2014 7th PARIS HEPATITIS CONFERENCE

13 & 14 January 2014

PARIS - Palais des Congrès

International Conference on the Management of Patients with Viral Hepatitis

Protease, polymerase and NS5A inhibitors: w

Raymond F. Schinazi, PhD, DSc

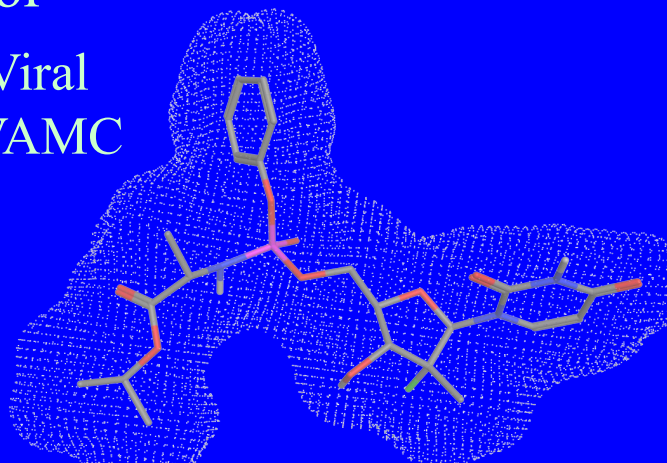
Frances Winship Walters Professor

Director, Scientific Working Group on Viral Eradication, Emory University CFAR/VAMC

Center for Drug Discovery

Paris, France– January13, 2014

rschina@emory.edu



Winning Combination For Anti-HCV Therapy
One size fits all

- Once a day or once a week/month oral Rx towards a **Cure** – Single pill. Easier for all.
- Pan-genotypic (1-6)
- Very high barrier to clinical resistance
- Short duration of Tx – < 12 weeks
- Safe with no or manageable side effects (no IFN or Ribavirin)
- High efficacy or **Cure** rates for all HCV diseases - Lowers cost to healthcare – Cost effective
- Suitable & affordable for all populations

HIV Regimen Simplification

1996

> 30 Pills a Day

Tenofovir DF
(2001)

Emtricitabine
(2003)

- Truvada
- (2004)

