DAA therapy – a (r)evolution in Hepatitis C therapy

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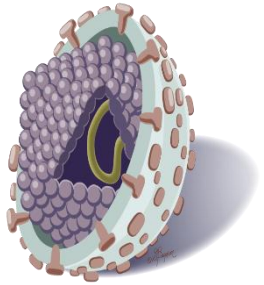
NOhep

ELIMINATE ~~HEPATITIS~~

NOhep

2019 marked the 30th anniversary since the formal discovery of Hepatitis C virus ("non-A non-B")



- **1989** Choo *et al (Chiron and CDC)* sequenced the *Hepatitis C virus*

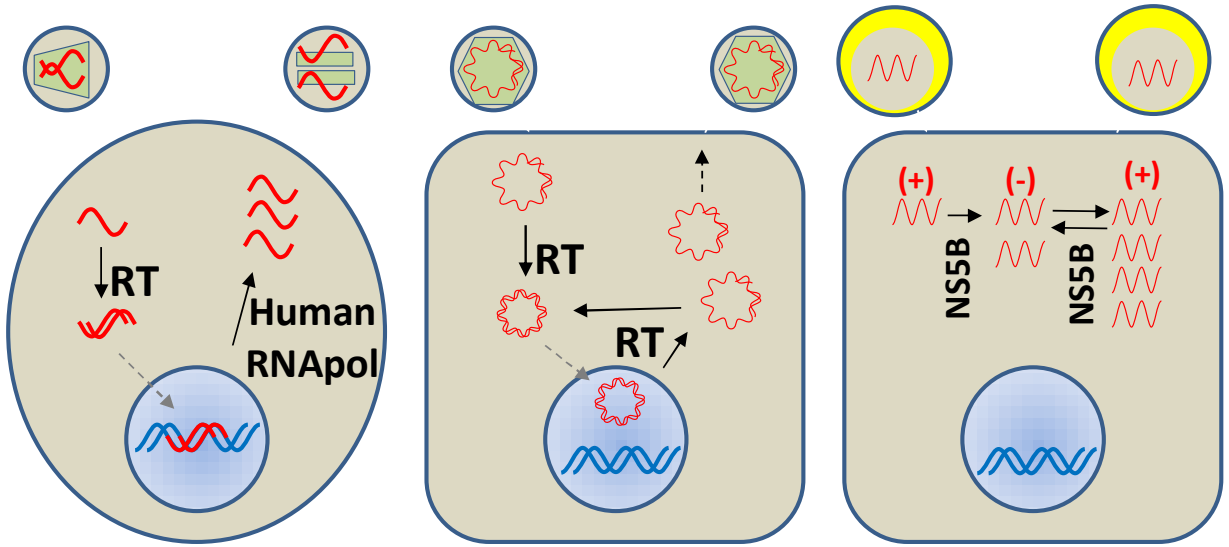
- *1st* HCV antibody assay 1990 : prevented > 40 000 new infections/year from blood transfusions

- Since 1997 no new cases of Post-Transfusion Hepatitis have been described

Qui-Lim Choo, Michael Houghton, George Kuo, Daniel Bradley. Science. 1989;244:359-362

Goal of HCV treatment is viral cure

HCV life Cycle favors resistance development not persistence



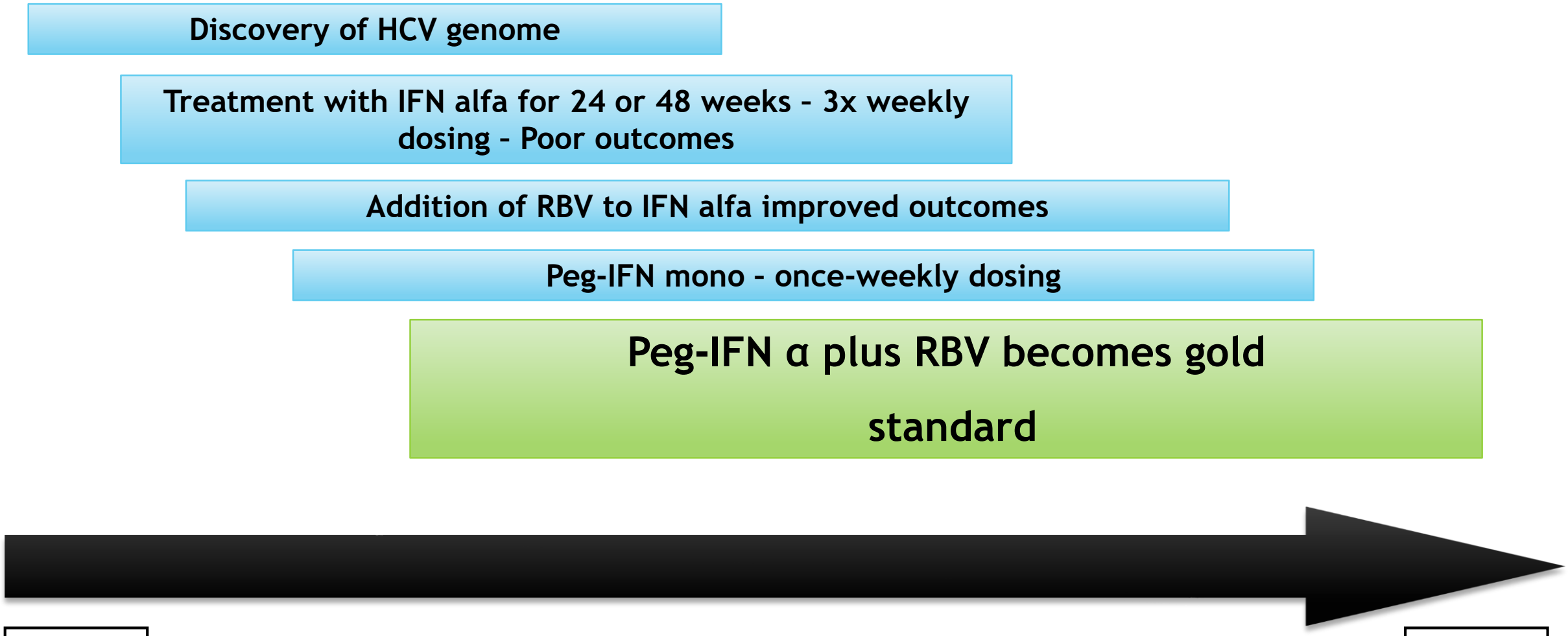
	HIV	HBV	HCV
Stable genome	Provirus	cccDNA	(none)
Virion NA polymerase	Host RNApol	HBV RT	HCV NS5B
Error-prone replications per cell	One	Multiple	Multiple
Plasticity of genome	High	Constrained	Very high
Recombination	Common	Common	Rare

From Interferon to why now HCV elimination is a reality…

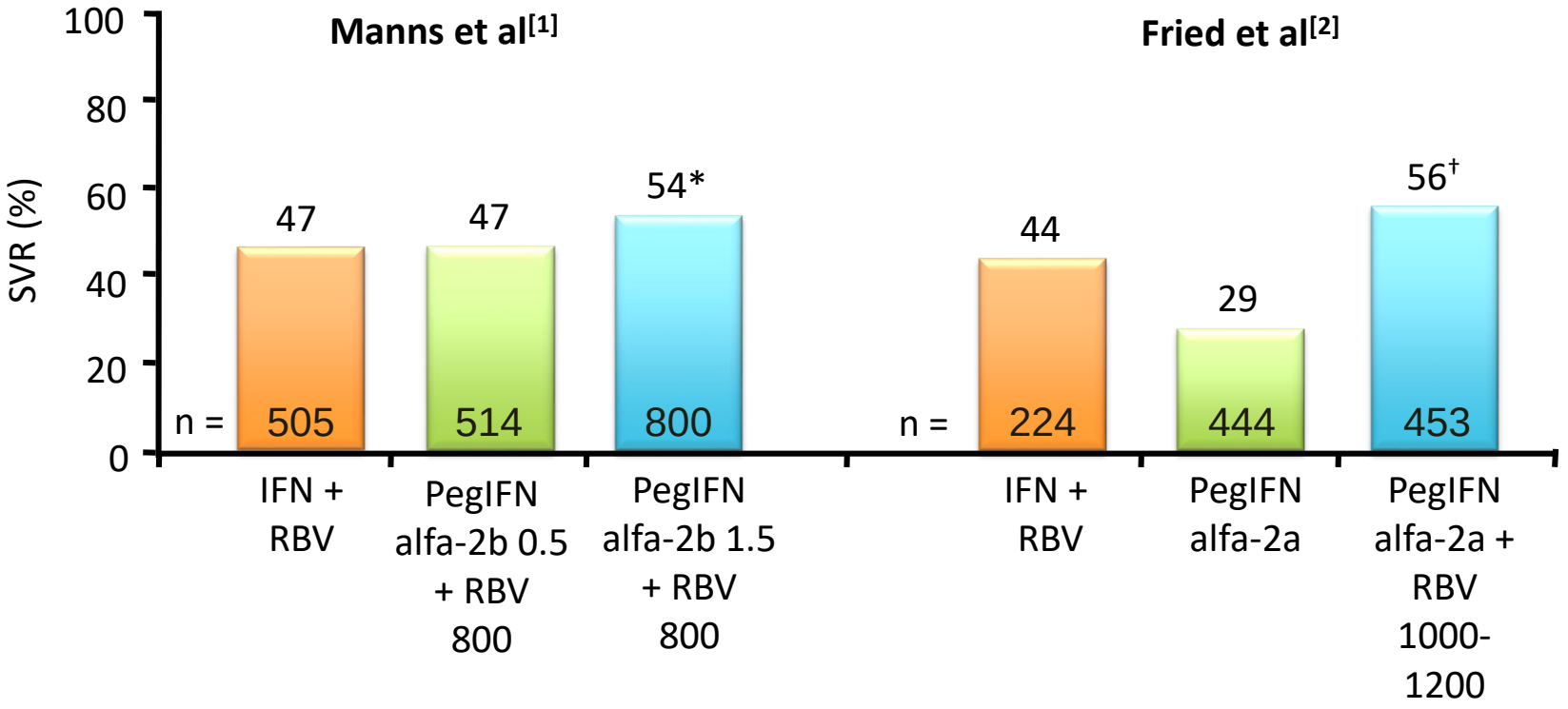
HCV – the beginning

- Interferon (and ribavirin)
- Many adverse effects
- Not suited to many patients

