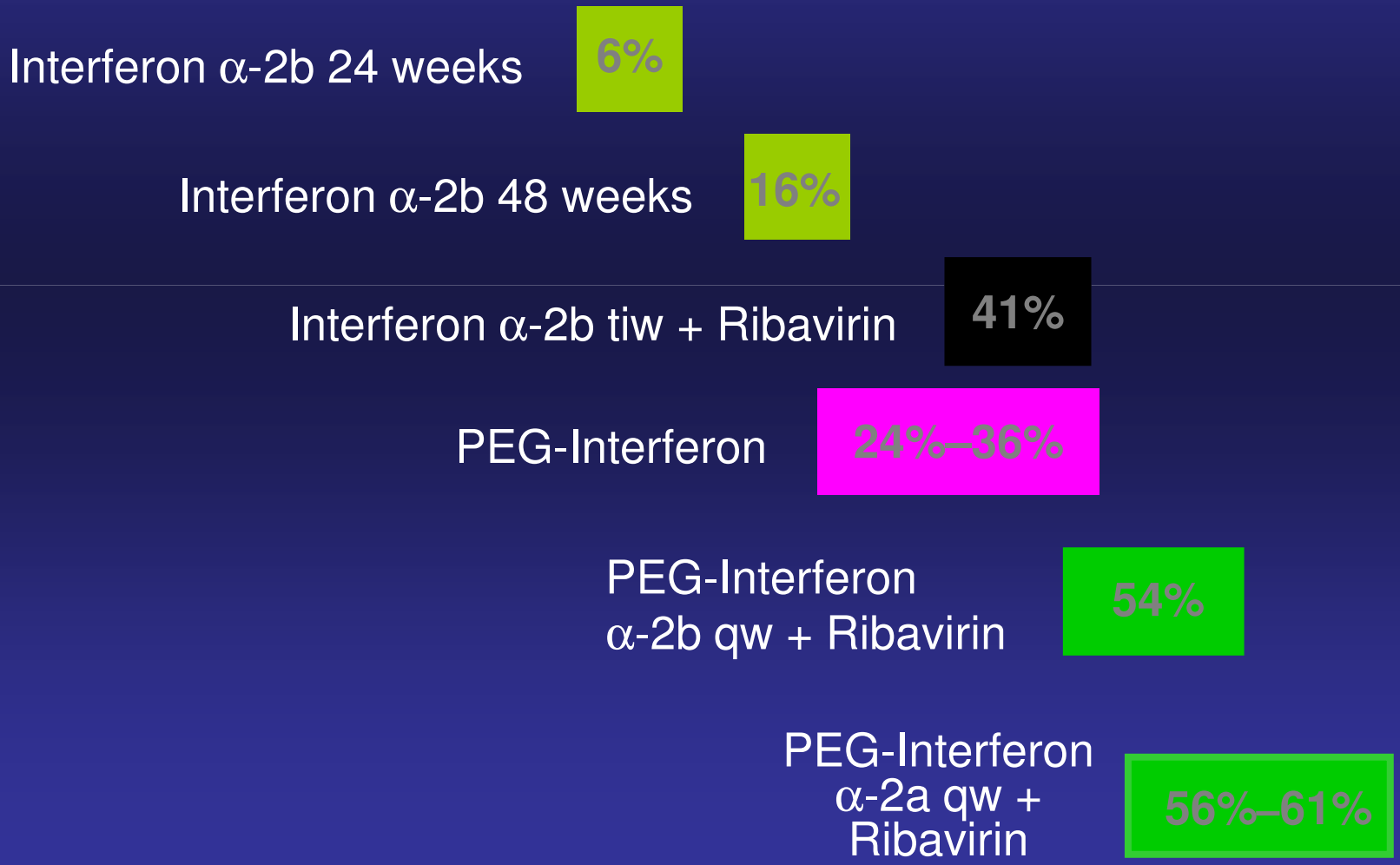
HCV DIVERSITY

- HCV replicates at high levels (>10 trillion virions/day
- Lack of error correction leads to drift
- Drift is observed in two forms
  - Quasispecies
  - Genotypes


6A
6B
7B
11A
8B
4A
9A
2C
5A
2A
1A
2B
1C
1B
10A
3A
Patient
10%

CURRENT TREATMENT

The Evolution of Efficacy With Interferon Based Therapy Over the Last 10 Years



HCV TREATMENT
Standard of Care 2007

Confirm HCV Present
Determine VL and Genotype
Evaluate Histology
Evaluate Contraindications to Rx

