Treatment of Chronic Hepatitis C

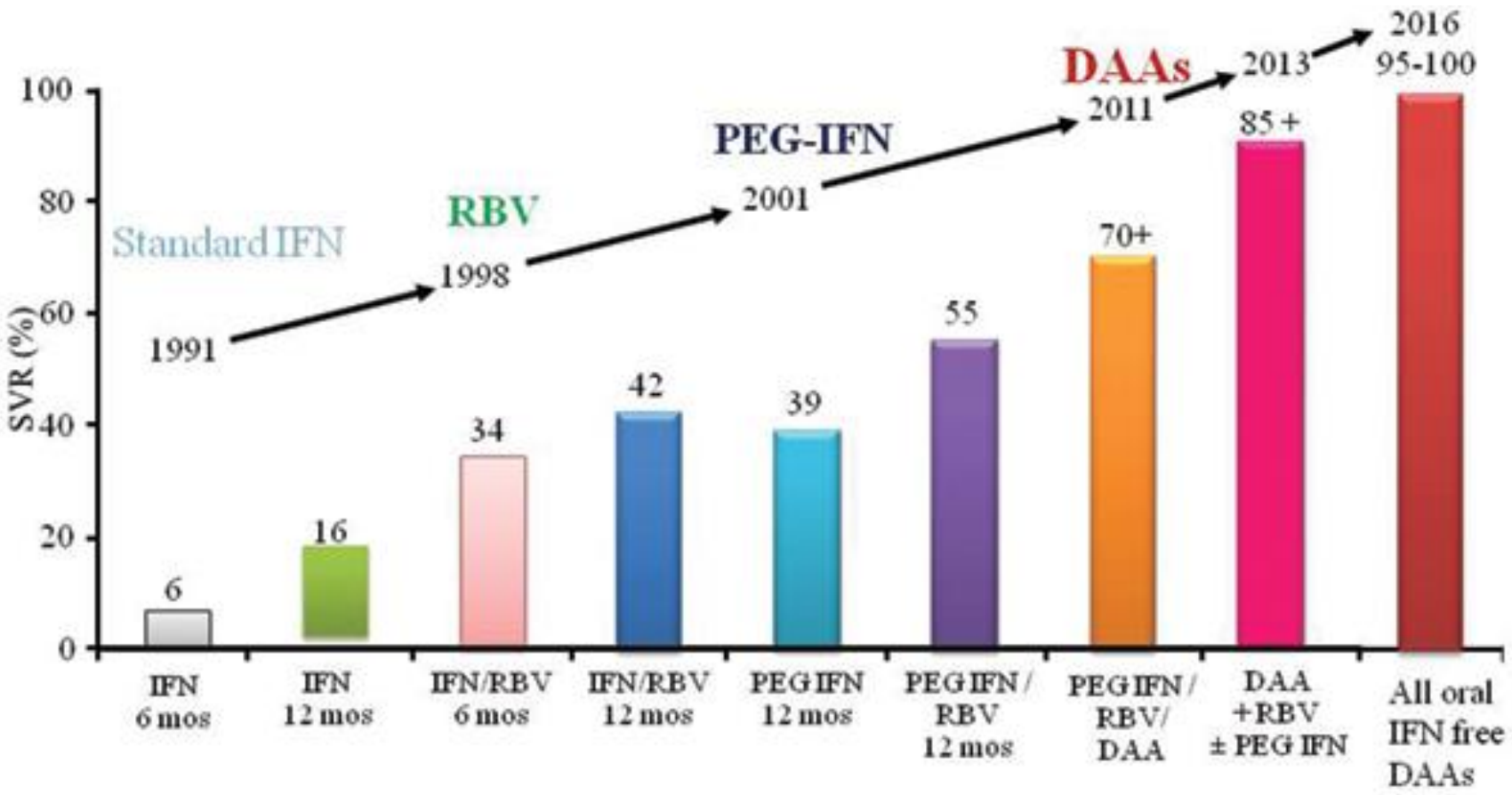
Raed ABOUHARB, M.D.