Evolution of hepatitis C treatment



SVR with Peg-IFN + RBV combination Rx

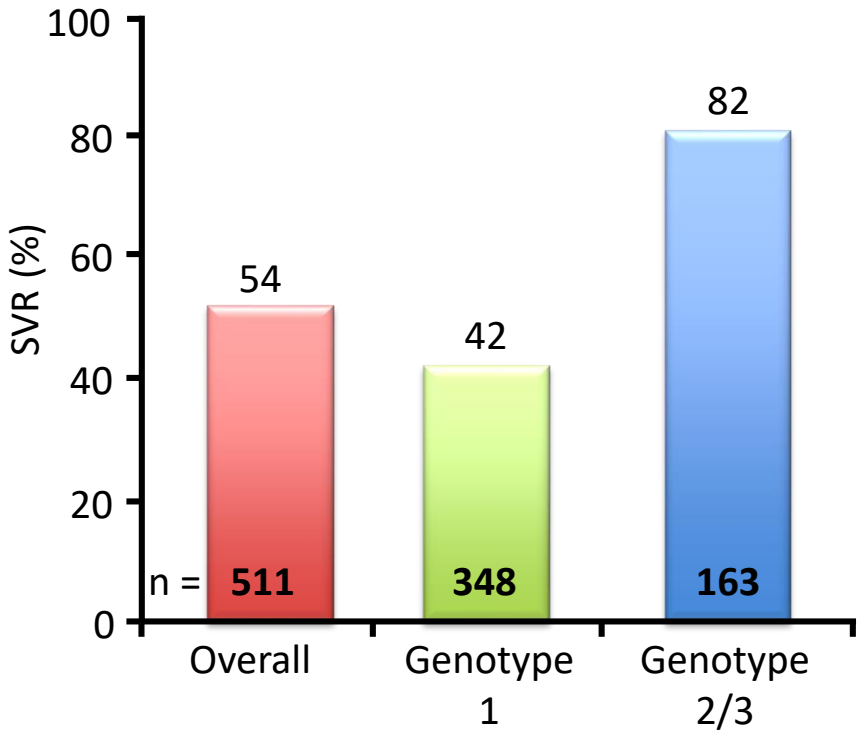


*P = .01 vs both arms, †P = .001 vs both arms

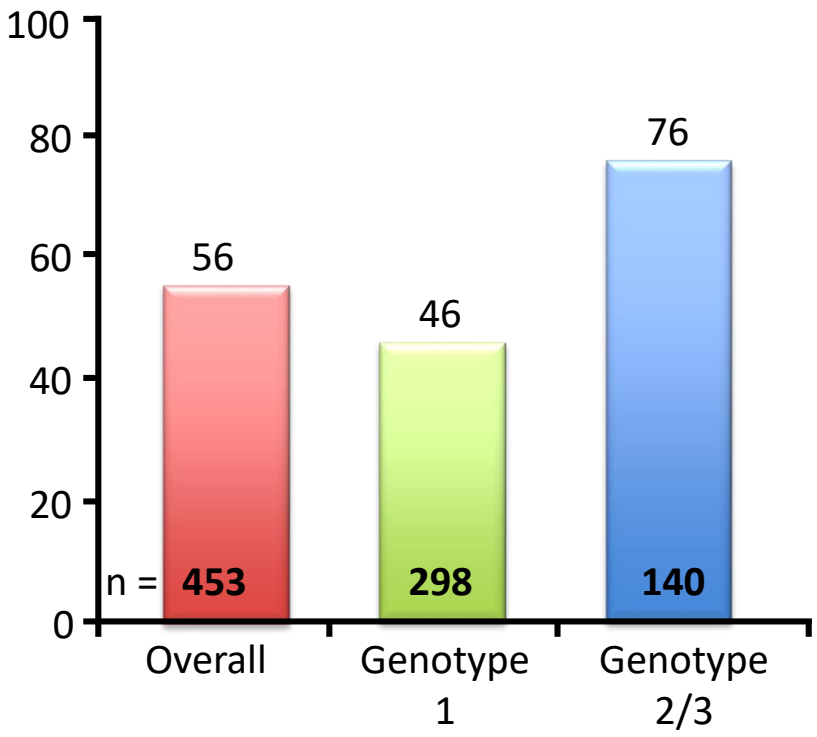
1. Manns MP, et al. Lancet. 2001;358:958-965. 2. Fried MW, et al. N Engl J Med. 2002;347:975-982.

Impact of Genotype on SVR Rates

- PegIFN alfa-2b 1.5 µg/kg/wk + RBV 800 mg/day for 48 wks

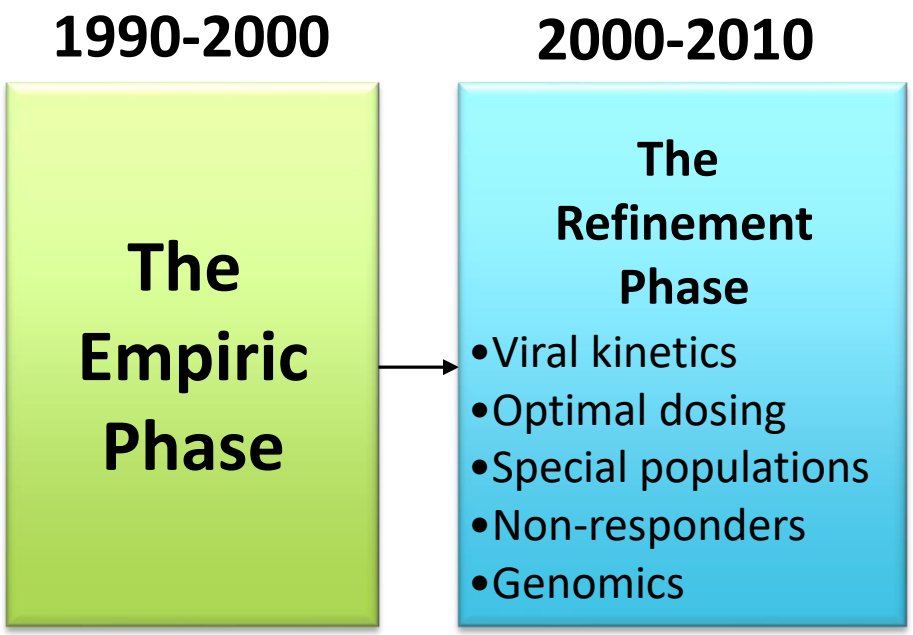


- PegIFN alfa-2a 180 µg/wk + weight-based RBV (1000 or 1200 mg/d) for 48 wks



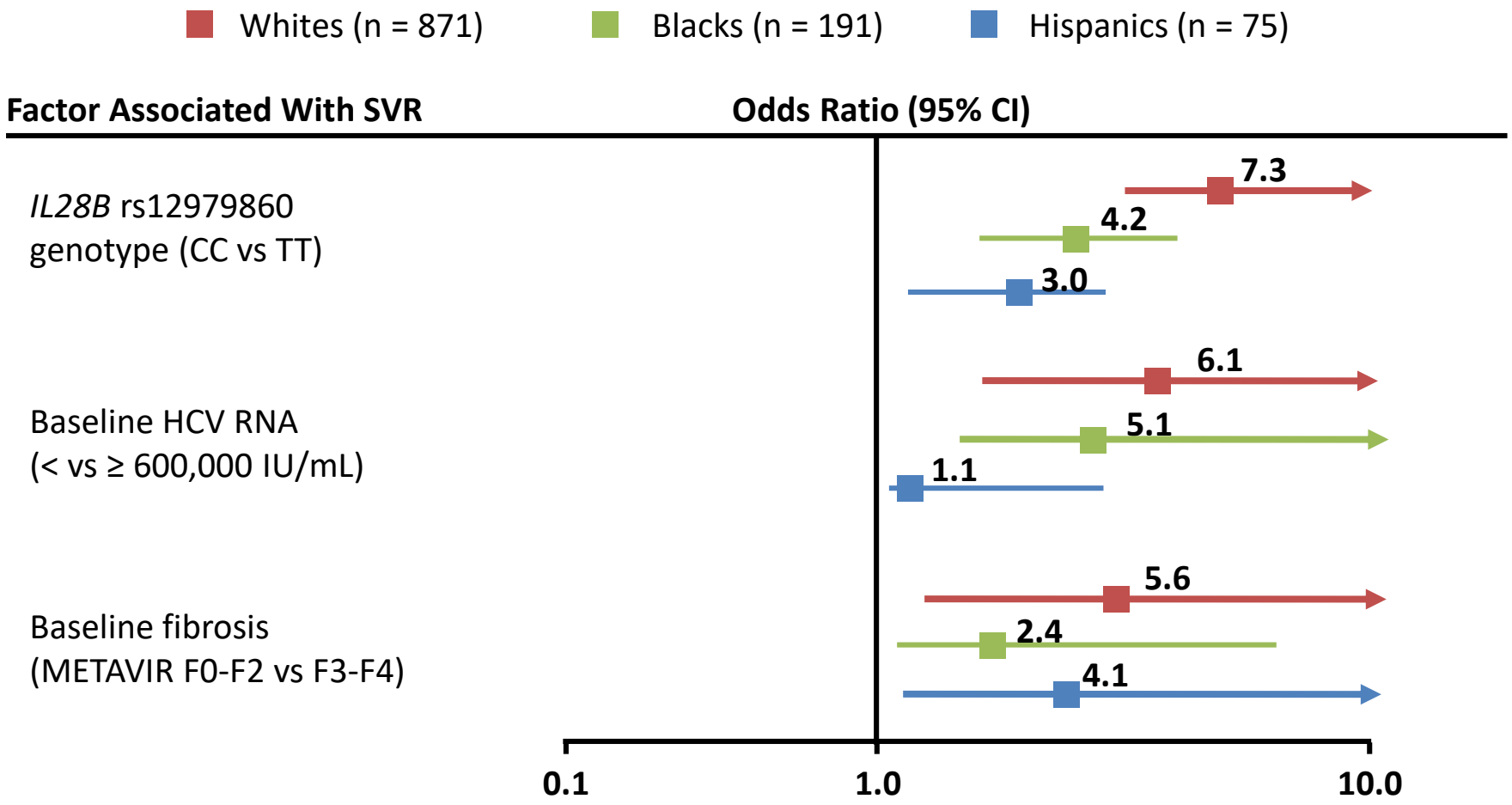
Manns M, et al. Lancet. 2001;358:958-965. Fried MW, et al. N Engl J Med. 2002;347:975-982.