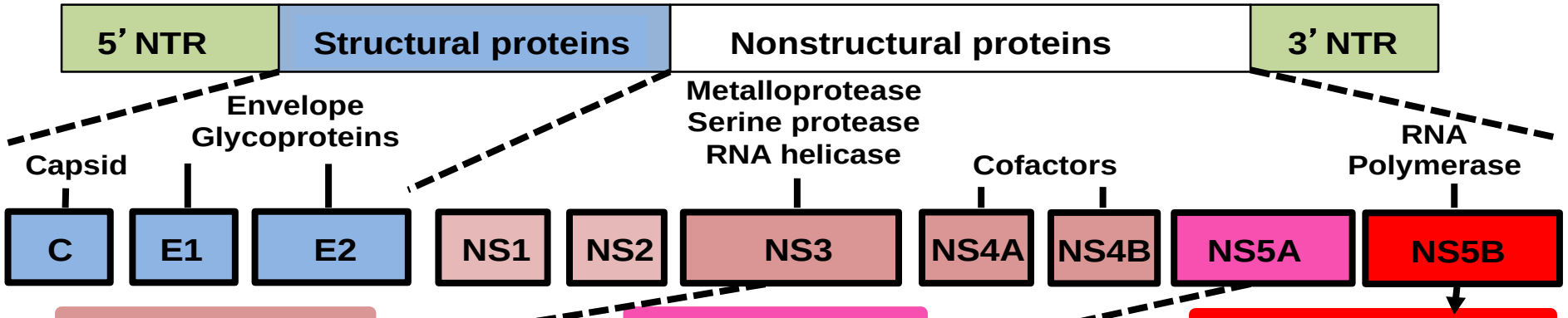
Gilead

Efavirenz
(1998)
BMS, Merck

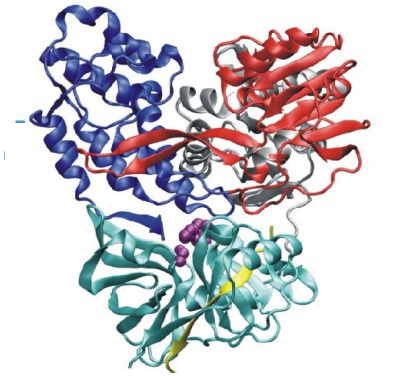
2006
Introduction of Atripla

1 Pill Once a Day

Market Will See An Influx of New Drugs Over the Next Few Years

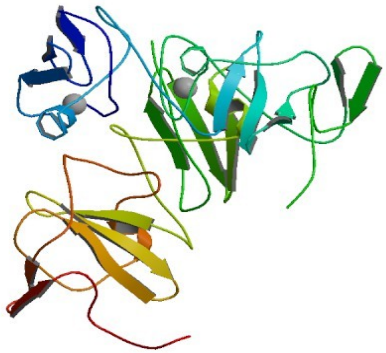


NS3/4A Protease Inhibitors



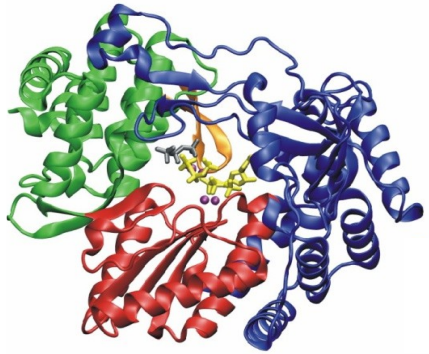
- Telaprevir
- Boceprevir
- Simeprevir
- Faldaprevir
- Asunaprevir
- ABT-450
- MK-5172
- Sovaprevir
- ACH-2684

NS5A Inhibitors



- Daclatasvir
- Ledipasvir
- ABT-267
- GS-5816
- ACH-3102
- PPI-668
- GSK-2336805
- Samatasvir
- MK-8742

NS5B Polymerase Inhibitors



Nucs	Non-Nucs
Sofosbuvir	ABT-333
VX-135	Deleobuvir
IDX-20963	BMS-791325
ACH-3422	PPI-383
GS-9669	
TMC-647055	

Nucleoside dominate in terms of Efficacy, resistance profile and pangenotypic activity (2014)

			DAA		
	PI, 1st Generation	PI, 2nd Generation	NS5A Inhibitors	NS5B Nucleoside Inhibitors	NS5B Non Nucleoside Inhibitors
Efficacy	🟡	🟢	🟢	🟢	🟡
Resistance Profile	🔴	🟡	🟡	🟢	🔴
Pangenotypic Efficacy	🔴	🟡	🟡	🟢	🔴