D.I.S.,D.I.U.,D.U.,C.A.M.U.-France

كلية الطب - جامعة دمشق

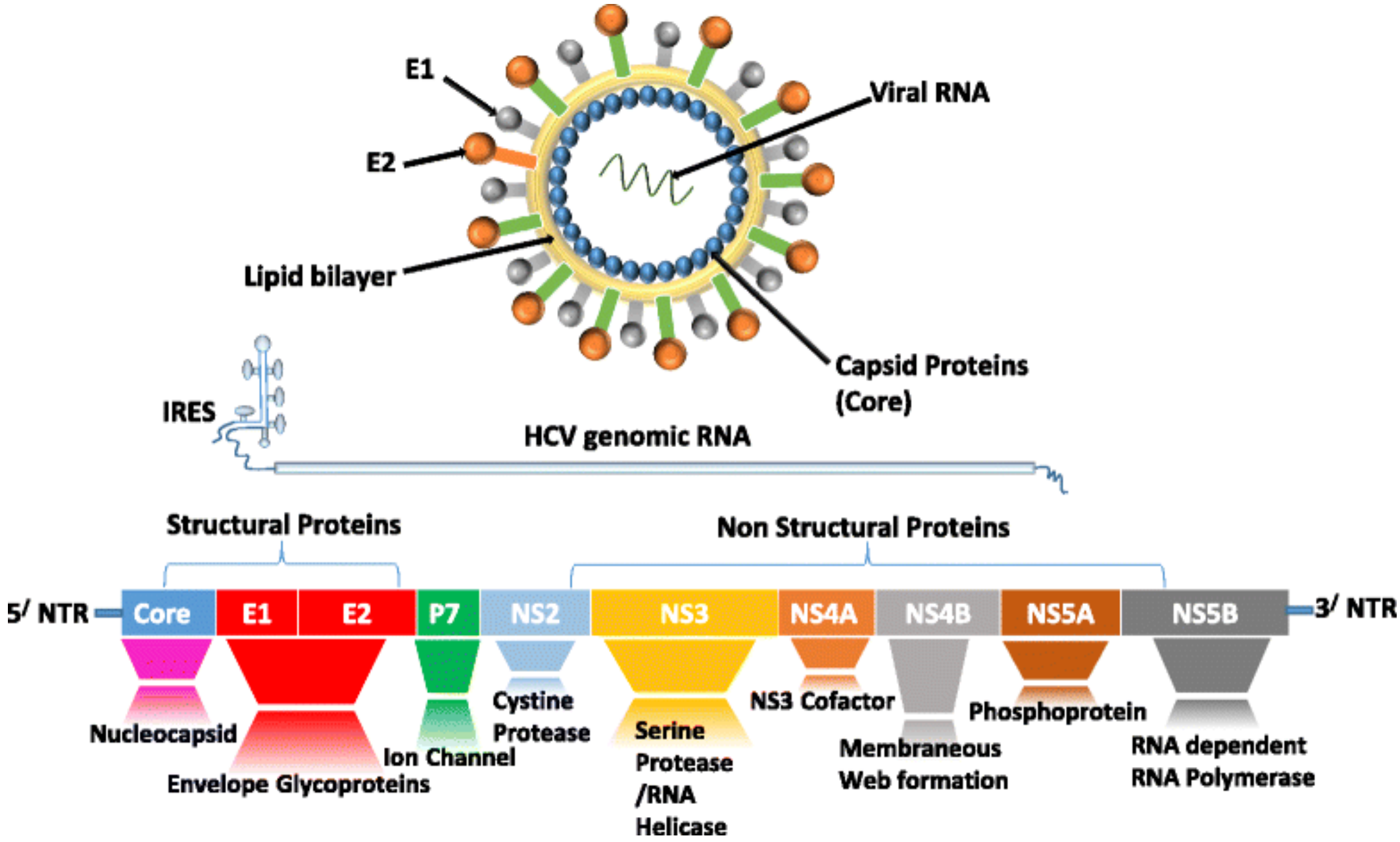
ندوة الجمعية السورية لأمراض الهضم
حماه – الجمعة ٠٦/٠٩/٢٠١٩