The (r)evolution of HCV therapy



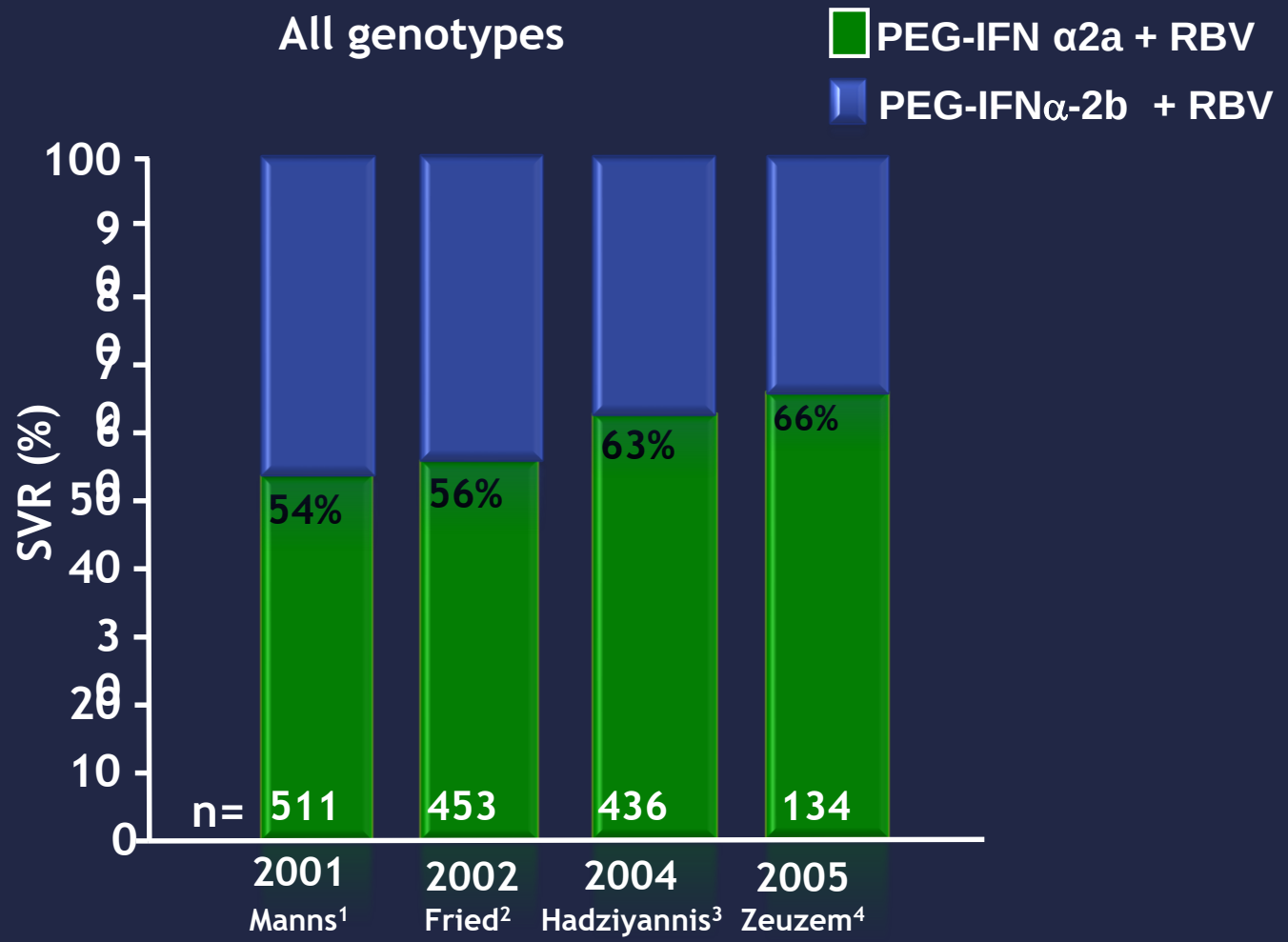
Weisberg IS, Sigal SH, Jacobson IM. *Current Hepatitis Reports.* 2007;6:75-82.

Major predictive factors ~2010



Ge D, et al. Nature. 2009;461:399-401.

Summary 1989 - 2011 : SVR rates increase over time but 30–50% of patients do not achieve SVR



1. Manns M, et al. Lancet 2001; 358: 958; 2. Fried M, et al. N Engl J Med 2002; 347: 975;
3. Hadziyannis S, et al. Ann Intern Med 2004; 140: 346 4. Zeuzem S, et al. J Hepatol 2005; 43: 250

1st generation NS3 Protease Inhibitors

2 HCV (NS3) Protease Inhibitors approved in 2011

- Active ONLY against HCV GENOTYPE 1
- TELAPREVIR (*INCIVO*^{R}*)* and BOCEPREVIR *(VICTRELIS*^{R})
- As triple therapy in combination with PEG-IFN and RBV
- SVR ~75% with treatment potentially at 24 weeks

HCV Treatment Landscape 2011-2013

	GT1	GT2/3	GT4/5/6
2010	PEG/RBV 48 week	PEG/RBV 24 week	PEG/RBV 48 week
2011 - 2013	PEG/RBV/PI 24-48 week		

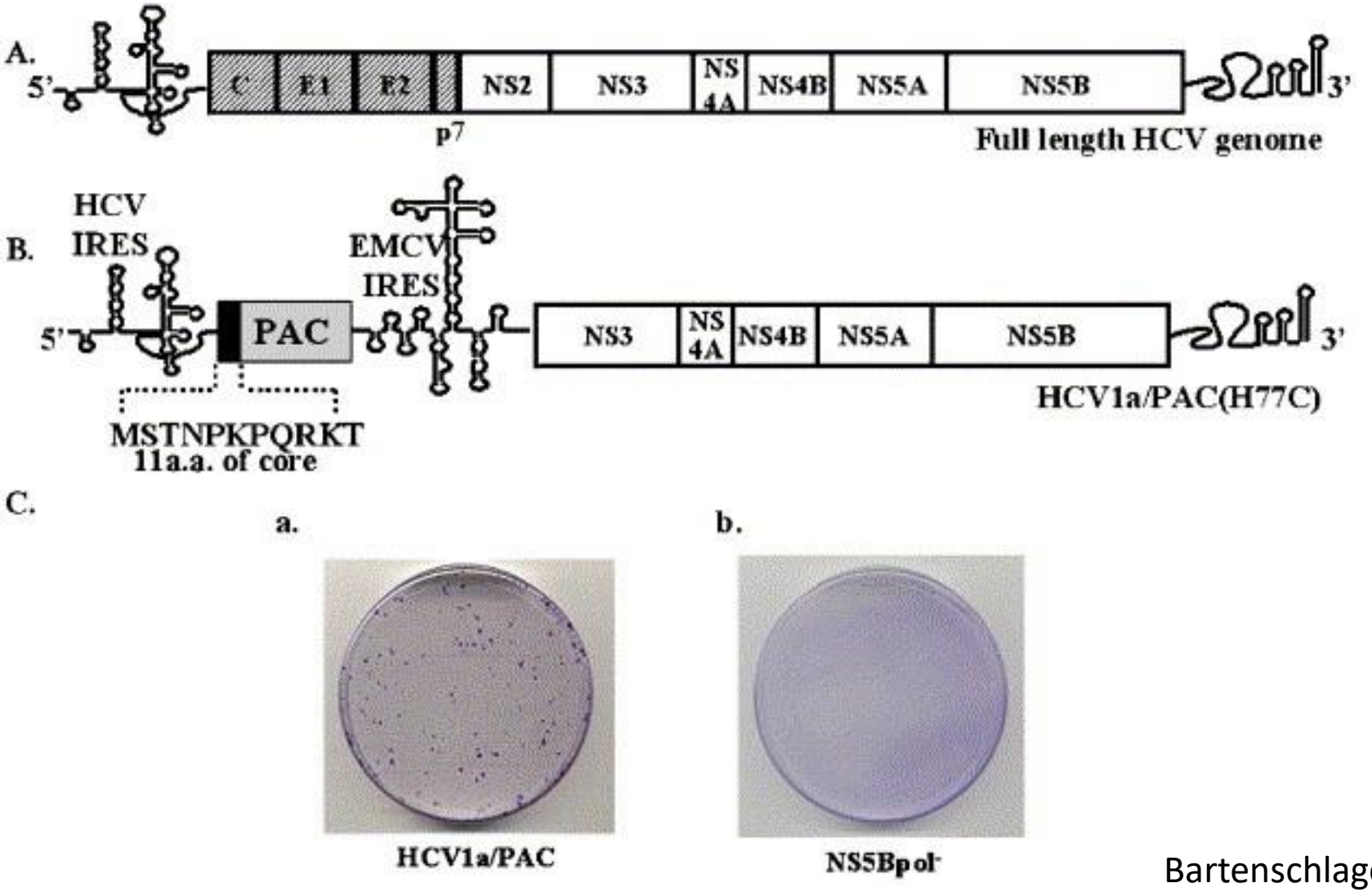
PI = protease inhibitor (Telaprevir/Boceprevir)

HCV – The way to a cure

Ralf Bartenschlager, Germany, University of Heidelberg

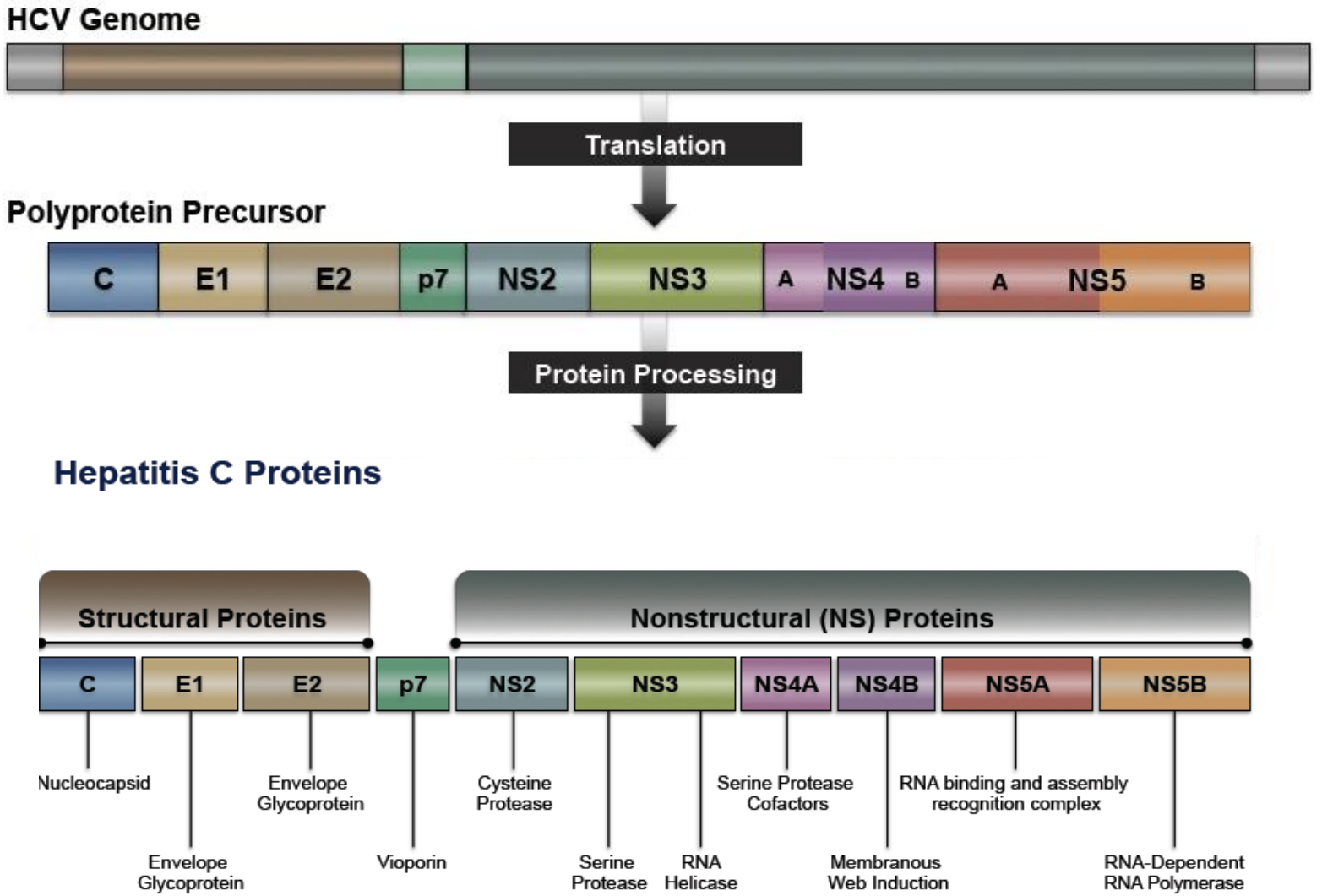
Charles Rice, USA Rockefeller University