Genotype 1 or 4

Peg IFN alfa 2a or 2b + ribavirin
(wt. based) for 48 wks

EVR Evaluation → Early d/c

SVR
40-45%

Genotype 2 or 3

Peg IFN alfa 2a or 2b + ribavirin
800 mg/qd for 24 wks

SVR
70-85%%

Pooled SVR
50-55% →

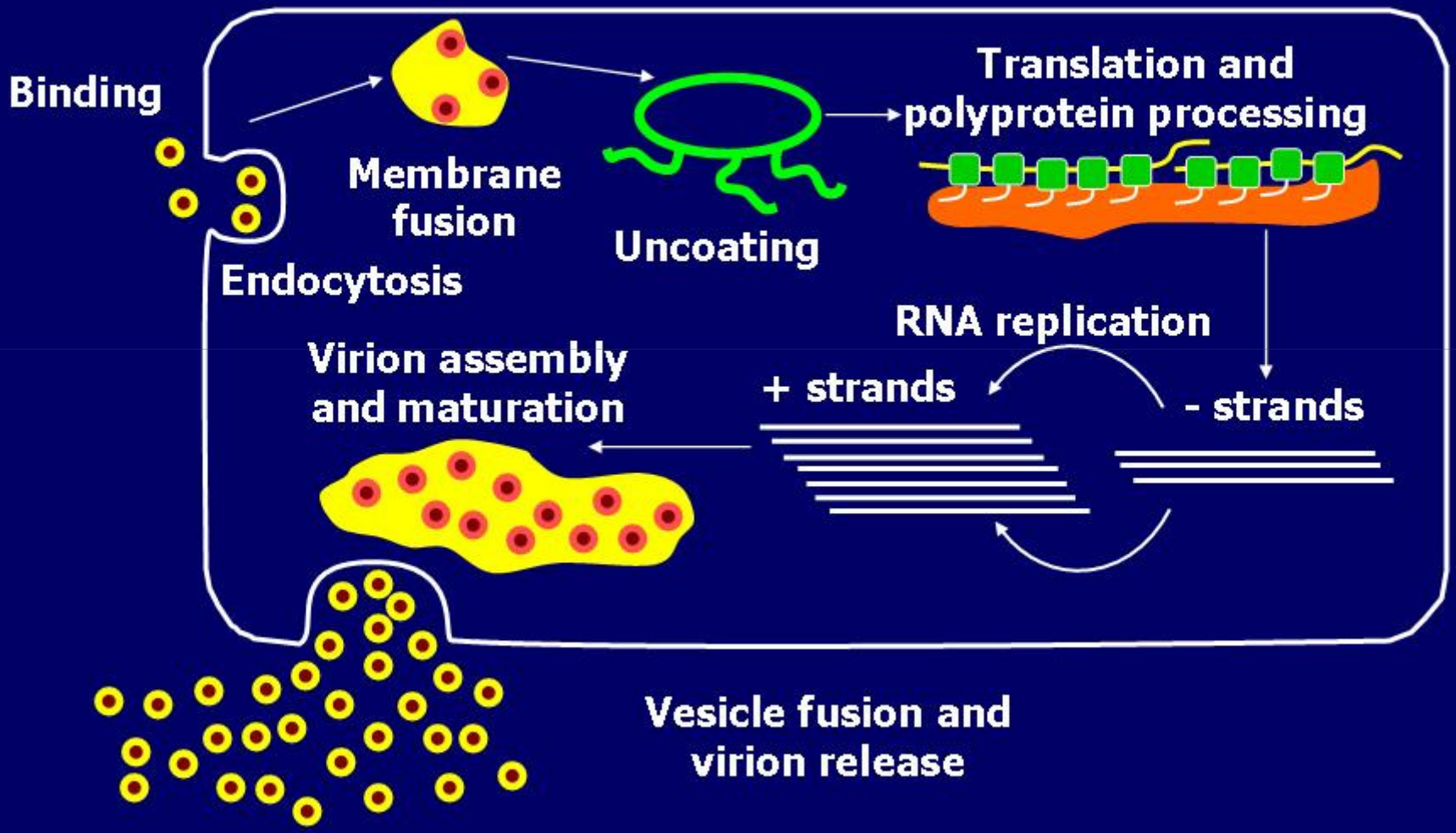
Worse Outcomes
Poor Adherance
Obesity
Immunosuppressed
Cirrhosis

FDA ANTIVIRAL ADVISORY COMMITTEE OCTOBER 2006

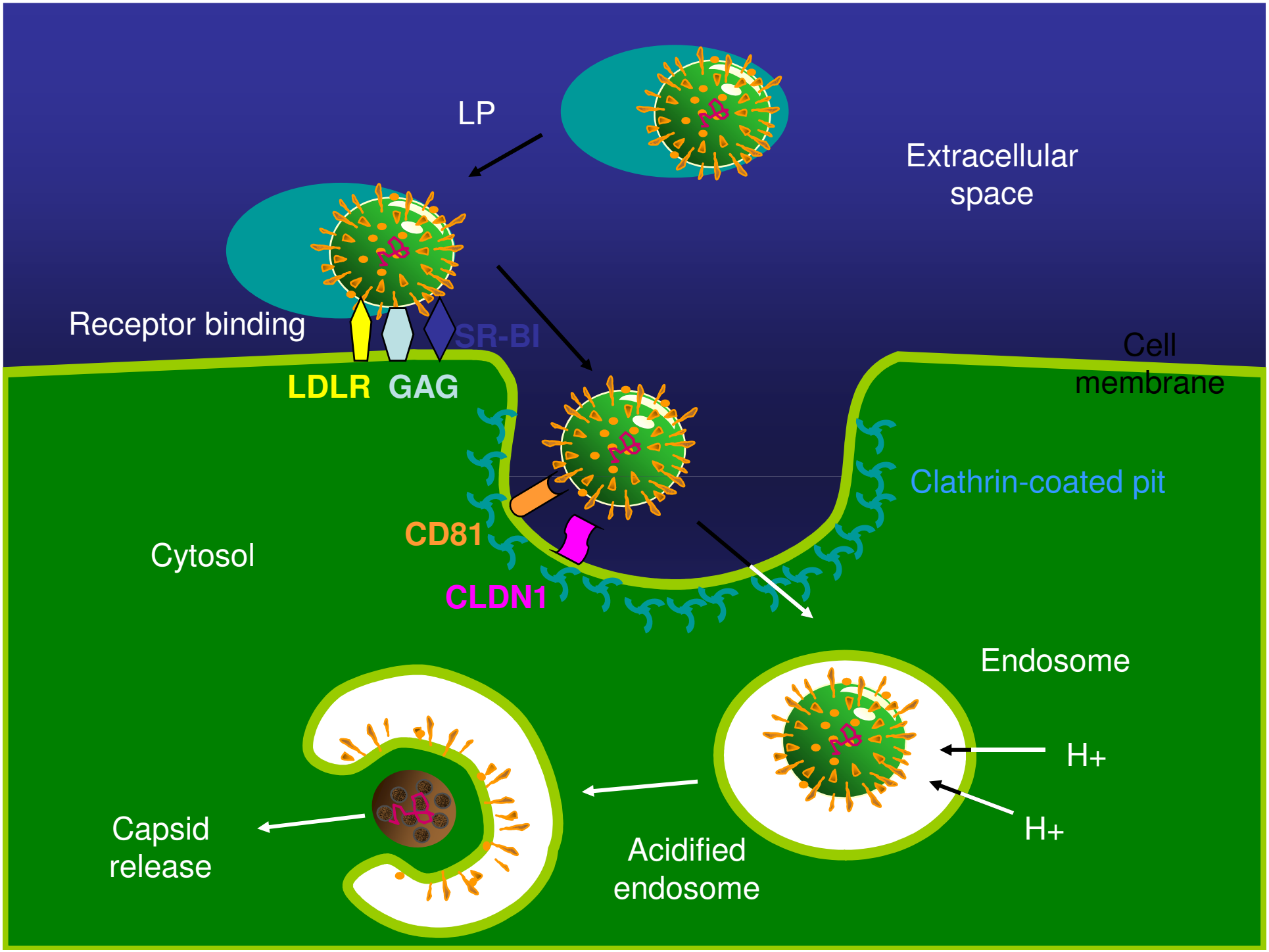
- Superiority should be required for first approval of small molecules
- Combination small molecule trials may be appropriate after Phase 2b evaluation of individual agents
- Prior to NDA studies MUST be initiated in special populations
  - HCV/HIV coinfection
  - Decompensated Liver Disease
  - Pediatric populations
- Appropriate representation of high prevalence minority groups is essential