🟢 Good profile 🟡 Average profile 🔴 Least favorable profile

Changing HCV Nucleoside Landscape

DPN-PD (A/G-like)
(RFS Pharma)
Preclinical

In development

On hold with FDA

Development status unknown

Development discontinued

IDX184 (G) & IDX-19368 (G) (Idenix)
Phase 2b
Clinical hold/abandoned

IDX20963 (U)
(Idenix)
Preclinical hold

BCX-5191
(Biocryst)
Preclnical

RG7348
(Roche-Ligand)
Phase I stopped

R1626 (C)
(Roche)
Safety issues

RG7432
(Roche)
Phase I stopped

MK-0608 (A)
(Merck)
Preclinical

TMC649128
(Medivir)
Insufficient activity

PSI-661 (G)
(Gilead/PSI)
Preclinical

GS-6620
(Gilead)
Phase 1
Suboptimal PK/activity

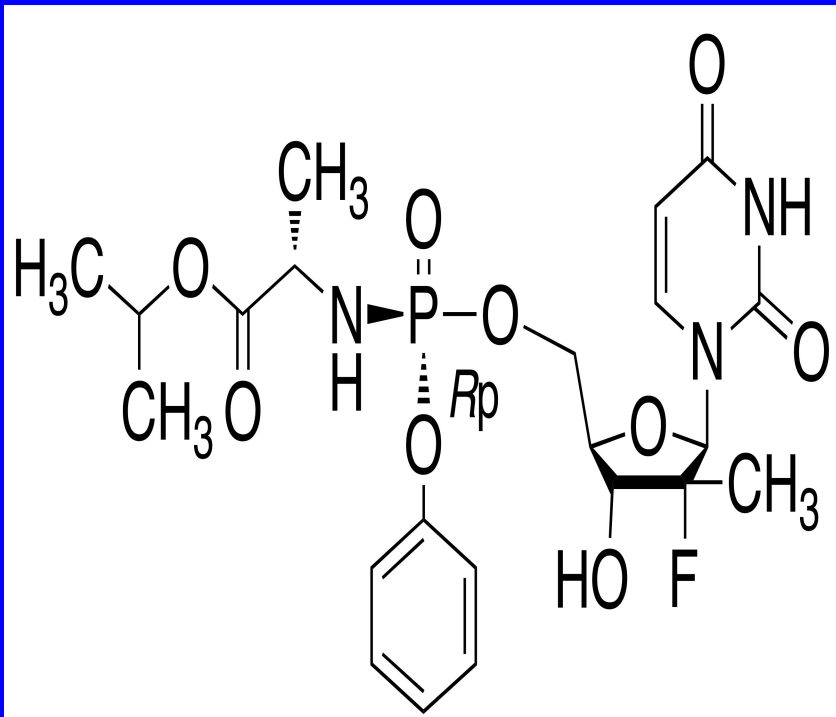
NM-283 (C)
(Idenix)
GI toxicity

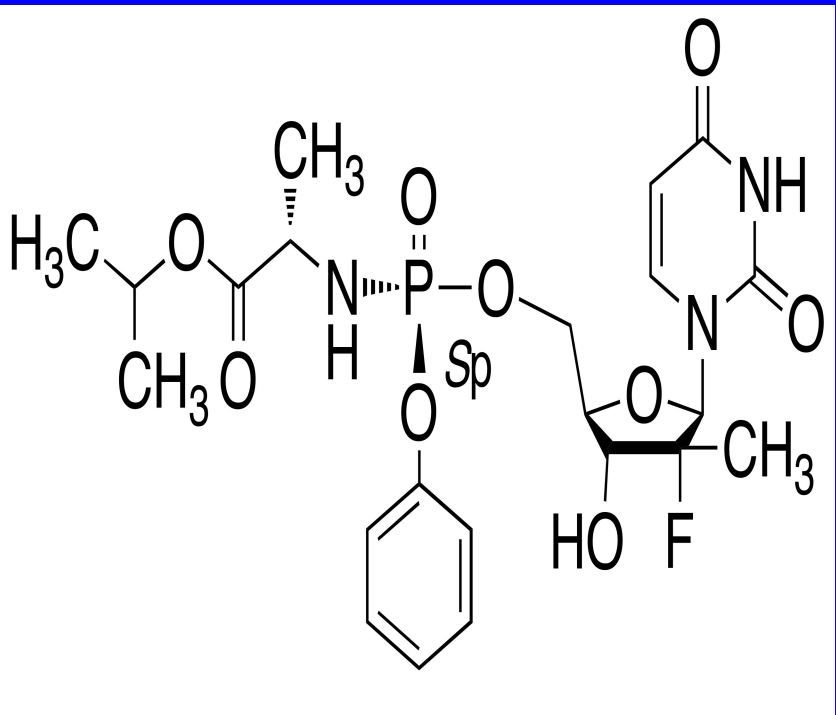
PSI-938 (G)
(Gilead/PSI)
Phase 1
Liver toxicity

ALS-2158
(Vertex/Alios)
Phase 1

INX-189 (G)
(BMS/Inhibitex)
Phase 2a
Cardiotoxicity

Activity of Diastereomericaly Pure Nucleotide Phosphoramidates





PSI-7976

HCV 1b replicon: EC90 = 7.5 µM (WT);