The HCV Replicon – in vitro system of HCV

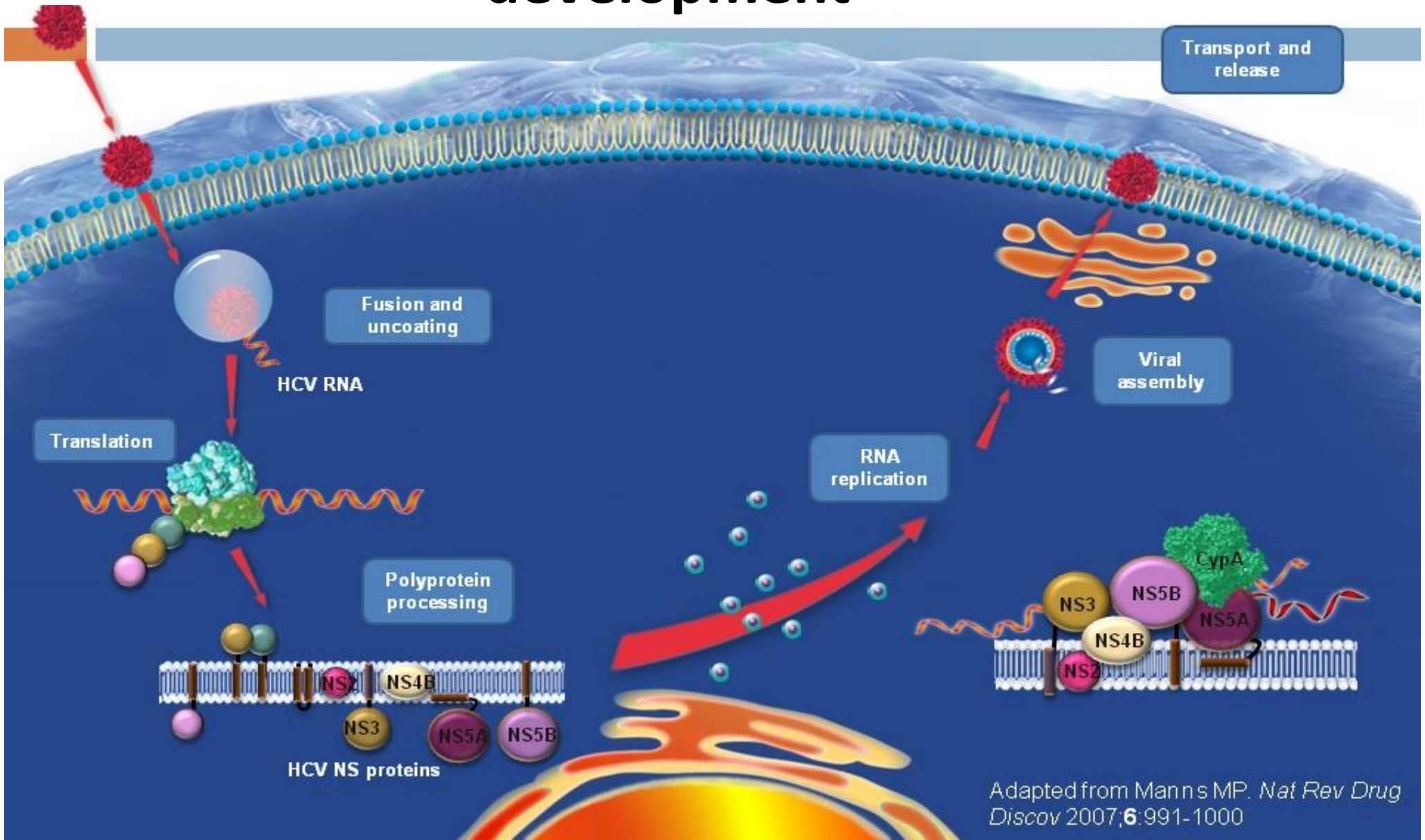


Bartenschlager and Rice, 2003

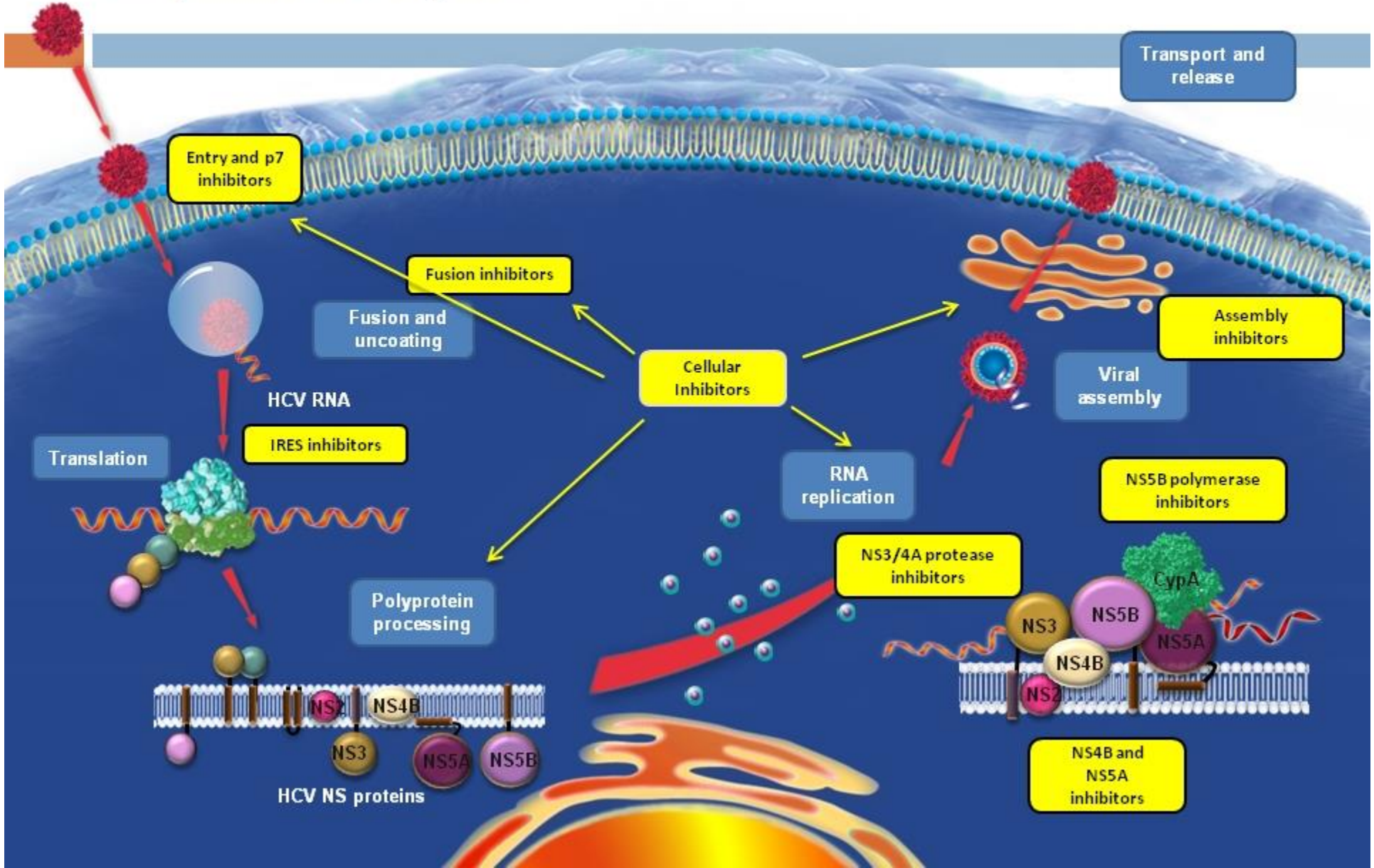
Lifecycle: Viral Polyprotein



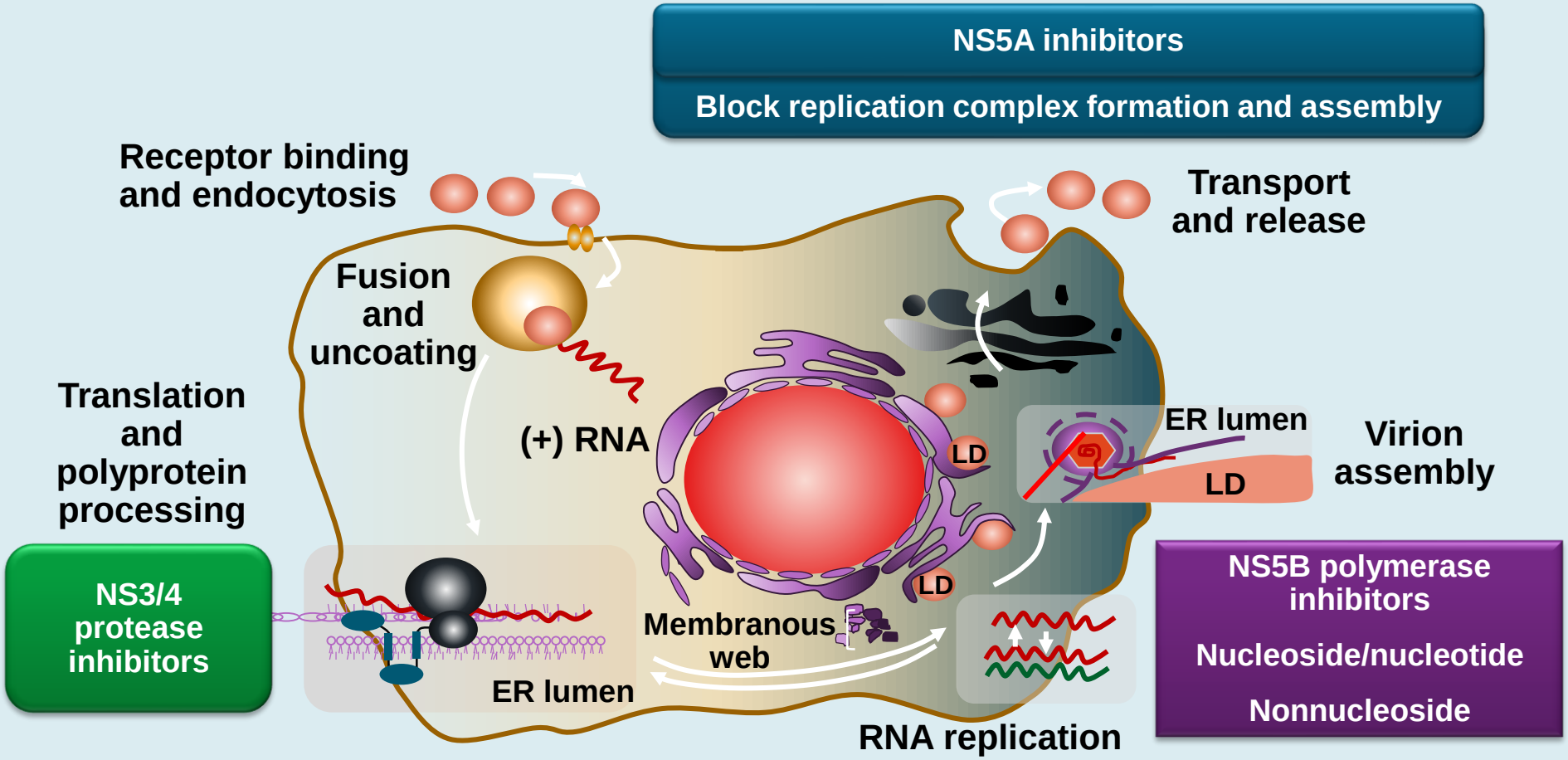
Elucidating HCV Life Cycle and replicon system – key to drug development