Development of HCV Therapy

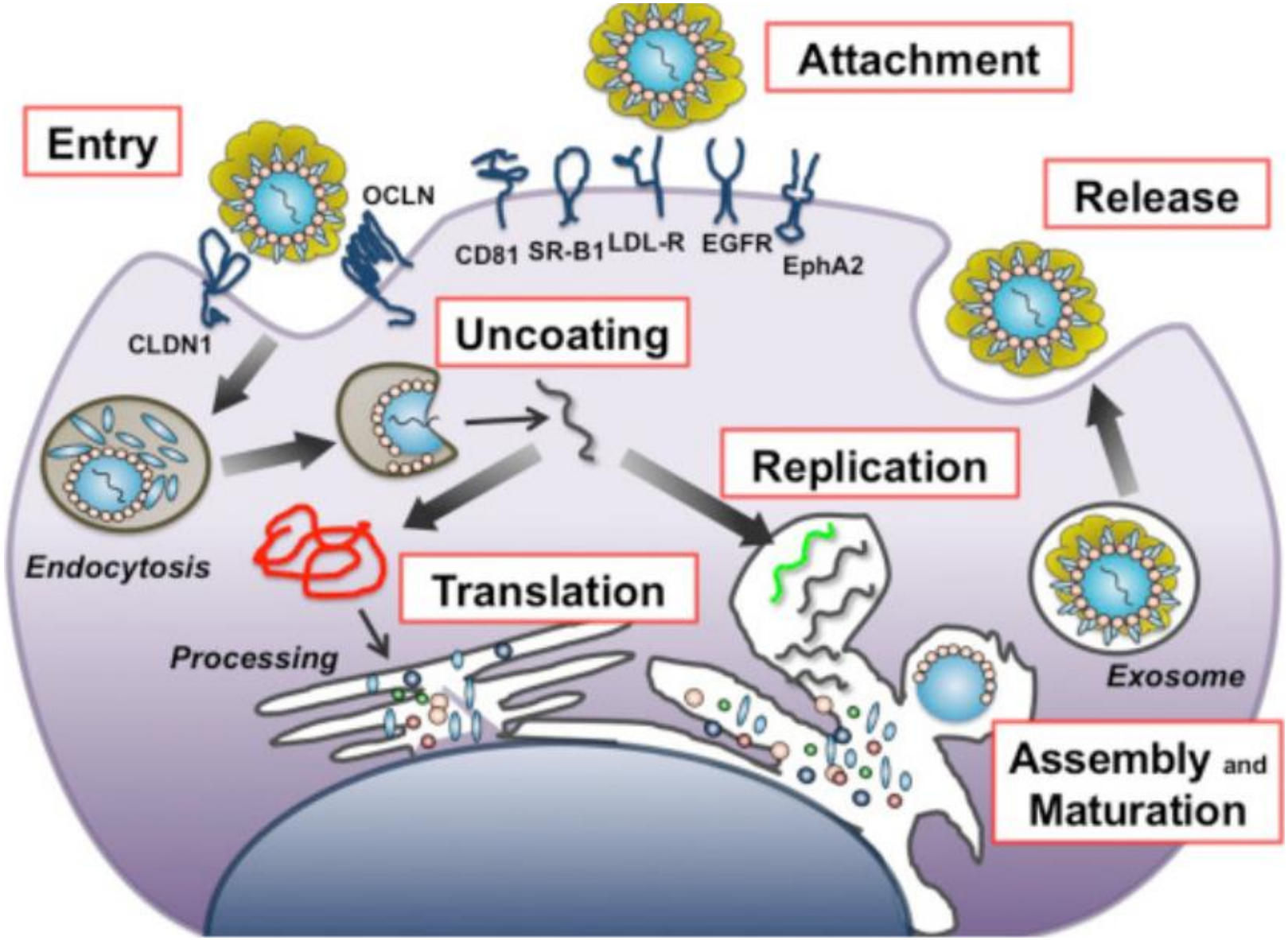


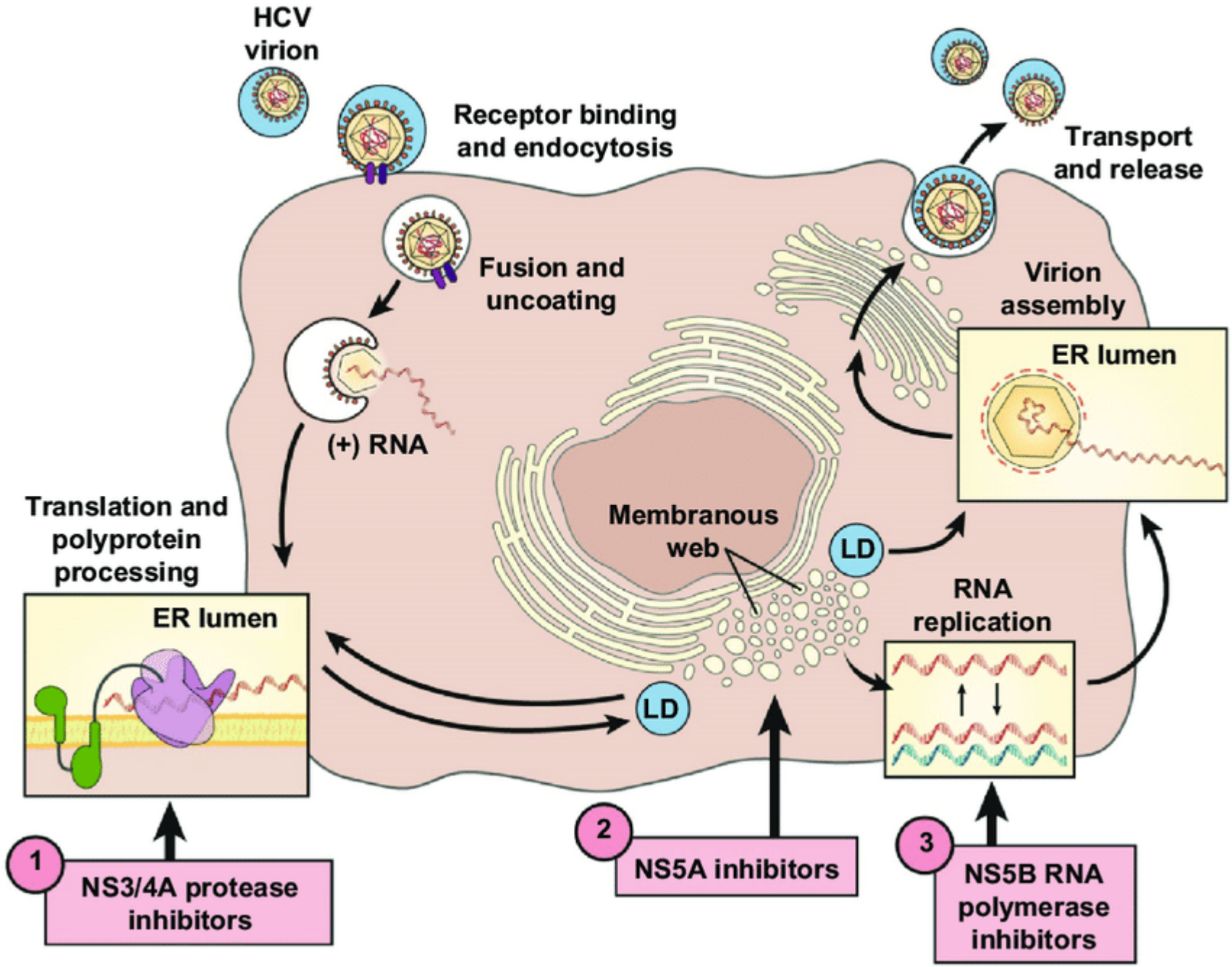
Adapted from the US Food and Drug Administration, Antiviral Drugs Advisory Committee Meeting, April 27-28, 2011, Silver Spring, MD.