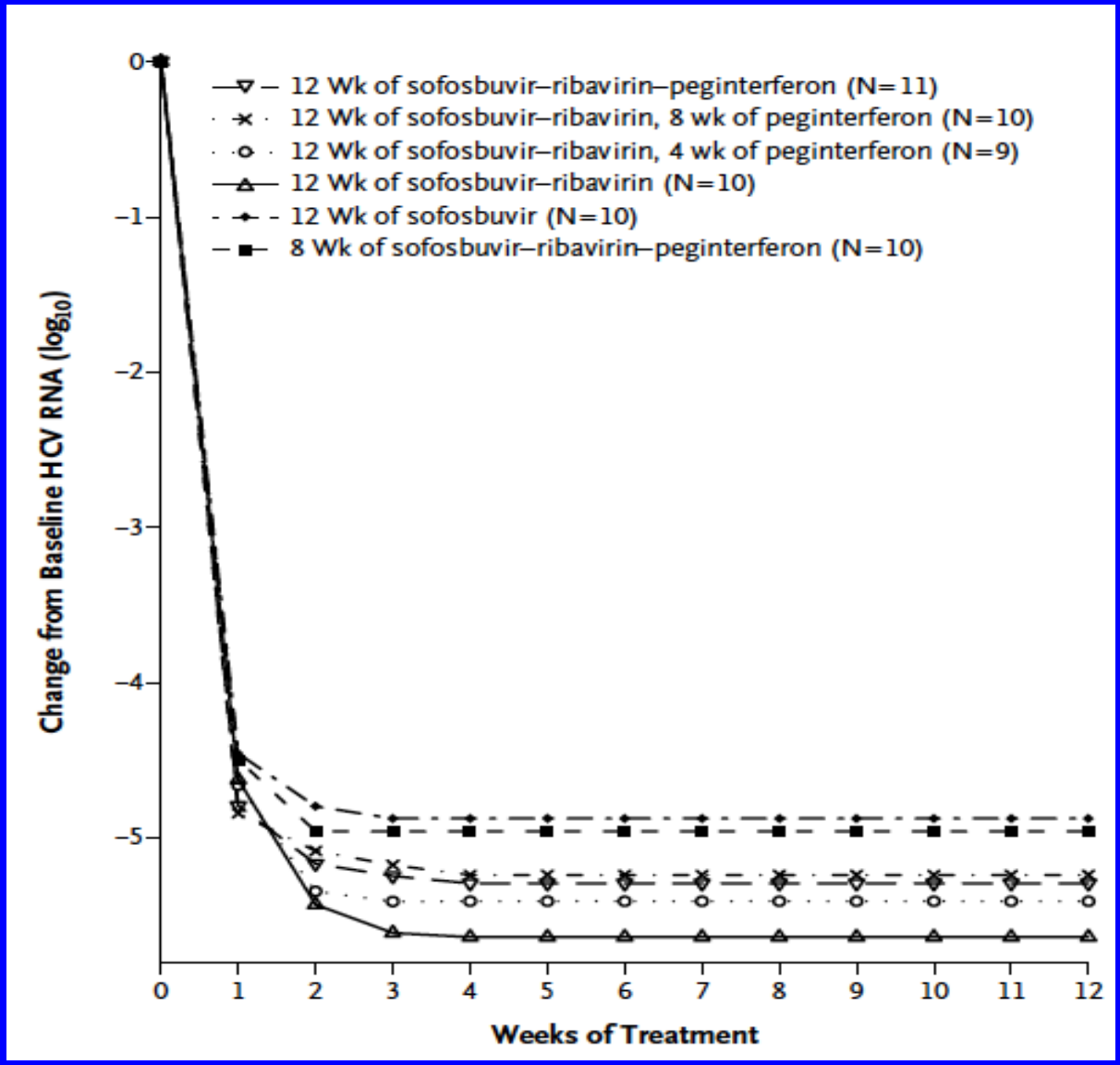
> 100 µM (S282T); 1.3 µM (S96T)

PSI-7977 (Sofosbuvir)

HCV 1b replicon: EC90 = 0.42 µM (WT);