Potential Therapeutic Targets in the HCV Replication Cycle



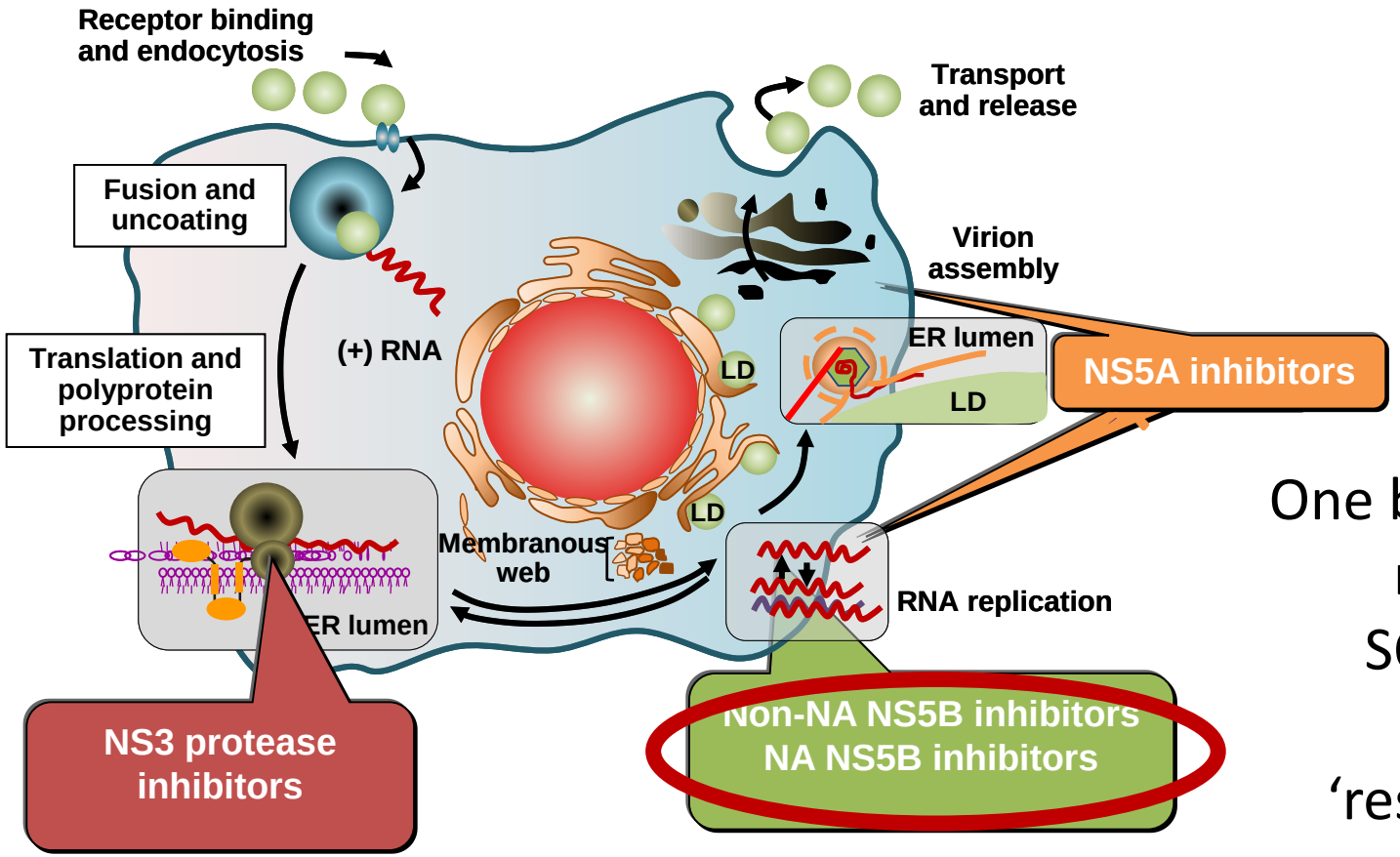
HCV Lifecycle – DAA Targets



Manns MP, et al. Nat Rev Drug Discov. 2007;6:991-1000.

Natural Selection takes over

DAAs that target different stages in the HCV lifecycle



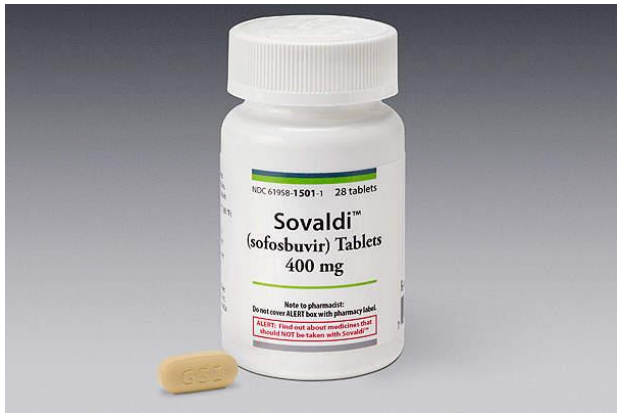
One backbone is the nucleotide SOFOSBUVIR

'resistance free'

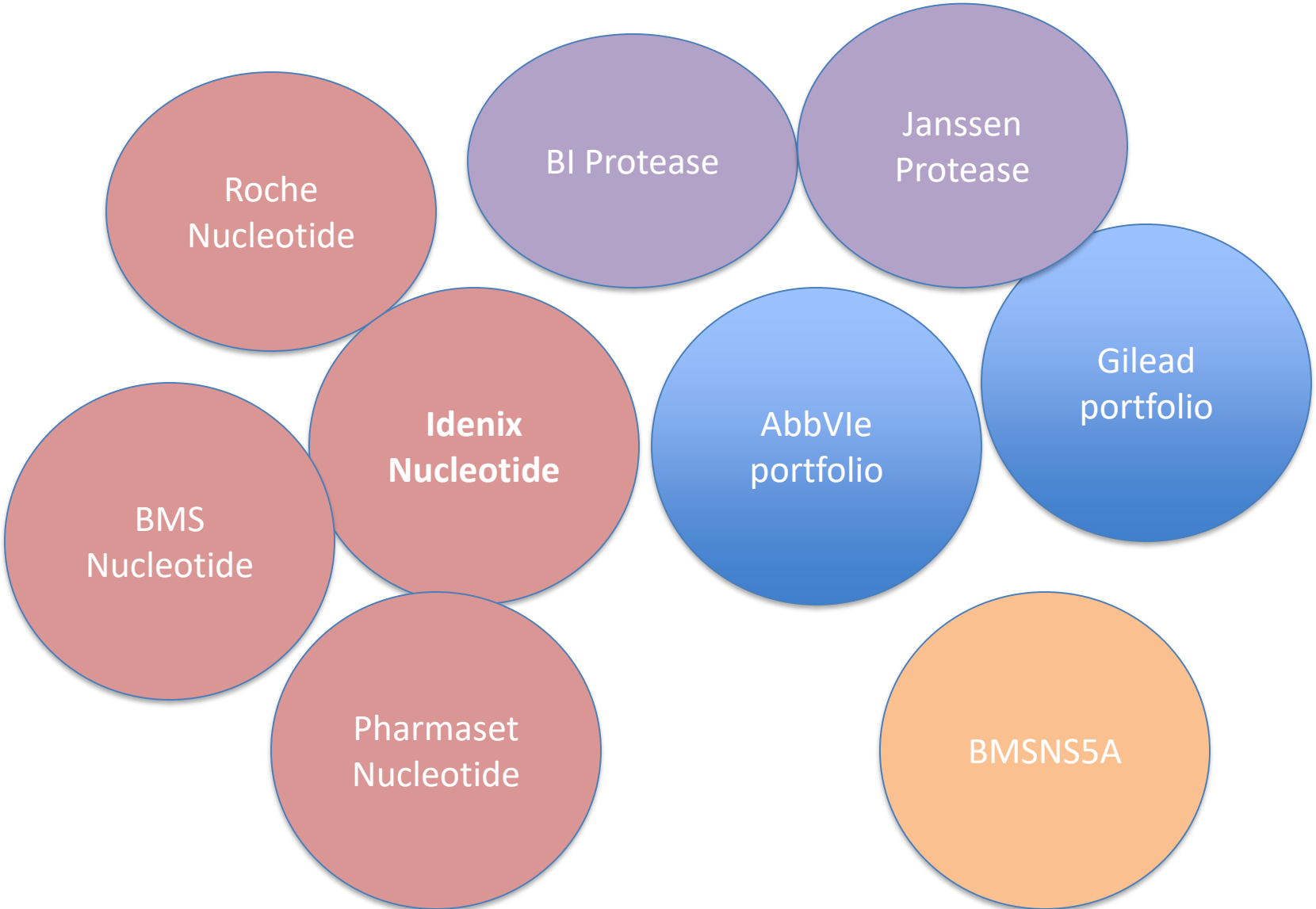
Lindenbach BD, Rice CM. Nature 2005;436(Suppl):933–8;
Liang J, Ghany MG. N Engl J Med 2014;370:2043–7.

Sofosbuvir

- First NS5B protease inhibitor
- Discovery of its anti-HCV efficacy attributed to Michael **Sof**ia
- Lead lab scientist at Pharmasset
- Pharmasset bought by Gilead in 2011 ($11.2 billion USD)
- FDA registered in Dec 2013
- $84 000 for 84 tablets
- Over 60,000 people were treated with sofosbuvir in its first 30 weeks in the USA
- $10 billion within first year



The Trials Began!



Select DAAs in Clinical Development

	Phase I	Phase II	Phase III
Protease Inhibitors	ABT-450 ACH-1625 GS 9451 MK-5172 VX-985	BMS-650032 CTS-1027 Danoprevir GS 9256 IDX320 Vaniprevir	BI 201335 Boceprevir Telaprevir TMC435
Nonnucleoside polymerase inhibitors	BI 207127 IDX375	ABT-333 ABT-072 ANA598 BMS-791325 Filibuvir Tegobuvir VX-759 VX-222	
Nucleoside polymerase inhibitors		IDX184 PSI-7977 RG7128	
NS5A inhibitors	A-831 PPI-461	BMS-790052 BMS-824393 CF102	

2011 AASLD

ORIGINAL ARTICLE

MAY 16, 2013

Sofosbuvir for Previously Untreated Chronic Hepatitis C Infection

Eric Lawitz, M.D., Alessandra Mangia, M.D., David Wyles, M.D., Maribel Rodriguez-Torres, M.D., Tarek Hassanein, M.D., Stuart C. Gordon, M.D., Michael Schultz, M.D., Ph.D., Mitchell N. Davis, D.O., Zeid Kayali, M.D., K. Rajender Reddy, M.D., Ira M. Jacobson, M.D., Kris V. Kowdley, M.D., Lisa Nyberg, M.D., G. Mani Subramanian, M.D., Ph.D., Robert H. Hyland, D.Phil., Sarah Arterburn, M.S., Deyuan Jiang, Ph.D., John McNally, Ph.D., Diana Brainard, M.D., William T. Symonds, Pharm.D., John G. McHutchison, M.D., Aasim M. Sheikh, M.D., Zobair Younossi, M.D., M.P.H., and Edward J. Gane, M.D.*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 16, 2013 VOL. 368 NO. 20

Sofosbuvir for Hepatitis C Genotype 2 or 3 in Patients without Treatment Options

Ira M. Jacobson, M.D., Stuart C. Gordon, M.D., Kris V. Kowdley, M.D., Eric M. Yoshida, M.D., Maribel Rodriguez-Torres, M.D., Mark S. Sulkowski, M.D., Mitchell L. Shiffman, M.D., Eric Lawitz, M.D., Gregory Everson, M.D., Michael Bennett, M.D., Eugene Schiff, M.D., M. Tarek Al-Assi, M.D., G. Mani Subramanian, M.D., Ph.D., Di An, Ph.D., Ming Lin, Ph.D., John McNally, Ph.D., Diana Brainard, M.D., William T. Symonds, Pharm.D., John G. McHutchison, M.D., Keyur Patel, M.D., Jordan Feld, M.D., M.P.H., Stephen Pianko, M.D., Ph.D., and David R. Nelson, M.D.