Sherman et. al., HEPATOLOGY (in press)

HCV Life Cycle



Davis G et al. *Semin Liver Dis*. 1999(suppl 1):103-112.

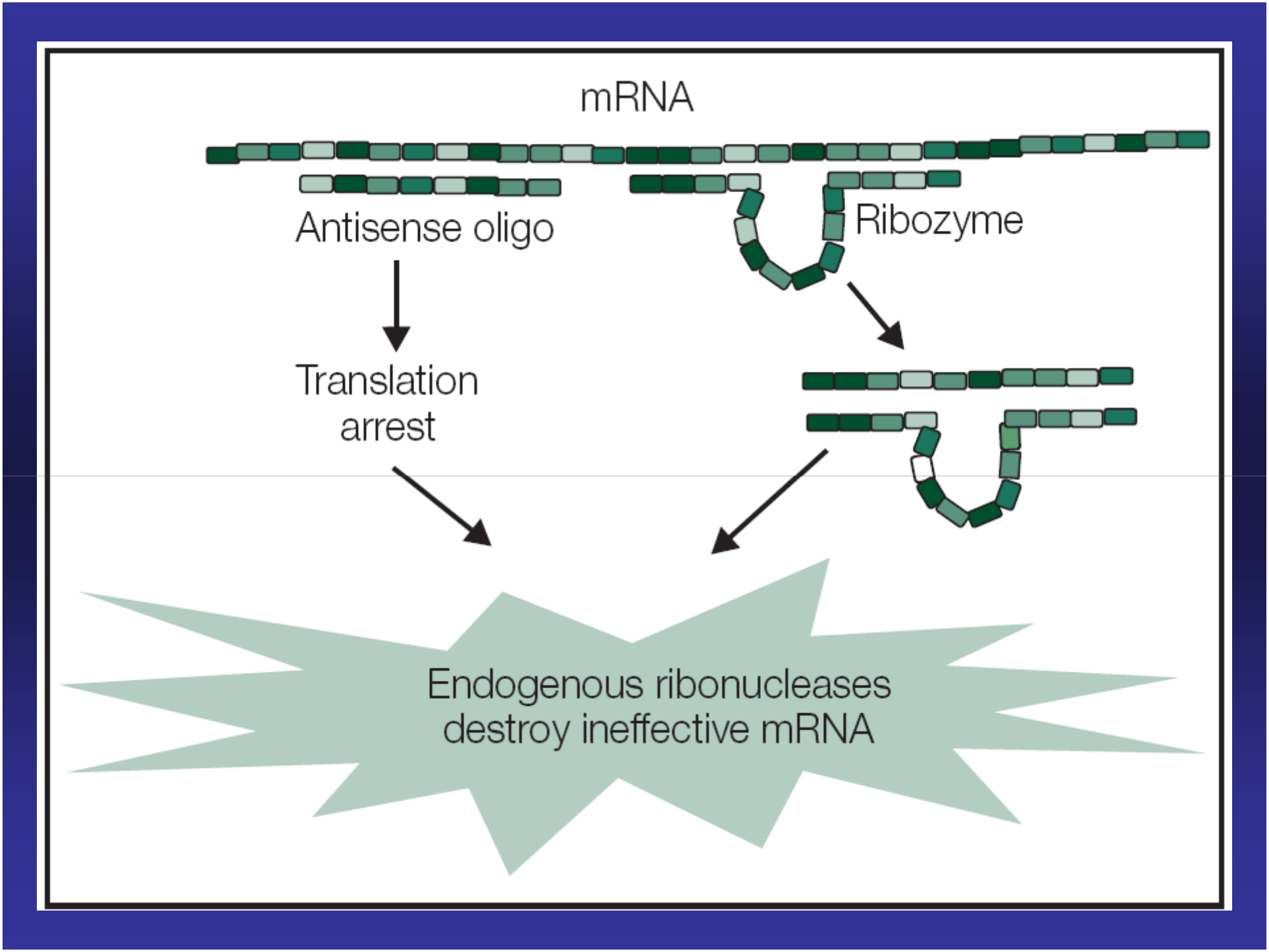

LP
Extracellular space
Receptor binding
SR-BI
LDLR
GAG
Cell membrane
Clathrin-coated pit
CD81
CLDN1
Cytosol
Endosome
H+
H+
Capsid release
Acidified endosome

Agents That Block Entry

- Antibodies
- Entry Inhibitors

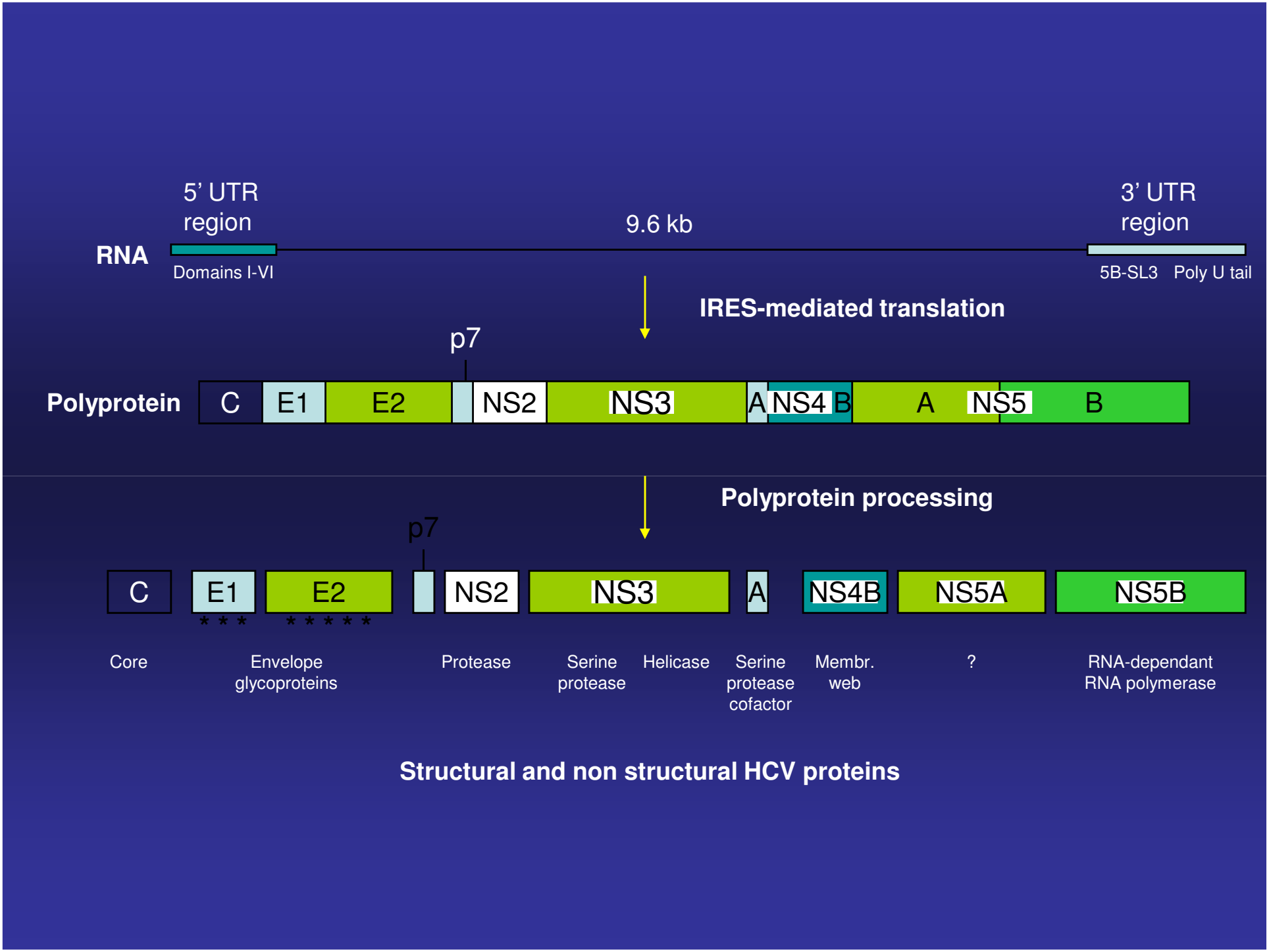
Agents That Block HCV Transport

- Antisense
- Ribozymes
- Small-interfering (si) RNA


mRNA
Antisense oligo
Ribozyme
Translation
arrest
Endogenous ribonucleases
destroy ineffective mRNA

Agents That Block Protease Function

- Protease Inhibitors
  - Blocks cleavage of structural proteins
  - Blocks cleavage of non-structural proteins from polyprotein
  - Blocks cleavage of non-structural proteins into individual proteins (NS3-NS4a serine protease inhibitors)



Structural and non structural HCV proteins

Agents That Block Transcription

- Polymerase Inhibitors
  - Nucleoside Analog
  - Non-nucleoside Analog
- Cyclophilin B Inhibitors
- Helicase Inhibitors