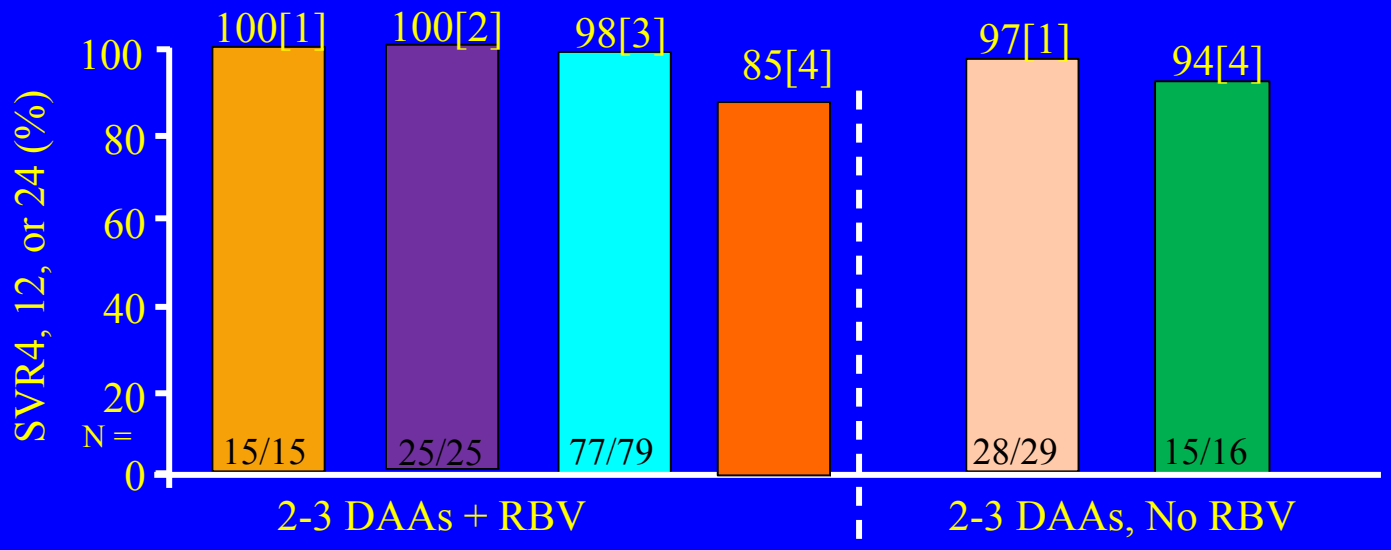
7.8 µM (S282T); 0.11 µM (S96T)

Sofosbuvir + RBV
G1 and also Genotype 2 and 3



Gane et al. NEJM 2013

Impressive Clinical Results with Different Combinations



- Sofosbuvir (Nuc) + Daclatasvir (NS5A) + RBV x 24 wks
- Sofosbuvir (Nuc) + GS-5885 (NS5A) + RBV x 12 wks
- ABT-450/r (PI) + ABT-333 (NNI) + ABT-267 (NS5A) + RBV x 12 wks
- Faldaprevir (PI) + Deleobuvir (NNI) + RBV x 24 wks (G1b)
- Sofosbuvir (Nuc) + Daclatasvir (NS5A) x 24 wks
- Daclatasvir (NS5A) + asunaprevir (PI) + BMS 791325 (NNI) x 12 wks