Lancet 2014; 383: 515-23

Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naive patients with hepatitis C genotype-1 infection (ATOMIC): an open-label, randomised, multicentre phase 2 trial

Kris V Kowdley, Eric Lawitz, Israel Crespo, Tarek Hassanein, Mitchell N Davis, Michael DeMicco, David E Bernstein, Naram Afdhal, John M Vierling, Stuart C Gordon, Jane K Anderson*, Robert H Hyland, Hadas Dvory-Sobol, Di An, Robert G Hinder*, Efstevia Albanis*, William T Symonds, M Michelle Barrey, David R Nelson, Ira M Jacobson

Sofosbuvir and ledipasvir fixed-dose combination with and without ribavirin in treatment-naive and previously treated patients with genotype 1 hepatitis C virus infection (LONESTAR): an open-label, randomised, phase 2 trial

Eric Lawitz, Fred F Poordad, Phillip S Pang, Robert H Hyland, Xiao Ding, Hongmei Mo, William T Symonds, John G McHutchison, Fernando E Membreno

HCV Treatment — No More Room for Interferonologists?

Joost P.H. Drenth, M.D., Ph.D.

ORIGINAL ARTICLE

N ENGL J MED 370;3 NEJM.ORG JANUARY 16, 2014

Phase 2b Trial of Interferon-free Therapy for Hepatitis C Virus Genotype 1

Kris V. Kowdley, M.D., Eric Lawitz, M.D., Fred Poordad, M.D., Daniel E. Cohen, M.D., David R. Nelson, M.D., Stefan Zeuzem, M.D., Gregory T. Everson, M.D., Paul Kwo, M.D., Graham R. Foster, F.C.R.P., Mark S. Sulkowski, M.D., Wangang Xie, Ph.D., Tami Pilot-Matias, Ph.D., George Liossis, B.A., Lois Larsen, Ph.D., Amit Khatri, Ph.D., Thomas Podsadecki, M.D., and Barry Bernstein, M.D.

ORIGINAL ARTICLE

Treatment of HCV Infection by Targeting MicroRNA

Harry L.A. Janssen, M.D., Ph.D., Hendrik W. Reesink, M.D., Ph.D., Eric J. Lawitz, M.D., Stefan Zeuzem, M.D., Maribel Rodriguez-Torres, M.D., Keyur Patel, M.D., Adriaan J. van der Meer, M.D., Amy K. Patick, Ph.D., Alice Chen, B.A., Yi Zhou, Ph.D., Robert Persson, Ph.D., Barney D. King, M.D., Sakari Kauppinen, Ph.D., Arthur A. Levin, Ph.D., and Michael R. Hodges, M.D.

ORIGINAL ARTICLE

N ENGL J MED 369;7 NEJM.ORG AUGUST 15, 2013

Faldaprevir and Deleobuvir for HCV Genotype 1 Infection

Stefan Zeuzem, M.D., Vincent Soriano, M.D., Ph.D., Tarik Asselah, M.D., Ph.D., Jean-Pierre Bronowicki, M.D., Ph.D., Ansgar W. Lohse, M.D., Beat Müllhaupt, M.D., Marcus Schuchmann, M.D., Marc Bourlière, M.D., Maria Buti, M.D., Stuart K. Roberts, M.D., Ed J. Gane, M.D., Jerry O. Stern, M.D., Richard Vinisko, M.A., George Kukolj, Ph.D., John-Paul Gallivan, Ph.D., Wulf-Otto Böcher, M.D., and Federico J. Mensa, M.D.

REVIEW ARTICLE

DRUG THERAPY

Current and Future Therapies for Hepatitis C Virus Infection

T. Jake Liang, M.D., and Marc G. Ghany, M.D., M.H.Sc.

Once-Daily Simeprevir (TMC435) With Pegylated Interferon and Ribavirin in Treatment-Naïve Genotype 1 Hepatitis C: The Randomized PILLAR Study

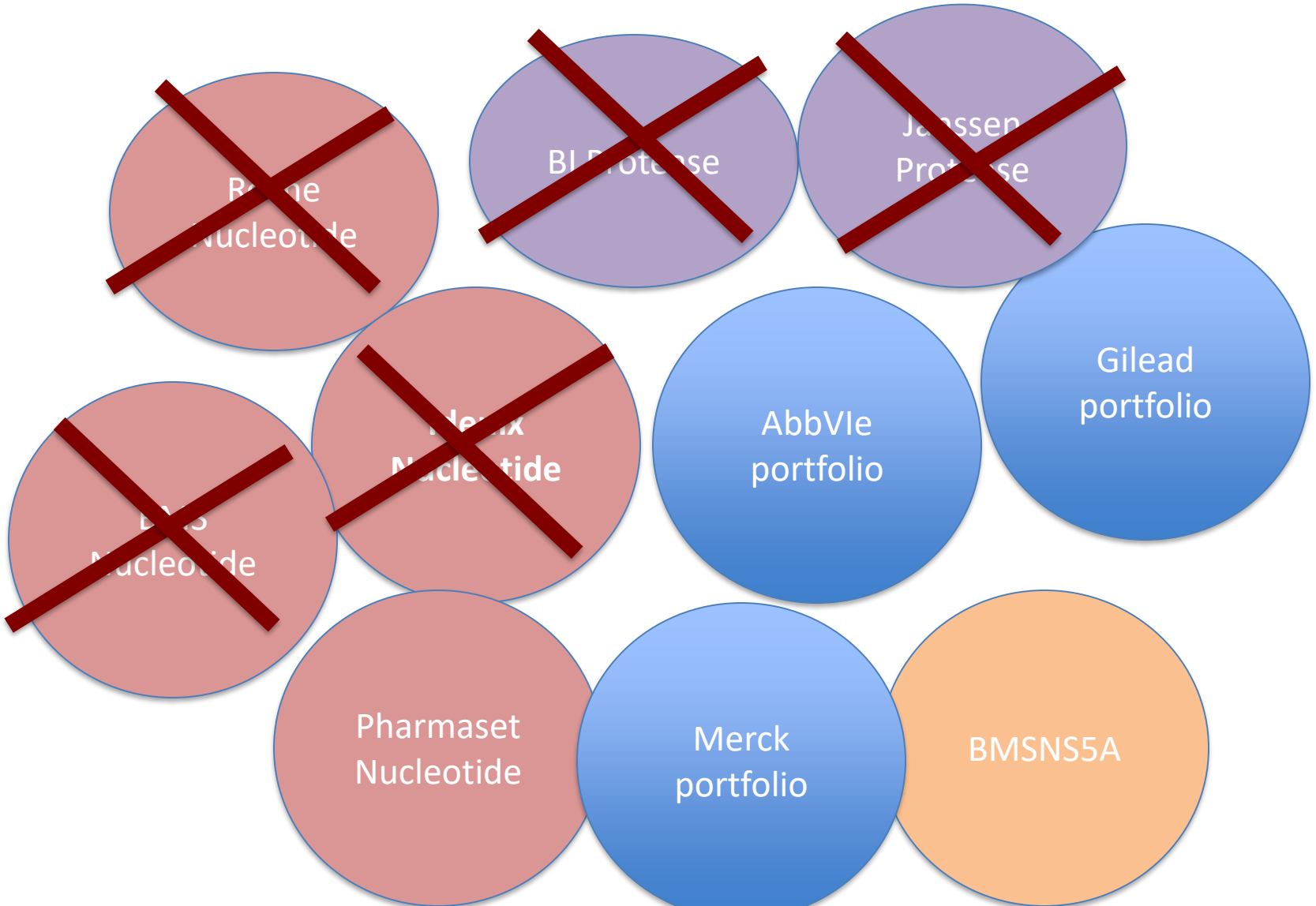
Michael W. Fried,[1] Maria Buti,[2] Gregory J. Dore,[3] Robert Flisiak,[4] Peter Ferenci,[5] Ira Jacobson,[6] Patrick Marcellin,[7] Michael Manns,[8] Igor Nikitin,[9] Fred Poordad,[10] Morris Sherman,[11] Stefan Zeuzem,[12] Jane Scott,[13] Leen Gilles,[14] Oliver Lenz,[14] Monika Peeters,[14] Vanitha Sekar,[15] Goedele De Smedt,[14] and Maria Beumont-Mauviel[14]

ORIGINAL ARTICLE

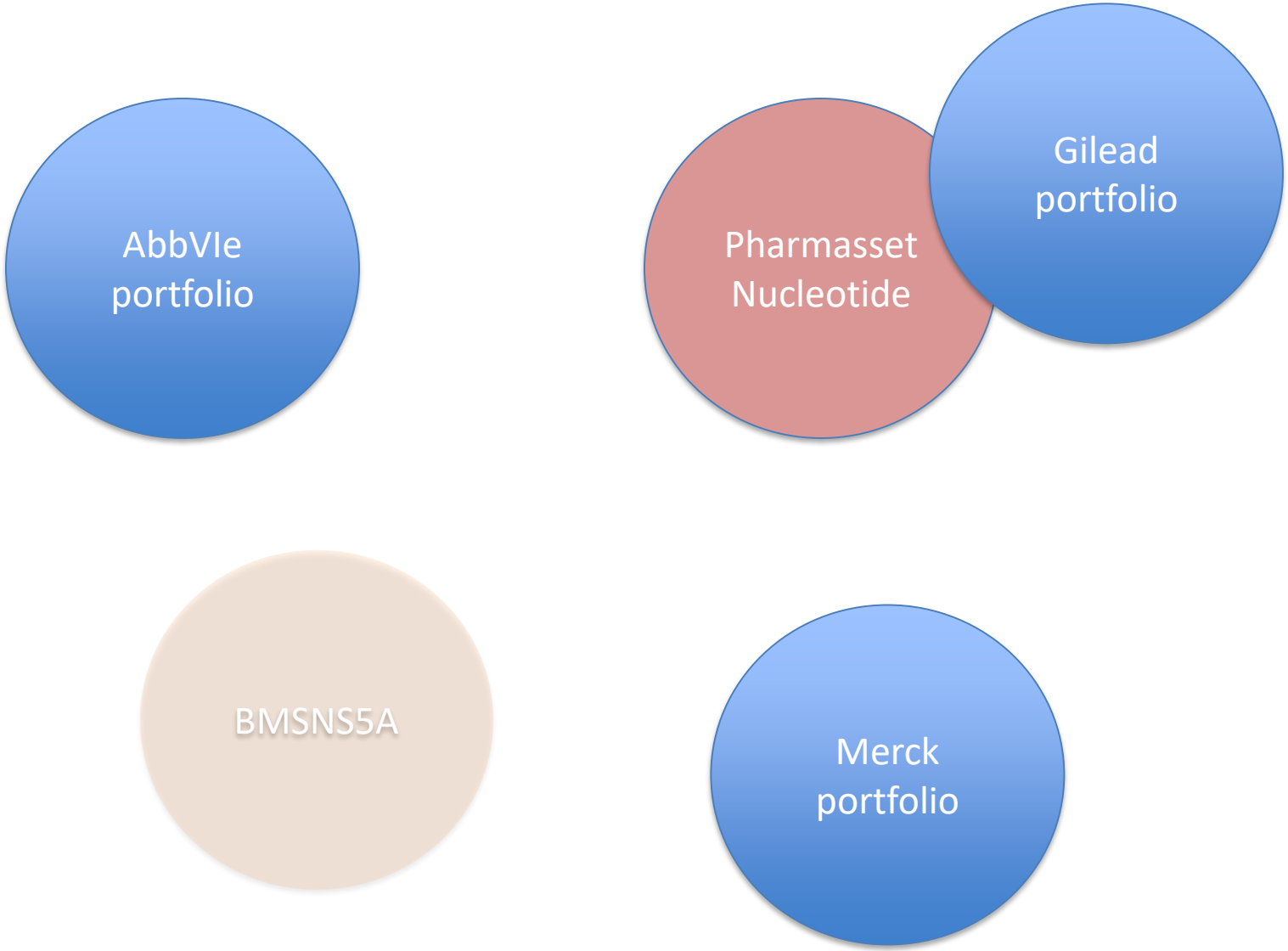
Daclatasvir plus Sofosbuvir for Previously Treated or Untreated Chronic HCV Infection