Inhibition of Viral Assembly and/or Release

- Alpha-glucosidase inhibitors
- Release Inhibitors

Innate Immune Response Modifiers

- Therapeutic Vaccines
- Immunomodulatory Agents
  - TLR Agonists
  - Peptides

EXPERIMENTAL HCV AGENTS

- Protease Inhibitors
  - BILN-2061
  - VX-950 (Telaprevir)
  - ITMN- 191
  - TMC-114
  - SCH 503034 (Boceprevir)
  - ACH-806
- Polymerase Inhibitors
  - Nucleoside Analogues
    - NM-283 (Valopicitibine)
    - A-837093
    - R1626
  - Non-nucleoside
    - AG-021541
    - HCV-796
    - BIL-1941
    - R-7128

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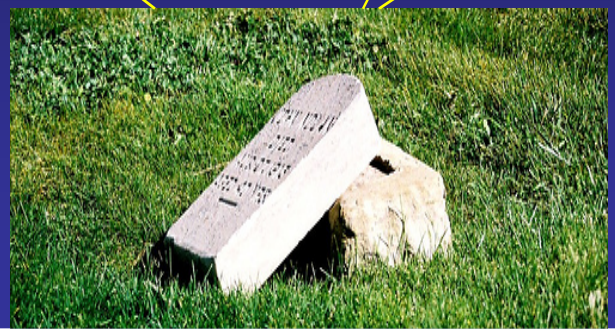
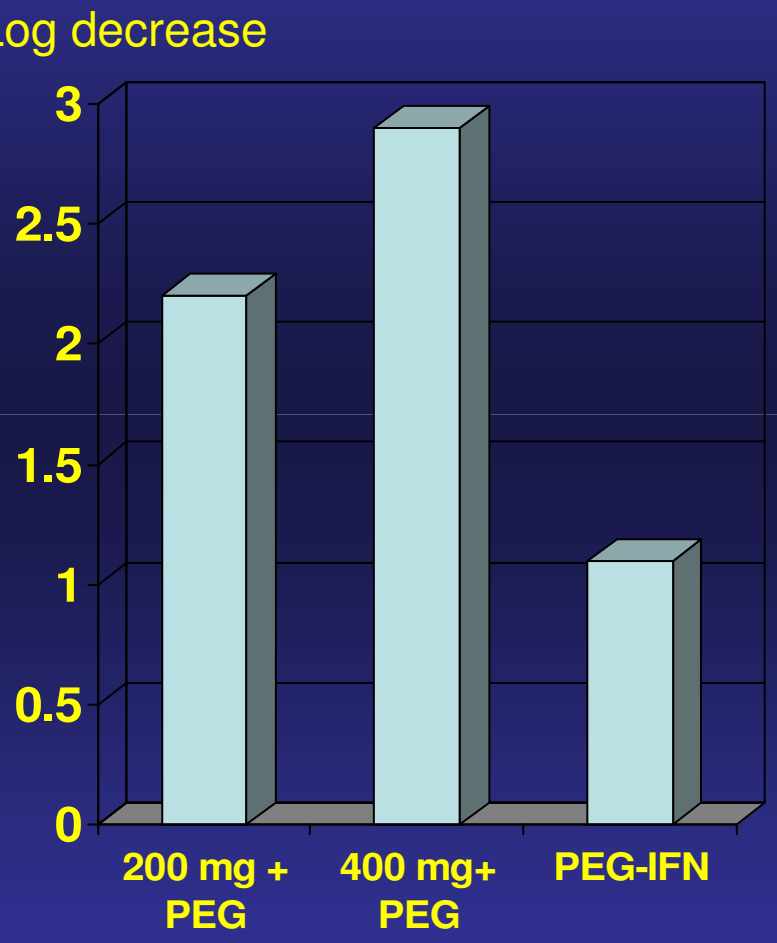


Experimental HCV Therapy Other Classes

- Alpha-Glucosidase 1 Inhibitor
  - Celgosivir
- Ribavirin Substitutes
  - Taribavirin (Viramidine)
- Caspase Inhibitor
  - PF-03491390 (IDUN 6556)
- TLR Agonists
  - CPG 10101
- Cyclophilin Inhibitors
  - DEBIO-025

SCH 503034
Boceprevir

- Non-responder to PEG-IFN + riba pts.
- Phase IIa trial
  - SCH 503034, 200 mg TID or 400 mg TID, for 7 days
  - Peginterferon alfa-2b, 1.5 µg/kg QW, for 14 days
  - SCH 503034, 200 mg TID or 400 mg TID plus peginterferon alfa-2b, 1.5 µg/kg QW, for 14 days
- RESULTS
  - 40% taking SCH 503034 + PegIFN reached limit of detection (29 IU/ml)



Zeuzem et. al. HEPATOLOGY ABS #201 2006

VX-950 Telaprevir

- Phase 1b study in HCV-infected patients
- N=34
- Regimen
  - VX-950 450 mg q8h
  - VX-950 750 mg q8h
  - VS-950 1250 mg q12h
  - Placebo
- RESULTS
  - Well tolerated with HA most common AE

Log Decline	450	750	1250	Placebo
0-1				6
1-2				
2-3	1		1	
3-4	7	3	9	
4-5		3		
>5	2	2		

Reesink et. al. HEPATOLOGY ABS#96 2006

VX-950
Telaprevir

- Viral mutation study
- N=16 Genotype 1 subjects
- Randomized
  - Telaprevir 750 mg q8h (VX-950) or
  - Telaprevir 750 mg q8h + peg-IFN
- HCV RNA mutations analyzed at Days 4,8,12,14