Ribavirin-Free Regimen

Shift in focus to difficult to treat persons

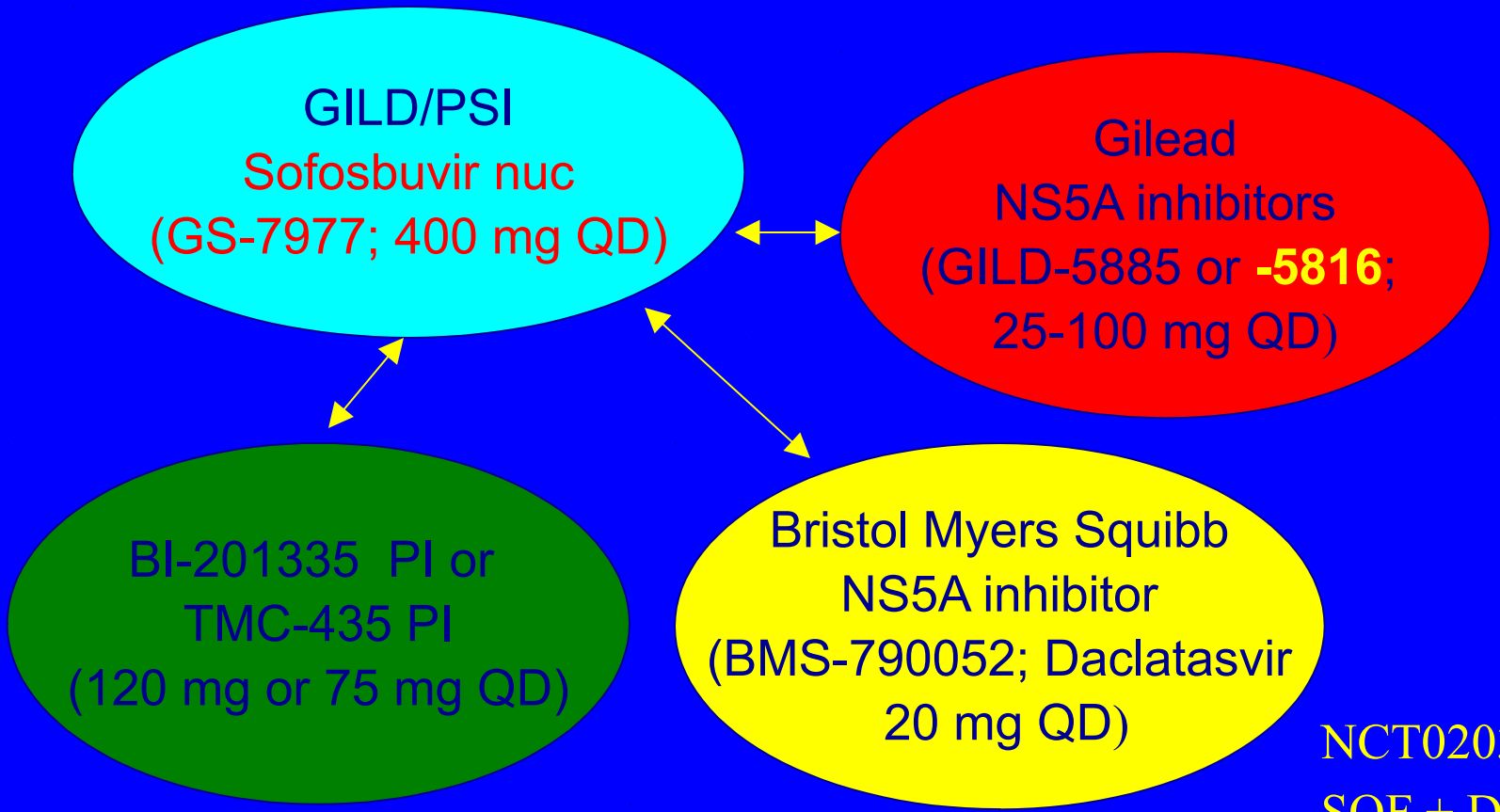
Several unmet needs remain:

- DAA/PR failures – DONE
- Null-responders – DONE
- Co-infected with HIV or HBV – ALMOST DONE
- non-GT1, especially GT3 – DONE
- IFN intolerant or contraindicated - DONE
- Cirrhosis - ALMOST DONE
- Bleeding disorders (hemolysis)
- Transplant subjects - ALMOST DONE
- Pediatrics & Mother to child transmission
- Opiate substitution therapy– ALMOST DONE

What Will Happen in the Real World? Two potent pangenotypic DAA will be

Inter/Intra-Company Combinations

Good Example: Two Molecules QD
(Truvada-like for HCV – IFN & Riba-free)



AASLD 2012: 7977+5885+ Riba = 100% SVR4

NCT02032875
SOF + DAC
Pan-genotypic?

Ideal 2 DAA Combo

TWO nucleoside analogs – Why?

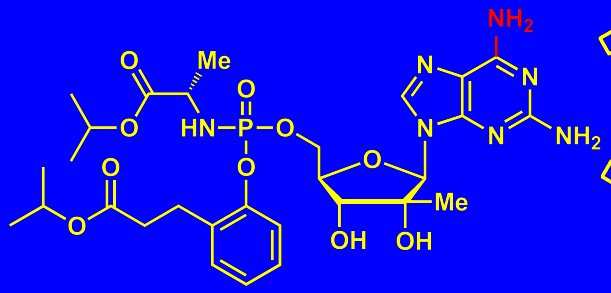
- Pan-genotypic
- High genetic barrier to resistance - Almost impossible to select resistant viruses to two nucs
- Long intracellular half life
- Highly potent

How about one drug that delivers two nucleosides intracellularly?
One pill does it all – no coformulation & low price

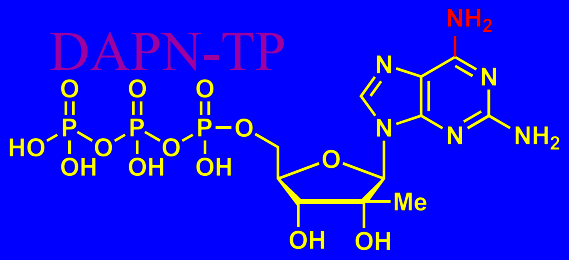
No need for second DAA could be the wave of the future