Mark S. Sulkowski, M.D., David F. Gardiner, M.D., Maribel Rodriguez-Torres, M.D., K. Rajender Reddy, M.D., Tarek Hassanein, M.D., Ira Jacobson, M.D., Eric Lawitz, M.D., Anna S. Lok, M.D., Federico Hinestrosa, M.D., Paul J. Thuluvath, M.D., Howard Schwartz, M.D., David R. Nelson, M.D., Gregory T. Everson, M.D., n Wind-Rotolo, Ph.D., Shu-Pang Huang, Ph.D., Min Gao, Ph.D., z, Ph.D., Fiona McPhee, Ph.D., Diane Sherman, M.S., lliam Symonds, Pharm.D., Claudio Pasquinelli, M.D., Ph.D., asela, Pharm.D., Ph.D., for the AI444040 Study Group

Selection time



The Winners Emerge

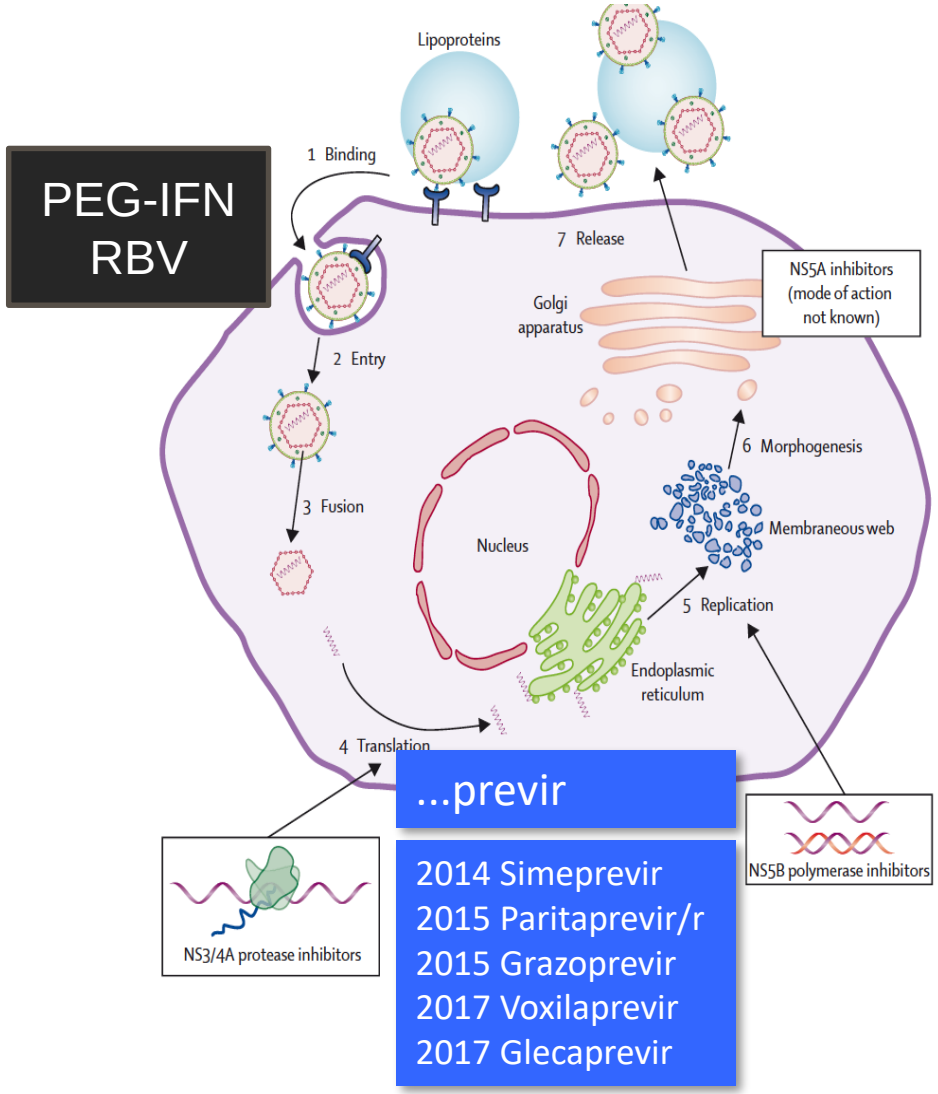


Oral DAA Regimens – Guiding Principles

- **Combine drugs from different classes**
  - Protease (NS3/4A) inhibitors
  - Polymerase (NS5B) inhibitors
  - NS5A inhibitors

- Multiple drugs combined to produce greater efficacy and reduce risk of viral resistance (~HIV ART principles)

HCV replication cycle and new direct acting antiviral agents (DAA)



PEG-IFN
RBV

...asvir

2014 Daclatasvir
2015 Ledipasvir
2015 Ombitasvir
2015 Elbasvir
2016 Velpatasvir
2017 Pibrentasvir

...previr

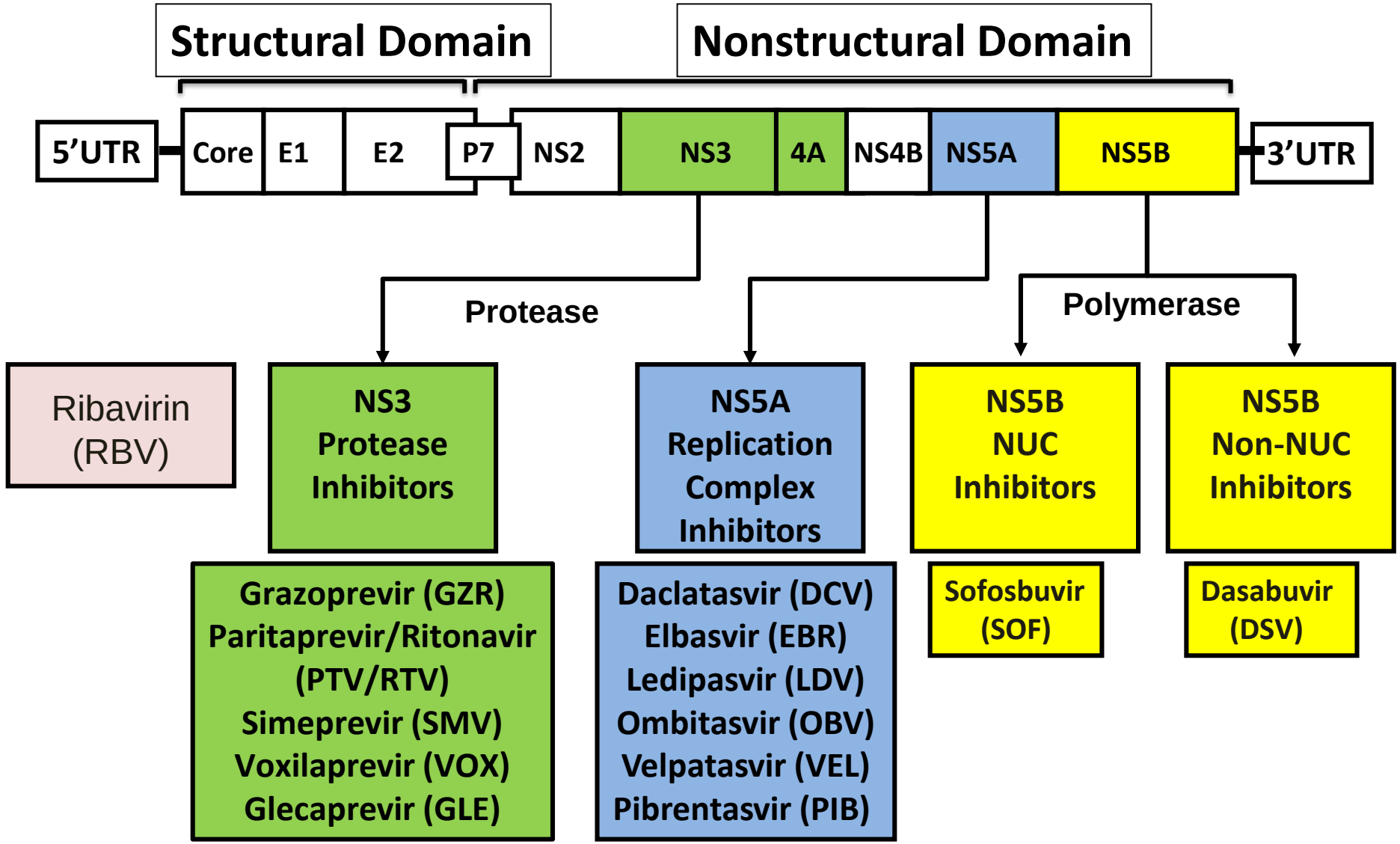
2014 Simeprevir
2015 Paritaprevir/r
2015 Grazoprevir
2017 Voxilaprevir
2017 Glecaprevir