Kieffer T et. al. 2006 Hepatology Abs. 92

VX-950

- Median viral load decline
  - VX-950= 4.4 log
  - VX-950 + Peg-IFN= 5.5 log
- VX-950 Mutation Rate= 50%
  - R155 and A156V/T appeared at Day 8
  - R155K/T and V36M/A predominant by Day 14
- No mutations on combo therapy
- All patients put on Peg + riba at day 15 and undetectable at 3 months

Kieffer T et. al, 2006 Hepatology Abs. 92

VX-950
Telaprevir 12 Week Arm Results

- PROVE 1
- 250 subjects
- 3 groups (75 each) randomly assigned to telaprevir 750 mg every 8 hours, Pegasys 180 mcg/week, and ribavirin 1000-1200 mg/day for 12 weeks, followed by 0, 12, or 36 weeks of Pegasys plus ribavirin or Peg/riba control
- Analysis performed after 80 subjects reached week 12

- RESULTS
- 12 week HCV RNA –
  - Triple Drug: 70%
  - Control 39%
- Modified SVR (20 week)
  - Triple Drug 35%

McHutchison et. al. EASL 2007

ITMN-191
Polymerase Inhibitor

- Study in 2 replicon systems
- Mathematical analysis demonstrates synergistic effect between pegylated interferon alfa-2a and ITMN-191 in reduction of HCV replication

Tan et. al., HEPATOLOGY 2006, Abs 933

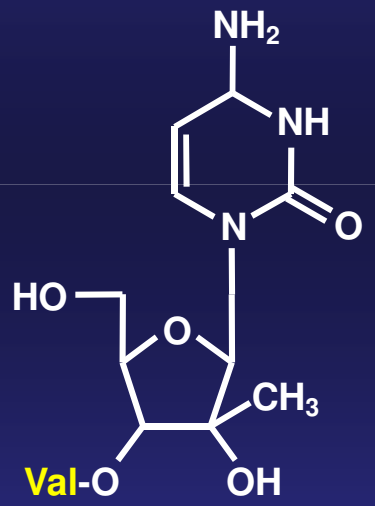
R1626
Polymerase Inhibitor

- Phase 1b
- N=41
- Randomization
  - 5 Arms including placebo with 4 doses in active treatment arms
  - Genotype 1 patients only
- Response
  - 3000 mg led to 2.64 log HCV RNA drop
  - 4000 mg led to 3.47 log HCV RNA drop
- Safety
  - Hematologic and other toxicities at highest dose (4500 mg)
- Phase II trial with Pegasys + riba in planning stage

Roberts S et. al., 2006 Abstract LB2

Valopicitabine
Polymerase Inhibitor

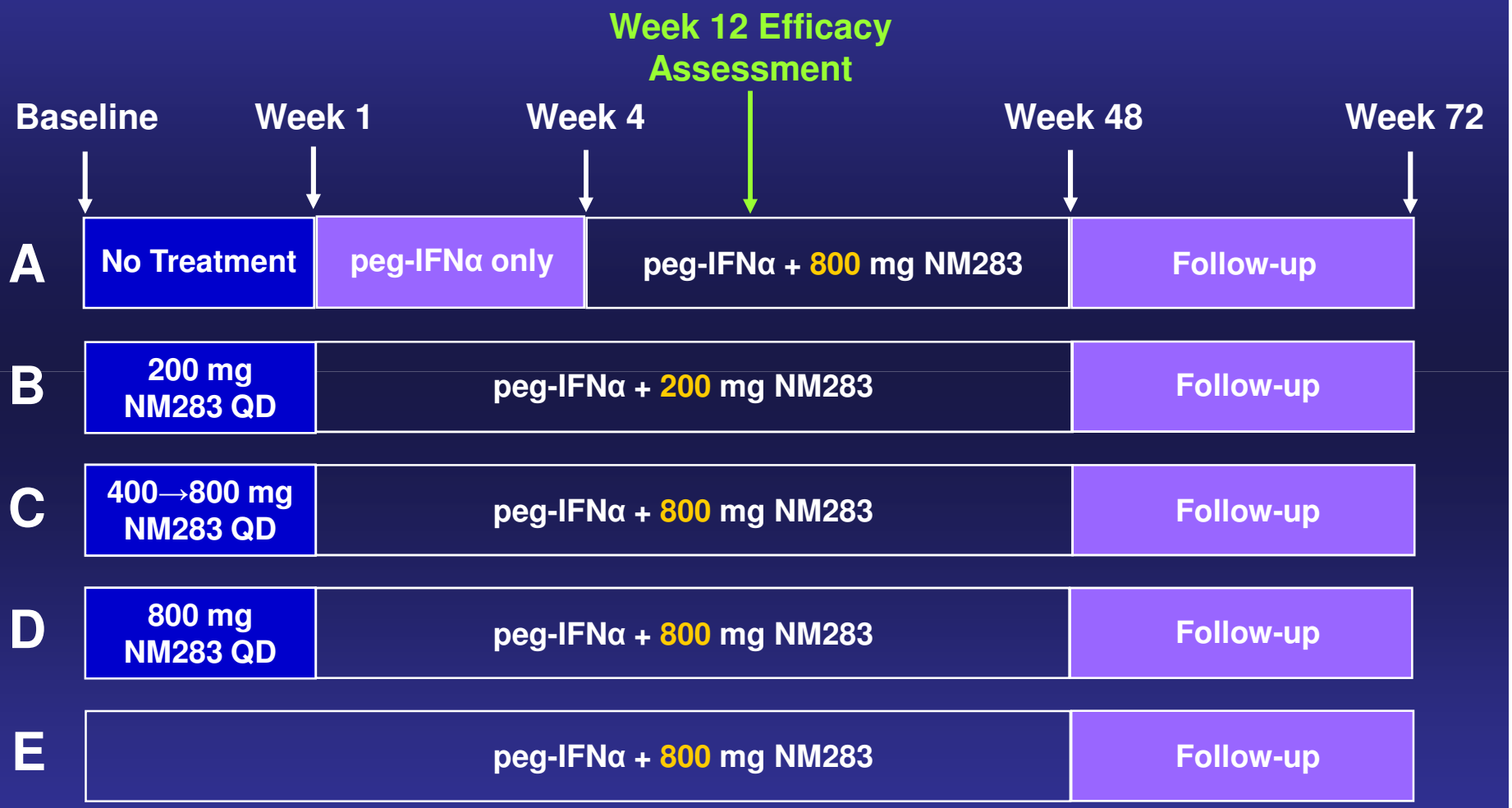
- **NS5b polymerase inhibitor**
  - **Ribonucleoside**
  - **NM107-triphosphate competitively inhibits viral polymerase and is incorporated into viral RNA, causing chain termination**
- **Oral agent**
  - **Valyl ester pro-drug provides high oral bioavailability**
  - **Plasma half life (4-6 hrs) & intracellular half life (15 hrs) support once daily dosing**