DAPN-PD (RS-1389) Delivers an A- and G-Triphosphate Analog

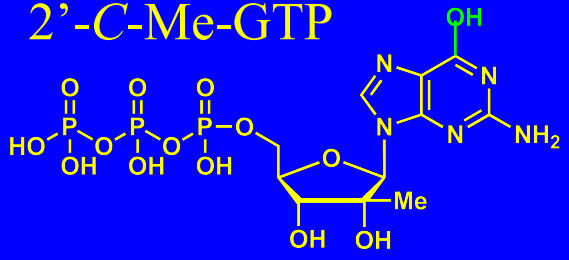
- RS-1389



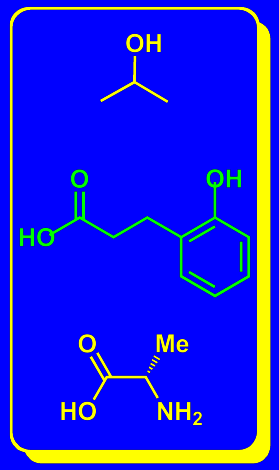
DAPN-TP



- 2'-*C*-Me-GTP



+



HCV 1b Replicon (μM) Huh7 cells)

EC50 = 0.7 ± 0.2 (5 fold increase)

EC90 = 2.5 ± 0.2

Cytotoxicity (μM)

Huh7 CC50 > 100

PBM CC50 > 100

CEM CC50 > 100

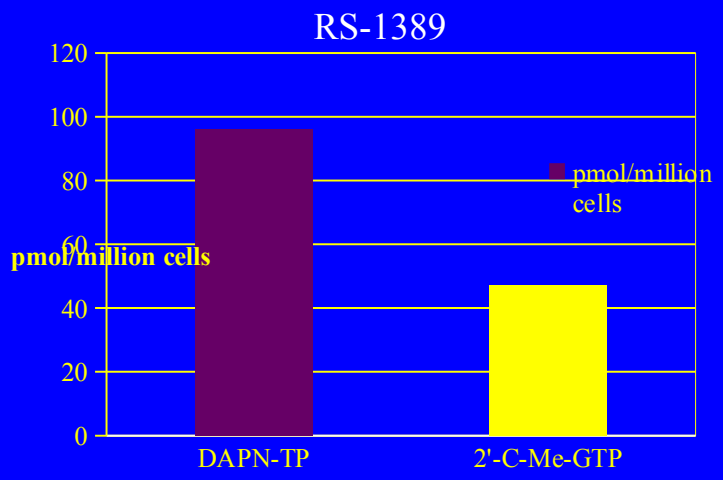
Vero CC50 > 100

Bone marrow > 100 μM

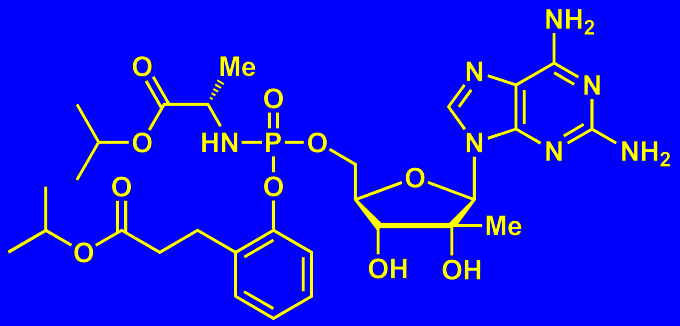
Mitochondria: > 100 μM

Ames test > 1000 μM

Incubation in human hepatocytes at 50 μM for 4 h (n = 6)