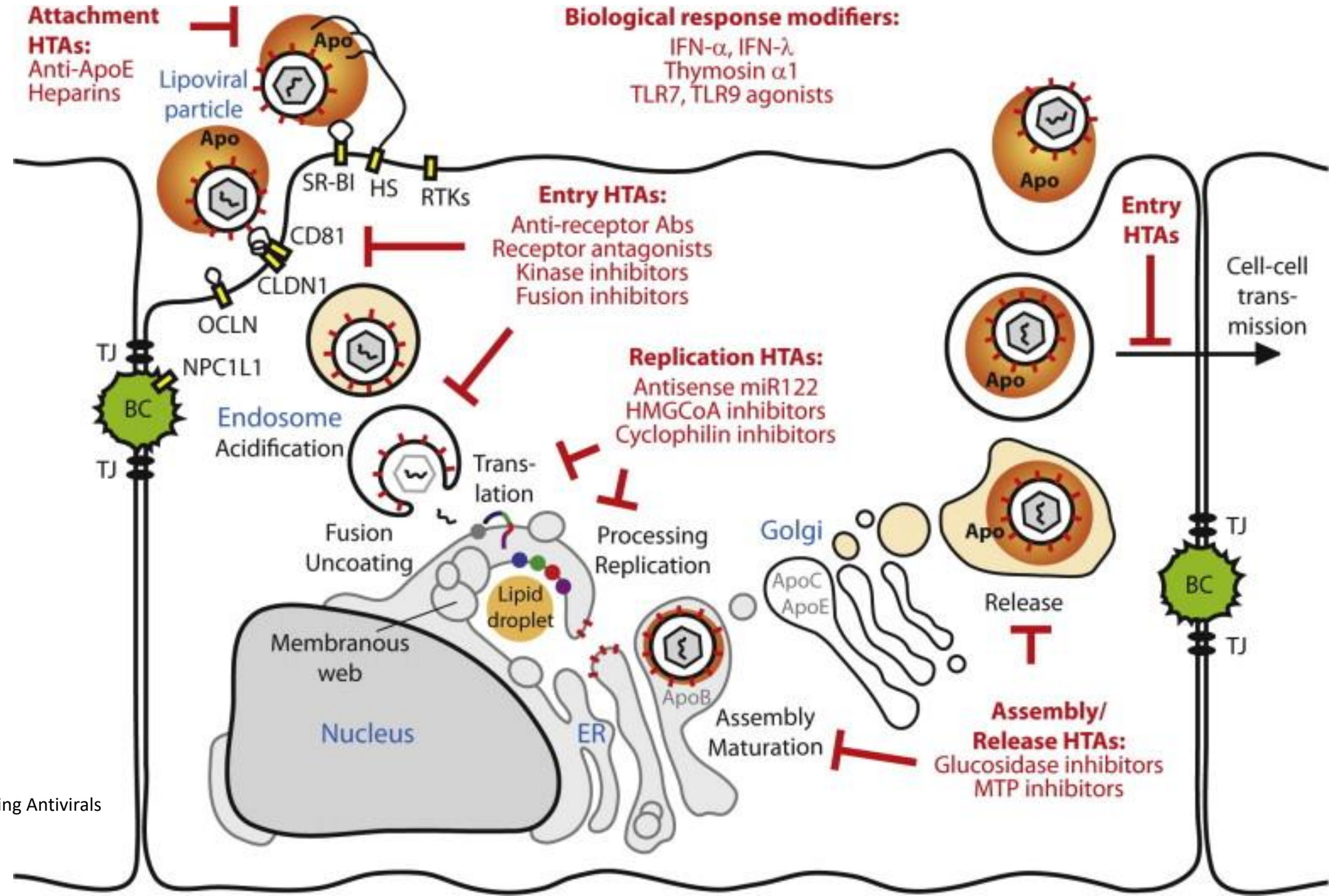
8-24 W


E1
E2
Viral RNA
Lipid bilayer
Capsid Proteins
(Core)
IRES
HCV genomic RNA
Structural Proteins
Non Structural Proteins
5/ NTR
Core
E1
E2
P7
NS2
NS3
NS4A
NS4B
NS5A
NS5B
3/ NTR
Nucleocapsid
Envelope Glycoproteins
Ion Channel
Cystine
Protease
Serine
Protease
/RNA
Helicase
NS3 Cofactor
Membraneous
Web formation
Phosphoprotein
RNA dependent
RNA Polymerase