Valopicitabine (NM283)

2'-C-methylcytidine-3'-O-L-valine ester

Valopicitabine Phase IIb Treatment Naïve Study

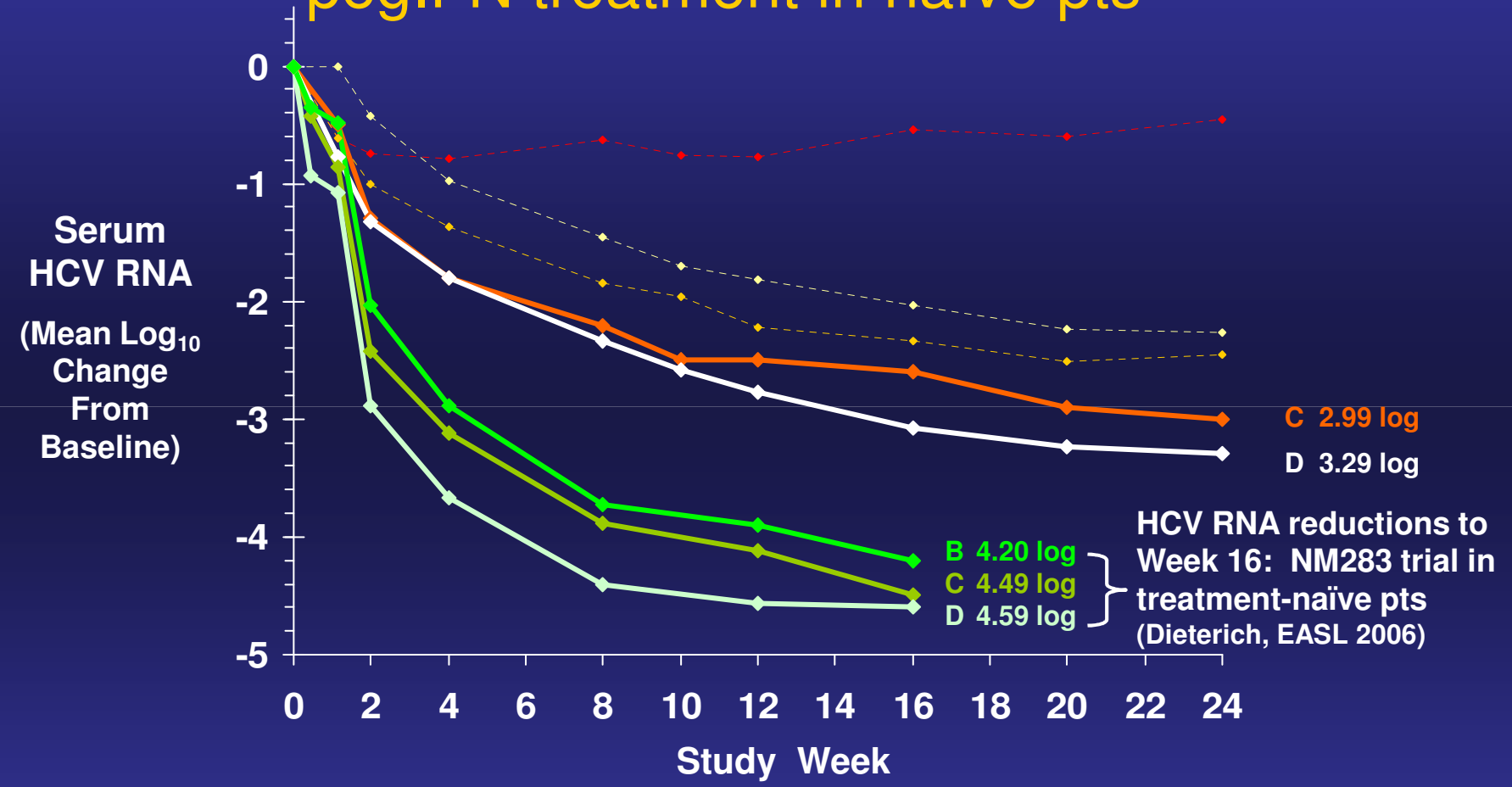


Week 12 HCV RNA Response Criterion to Proceed: ≥ 2 log drop

Lawitz et. al., HEPATOLOGY, 2006, Abs #93

Mean Reduction of HCV RNA

Greater HCV RNA reduction with same NM283 + pegIFN treatment in naïve pts



Non-responders

C	NM283 400→800 mg QD ramp (1st week)→ 800 mg QD +peg-IFN 180 µg QW	(n=41)
D	NM283 800 mg QD + peg-IFN 180 µg QW	(n=41)