Conclusions

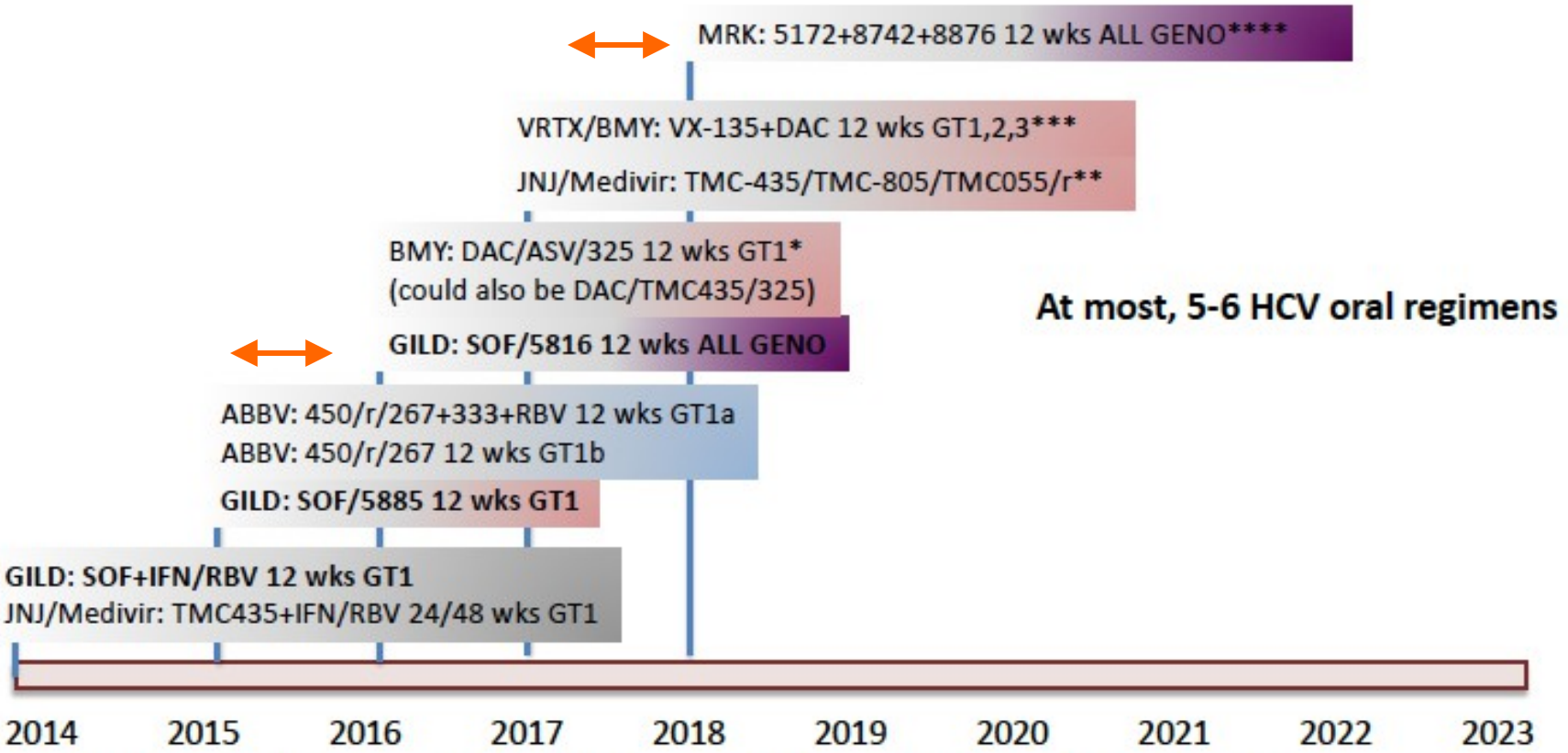


RS-1389

- *RS-1389 represents a new series of investigational drug for treatment of HCV*
- DAPN PD are non-toxic in multiple cell culture systems including mitochondria
- Non-mutagenic in AMES test
- No apparent hERG inhibition observed in a cardiomyocyte assay up to 100 μM
- The delivery of two nucleotide analogs (best class – A & G analog) with different viral RNA incorporation profiles may improve clinical potency and/or prevent selection of mutant viruses

Market Time Lines: Shaping the Future

If current strategies were to be successfully developed and approved with no major hiccups:



At most, 5-6 HCV oral regimens

*ASV has shown liver tox signals at higher doses; overall regimen is BID because PI needs BID dosing

** JNJ acquired GSK's NS5a inhibitor GSK2336805

***VX-135 on partial clinical hold, safety concerns and lower efficacy key risks

**** MK-5172 has liver tox signal, is not pan geno at safer 100mg dose; 8876 just going into the clinic

"The best is yet to come"

Supported by NIH, CFAR, and the Department of Veterans Affairs
COI: I am a founder & shareholder of Idenix & RFS Pharma LLC