HCV life cycle and host–cell interactions

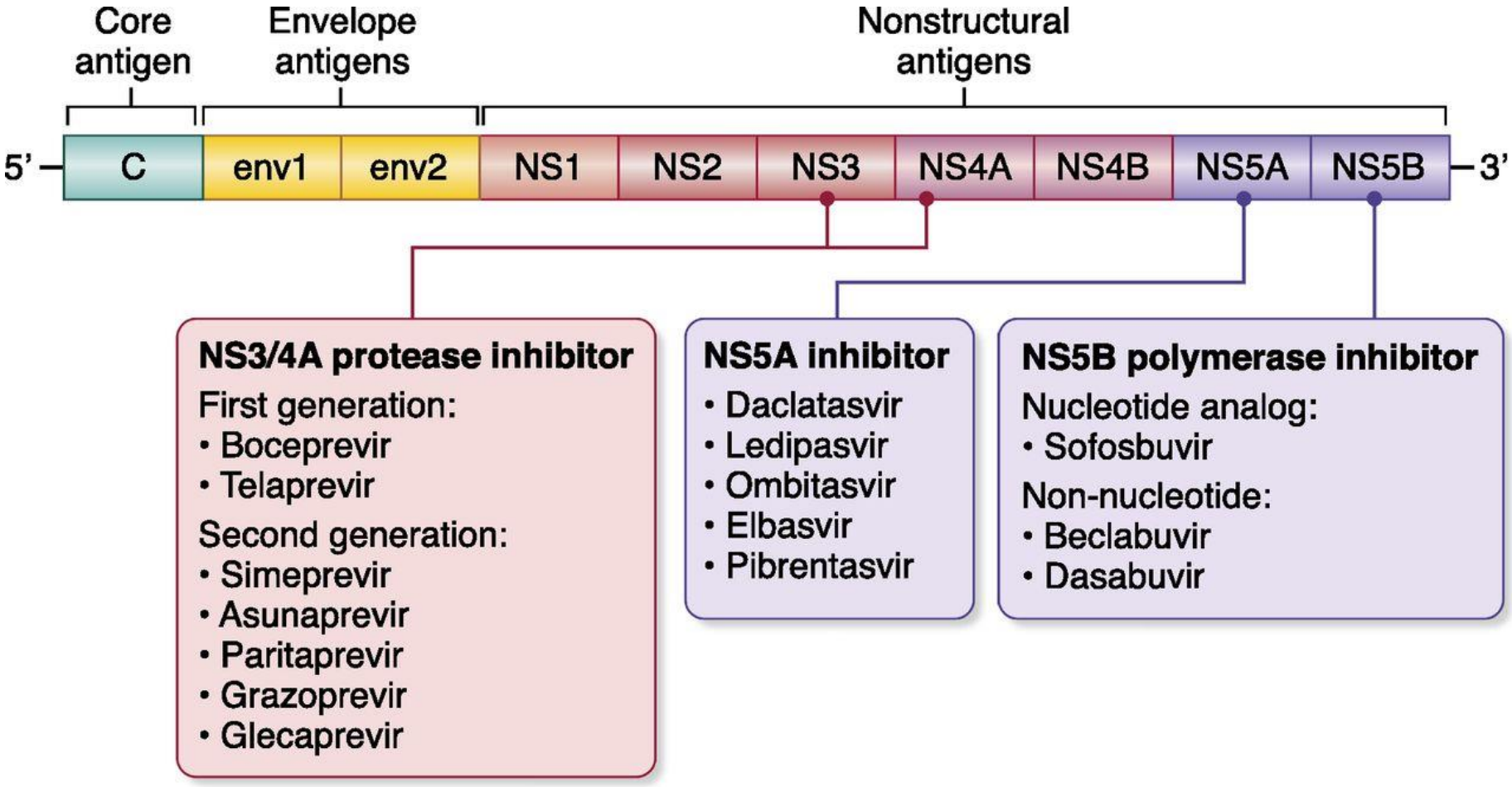



HCV virion
Receptor binding and endocytosis
Transport and release
Fusion and uncoating
Virion assembly
ER lumen
(+) RNA
Translation and polyprotein processing
Membranous web
LD
RNA replication
ER lumen
LD
1
NS3/4A protease inhibitors
2
NS5A inhibitors
3
NS5B RNA polymerase inhibitors



HTAs:Host Targeting Antivirals

Approved DAAs From Multiple Classes Basis of 2018 Combination HCV Regimens



Direct-acting Antiviral Agents(DAAs)

NS3/4A Protease Inhibitors -PREVIR	NS5A Inhibitors -ASVIR	NS5B Polymerase Inhibitor -BUVIR

• Boceprevir
• Telaprevir
• Simeprevir
• Paritapriver
• Grazoprevir
• Voxilaprevir
• Glecaprevir
	• Ledipasvir
	• Daclatasvir
	• Ombetasvir
	• Elbasvir
	• Velpatasvir
	• Pibrentasvir
		• Nucleos(t)ide Inhibitors(NI)
		  • Sofosbuvir
		• Nonnucleos(t)ide Inhibitors(NNI)
		  • Dasabuvir

- Number of approved drugs that block each of the different enzymes that allow the virus to replicate
- The 2 mainstays are combining a protease inhibitor with an NS5A inhibitor and then combining a nucleoside NS5B polymerase inhibitor with an NS5A inhibitor.