Treatment-naïve

B	NM283 200 mg QD @ D1 + Peg-IFN 180 µg QW @ D8	(n=29)
C	NM283 400→800 mg QD ramp (1st week)→ 800 mg QD +peg-IFN 180 µg QW	(n=28)
D	NM283 800 mg QD + peg-IFN 180 µg QW	(n=28)

Sherman ISVHLD 2006

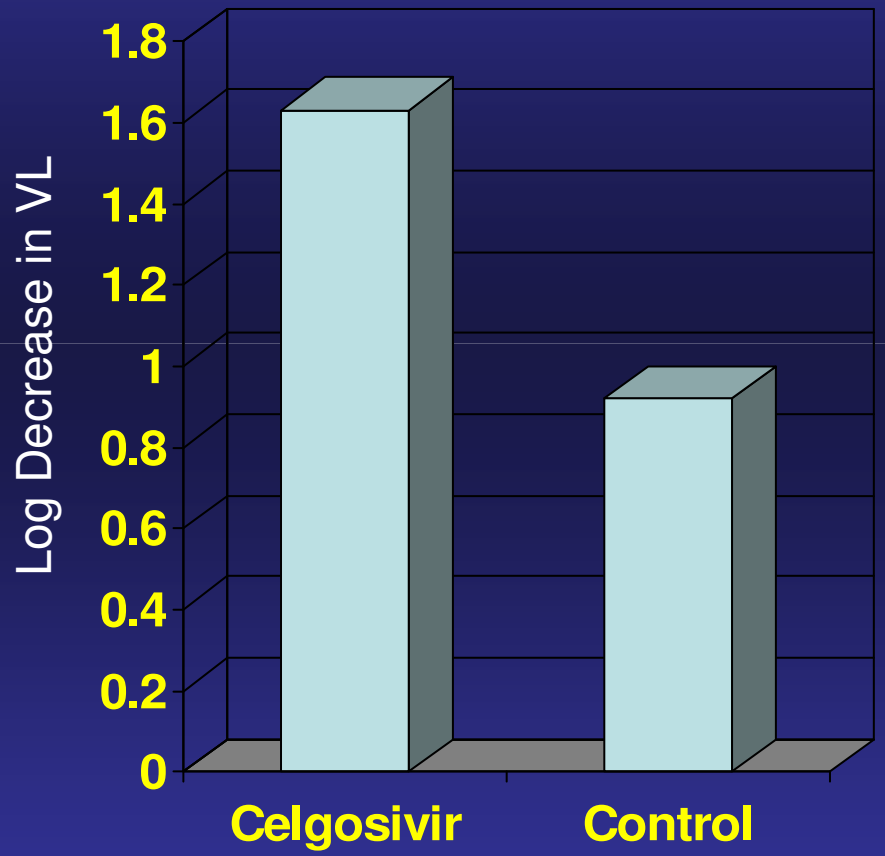
PF-03491390
Caspace Inhibitor

- Inhibitor of caspase which increases apoptosis of hepatocytes
- Design
  - N=204
  - Prior treatment non-responders
  - ALT> 1.5x ULN
  - Randomized to placebo or 3 dose regimens for 12 weeks
- Results
  - All active treatment arms significantly ($p<0.001$) reduced ALT and AST levels vs. Placebo arm
  - Non-significant dose response observed

Shiffman et. al., HEPATOLOGY, 2006 Abs 95

Celgosivir

- Phase II trial
- N=36
- Genotype 1 NR
- Peg-IFN alfa-2b + riba + celgosivir vs. Peg-IFN + riba
- 12 Week Response Reported



Kaita et. al., DDW 2007

LIMITATIONS OF SMALL MOLECULE BASED THERAPIES

- Safety
  - NM-283 (Valopicitibine) GI toxicity- No longer in development
  - BILN-2061 Animal cardiotoxicity- No longer in development
  - VX-950 (Telaprevir)- Rash
  - ACH861- Nephrotoxicity
  - HCV796- Hepatotoxicity
- Antiviral Activity
  - Genotype specific to varying degrees
  - Unknown whether wide quasispecies variation in population will limit therapy
  - Maximal SVR unknown for any agent
- RESISTANCE
  - Observed within 14 days with all protease inhibitors
  - Higher barrier of resistance to nucleoside analogues

Pre-existing mutation HCV/HIV Coinfected Patients

- Comparison of signature mutations for NS3 protease inhibitor
- Design
  - 38 coinfected patients sequenced
  - 250 monoinfected sequences from GenBank analyzed
- A156G/T changes evaluated
- Results
  - Mutation found in 7.8% of coinfected vs. 0.8% of monoinfected ($p<0.02$
  - All changes in coinfected among those who received prior HIV protease inhibitors

Morsica et. al, HEPATOLOGY 2006 Abs 436

SUMMARY

- Many targets for directed HCV therapy are available
- Some agents show promise, but development is slow and should not delay treatment in individual patients now
- Expect need for Pegylated Interferon for the foreseeable future