...buvir

2014 Sofosbuvir
2014 Dasabuvir

Spearman, Dusheiko, Hellard, Sonderup, *Lancet* 2019

Approved DAAs From Multiple Classes: 2018



SVR Rates > 95% for All Recommended First-line HCV Regimens

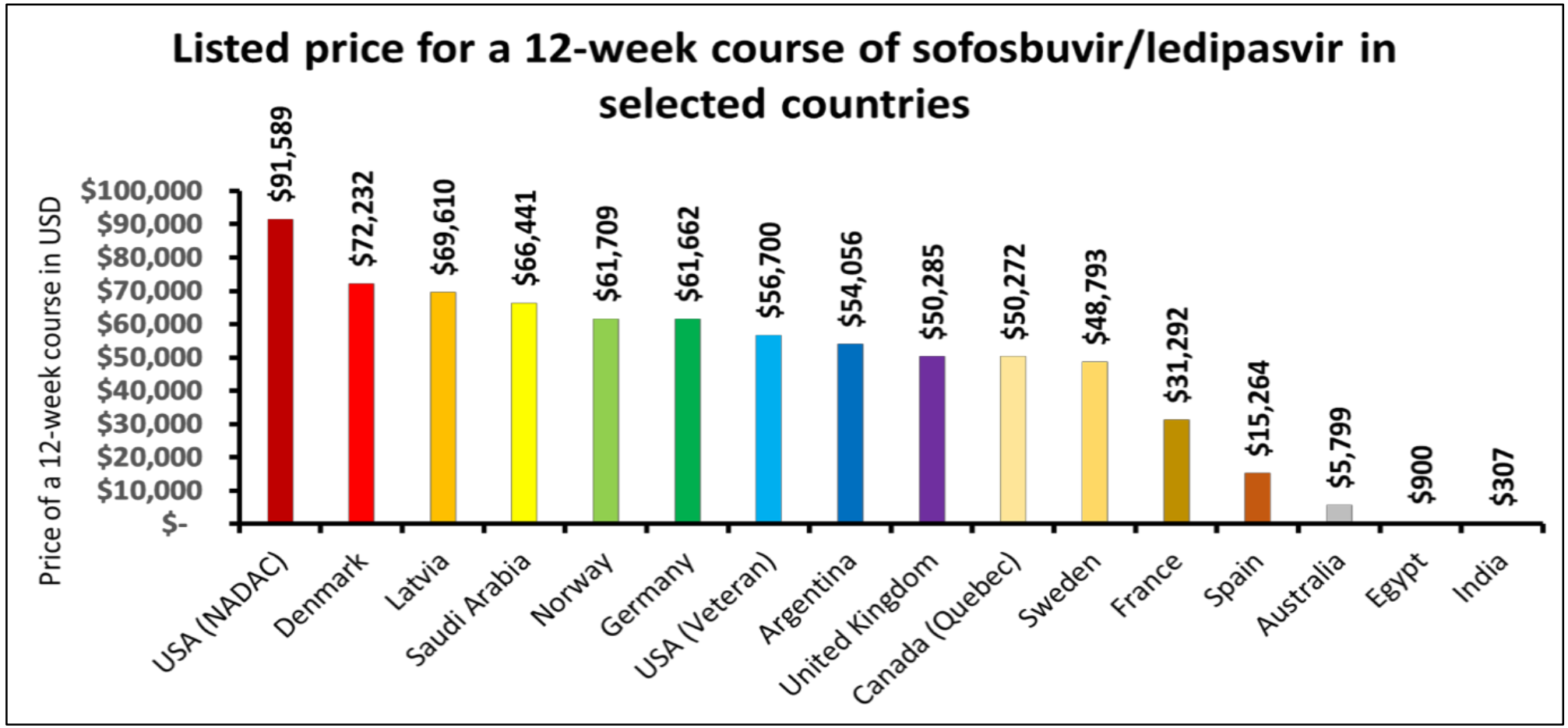
‘Perfectovir’

- We now have almost perfect regimens
- Are they really perfect?

The drugs are almost perfect

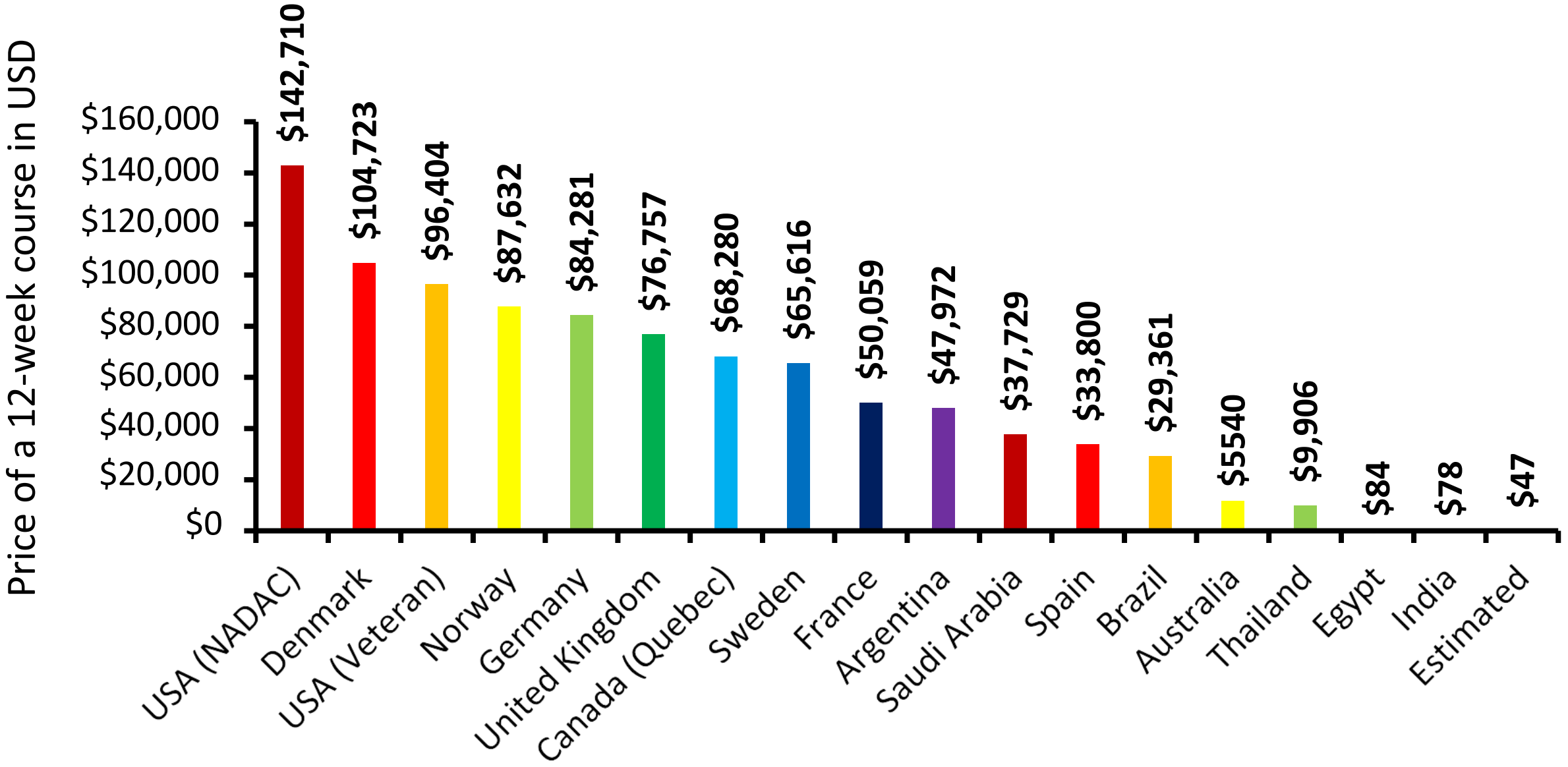
- The drugs cure nearly everyone
- They stop people getting liver cancer, dying of cirrhosis
- People feel better with hep C cured!!!
- Challenge : get it out there and make people better and eliminate hep C!

Treatment is now more affordable

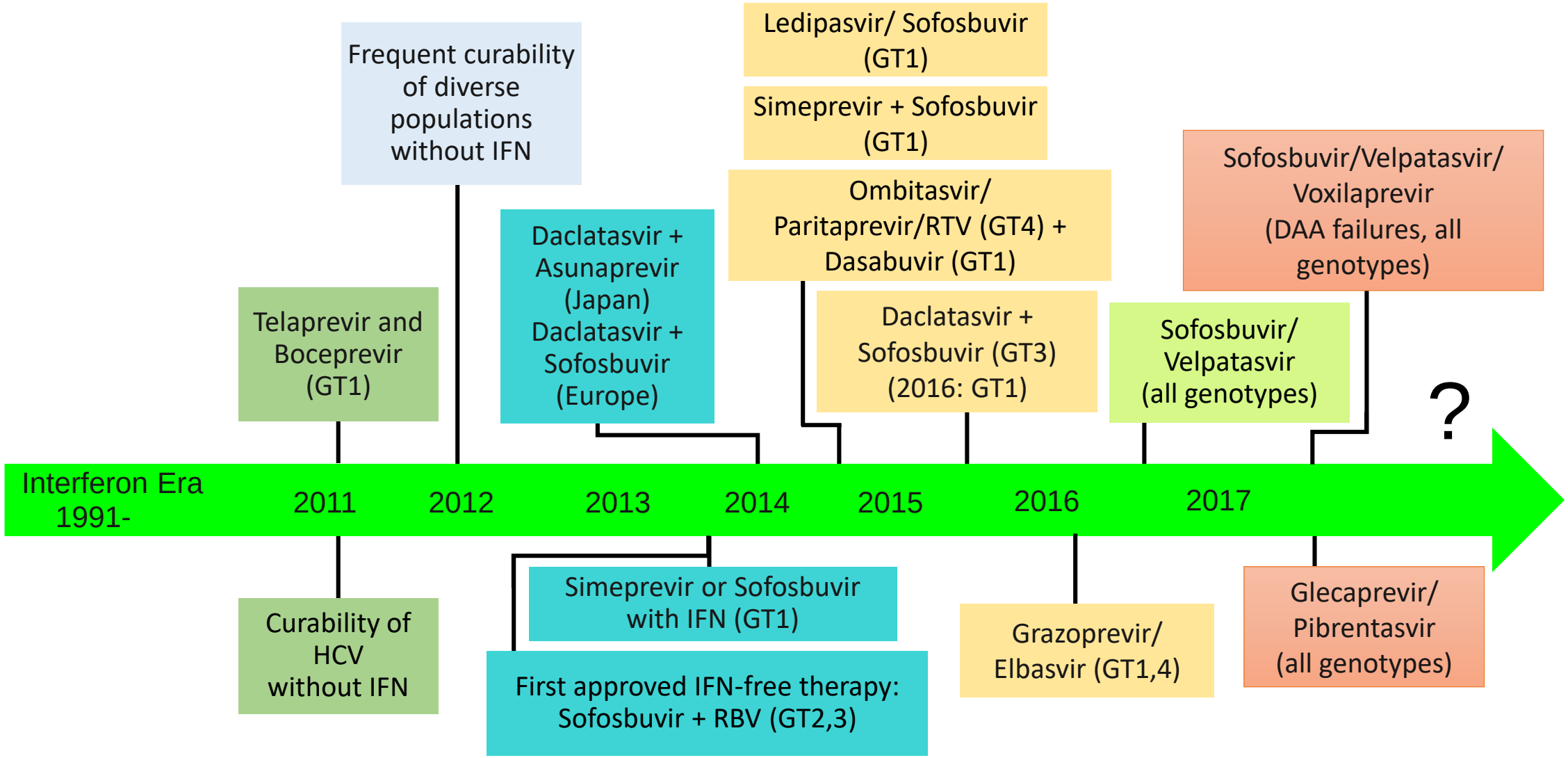


A Hill, and G Cooke

Lowest prices of SOF/DCV in selected countries



The (Re)Evolution of HCV Therapy



HCV can now be treated successfully

- Very high SVR rates; therapies highly tolerable
- All-oral therapy for almost every patient
- Treatment generally 8-12 weeks