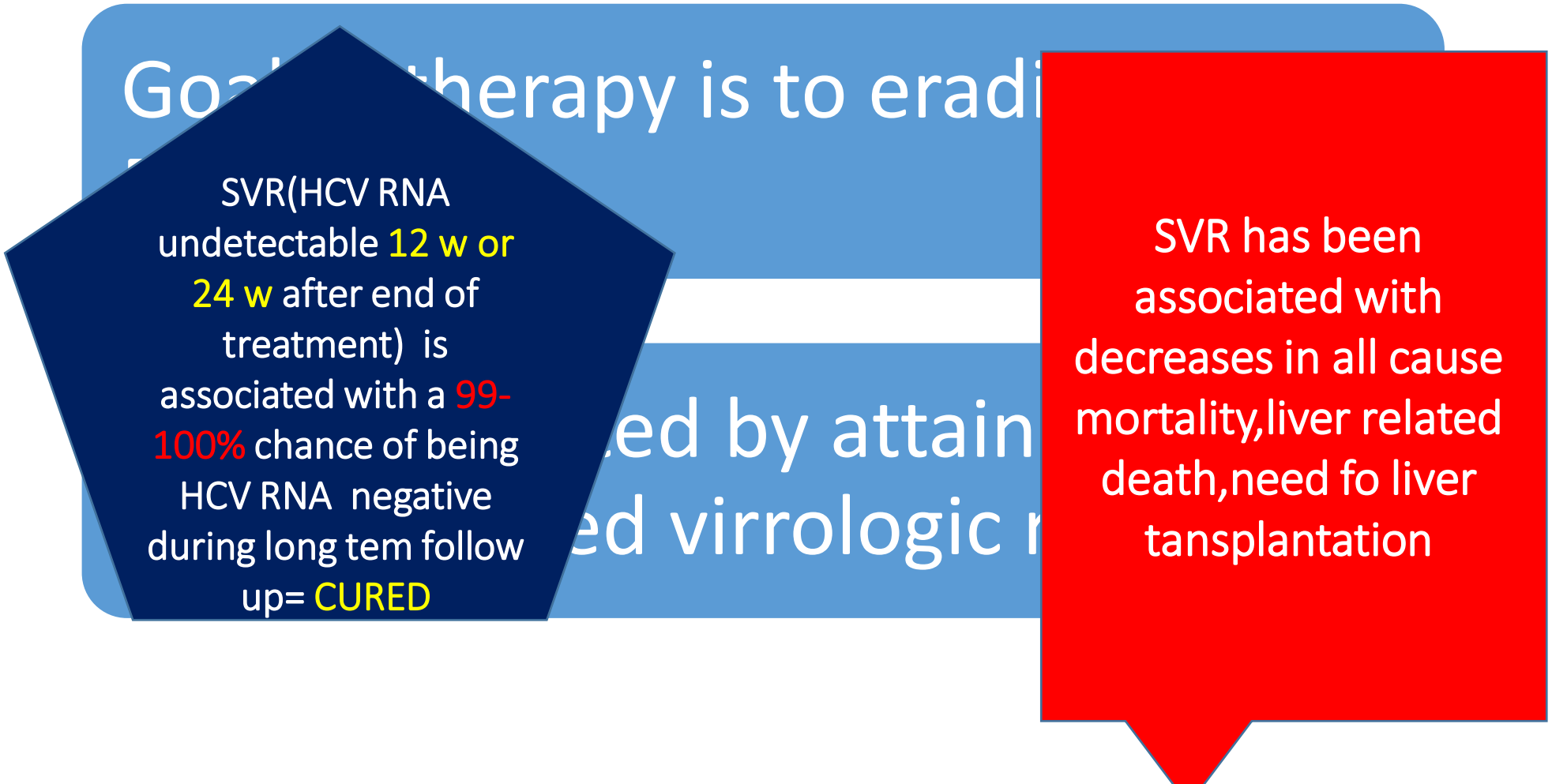
Host-targeting therapies for hepatitis C virus infection (HTAs)

- Targeting conserved host proteins involved in the HCV life cycle, host-targeting agents (HTAs) offer opportunities for pan-genotypic antiviral approaches with a high barrier to drug resistance. Moreover, when applied in combination with DAAs, HTAs could improve the management of difficult-to-treat patients by acting through a complementary mechanism of action

Novel Drugs Against HCV

- **Direct-Acting Antivirals (DAAs)** targeting HCV enzymes
- **Host-Targeting Antiviral Agents (HTAs)** boost the host's innate immunity or interfere with host factors required for pathogenesis
- **And teir combinations (**synergistic)

Goal of treatment



Pre-therapeutic assessment I

- Liver disease severity must be assessed prior to therapy
- Fibrosis stage must be assessed by non-invasive methods initially
- Renal function (creatinine/estimated glomerular filtration rate [eGFR]) should be ascertained
- Extra-hepatic manifestations of HCV infection should be identified in case of symptoms

Staging of Hepatic Fibrosis is Essential Prior to HCV Treatment: Do Not Miss Cirrhosis!

Liver biopsy:

Gold standard

Rarely done

Serum Biomarkers of Fibrosis:

APRI, FIB-4: Very good negative predictive value. APRI < 0.5, FIB-4 < 1.45 rule out cirrhosis.

Commercial serum fibrosis tests also available (*FIBROSpect, FibroSURE*)

Elastography:Fibroscan

> 12.5 kPa = cirrhosis

CT/MRI, US

Can demonstrate cirrhotic morphology, portal hypertension

APRI Score:AST to Platelet Ratio Index

FIB-4 :The Fibrosis 4 score is a non-invasive scoring system based on several laboratory tests that help to estimate the amount of scarring in the liver.

Pre-therapeutic assessment II

- HBV and HAV vaccination should be proposed to patients who are not protected
- HCV genotype determination , to tailor the treatment regimen and its duration
- With pan-genotypic HCV drug regimens, it is possible to treat individuals without identifying their HCV genotype

- In patients with an eGFR <30 ml/min/1.73 m2, sofosbuvir should only be used if no alternative treatment approved for use in patients with severe renal impairment is available

HCV DAAs approved in Europe in 2018

Product	Presentation	Posology
Pangenotypic drugs or drug combinations		
Sofosbuvir	Tablets containing 400 mg of sofosbuvir	One tablet once daily
Sofosbuvir/velpatasvir	Tablets containing 400 mg of sofosbuvir and 100 mg of velpatasvir	One tablet once daily
Sofosbuvir/velpatasvir/ voxilaprevir	Tablets containing 400 mg of sofosbuvir, 100 mg of velpatasvir and 100 mg of voxilaprevir	One tablet once daily
Glecaprevir/pibrentasvir	Tablets containing 100 mg of glecaprevir and 40 mg of pibrentasvir	Three tablets once daily
Genotype-specific drugs or drug combinations		
Sofosbuvir/ledipasvir	Tablets containing 400 mg of sofosbuvir and 90 mg of ledipasvir	One tablet once daily
Paritaprevir/ombitasvir/ ritonavir	Tablets containing 75 mg of paritaprevir, 12.5 mg of ombitasvir and 50 mg of ritonavir	Two tablets once daily
Dasabuvir	Tablets containing 250 mg of dasabuvir	One tablet twice daily (morning and evening)
Grazoprevir/elbasvir	Tablets containing 100 mg of grazoprevir and 50 mg of elbasvir	One tablet once daily

DAA, direct-acting antiviral; HCV, hepatitis C virus.

Therapy Options: which One to Use?

- Genotype
- Stage of disease
- Prior HCV treatment
- Drug interaction
- availability

DAA recommended for each HCV genotype/subtype in 2018

Genotype	Pangenotypic regimens			Genotype-specific regimens		
	SOF/ VEL	GLE/PIB	SOF/ VEL/ VOX	SOF/ LDV	GZR/ EBR	OBV/ PTV/r + DSV
Genotype 1a	Yes	Yes	No*	Yes[a]	Yes[b]	No
Genotype 1b	Yes	Yes	No*	Yes	Yes	Yes
Genotype 2	Yes	Yes	No*	No	No	No
Genotype 3	Yes[c]	Yes	Yes[d]	No	No	No
Genotype 4	Yes	Yes	No*	Yes[a]	Yes[e]	No
Genotype 5	Yes	Yes	No*	Yes[a]	No	No
Genotype 6	Yes	Yes	No*	Yes[a]	No	No

DSV, dasabuvir; EBR, elbasvir; GLE, glecaprevir; GZR, grazoprevir; IFN, interferon; LDV, ledipasvir; OBV, ombitasvir; PIB, pibrentasvir; PTV, paritaprevir; r, ritonavir; SOF, sofosbuvir; VEL, velpatasvir; VOX: voxilaprevir.

* Triple combination therapy efficacious but not useful due to the efficacy of double combination regimens.

[a] Treatment-naïve patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis.

[b] Treatment-naïve and treatment-experienced patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis with an HCV RNA level ≤800,000 IU/ml (5.9 Log_{10} IU/ml).

[c] Treatment-naïve and treatment-experienced patients without cirrhosis.

[d] Treatment-naïve and treatment-experienced patients with compensated (Child-Pugh A) cirrhosis.

[e] Treatment-naïve patients without cirrhosis or with compensated (Child-Pugh A) cirrhosis with an HCV RNA level ≤800,000 IU/ml (5.9 Log_{10} IU/ml).

Journal of Hepatology 2018 vol. 69 j 461–511

Treatment recommendations for HCV chronic hepatitis C without cirrhosis

Patients	Prior treatment experience	SOF/VEL	GLE/PIB	SOF/VEL/VOX	SOF/LDV	GZR/EBR	OBV/PTV/r + DSV
Genotype 1a	Treatment-naïve	12 wk	8 wk	No	8-12 wk	12 wk (HCV RNA ≤800,000 IU/ml)	No
	Treatment-experienced	12 wk	8 wk	No	No	12 wk (HCV RNA ≤800,000 IU/ml)	No
Genotype 1b	Treatment-naïve	12 wk	8 wk	No	8-12 wk	8 wk (F0-F2) 12 wk (F3)	8 wk (F0-F2) 12 wk (F3)
	Treatment-experienced	12 wk	8 wk	No	12 wk	12 wk	12 wk
Genotype 2	Treatment-naïve	12 wk	8 wk	No	No	No	No
	Treatment-experienced	12 wk	8 wk	No	No	No	No
Genotype 3	Treatment-naïve	12 wk	8 wk	No	No	No	No
	Treatment-experienced	12 wk	12 wk	No	No	No	No
Genotype 4	Treatment-naïve	12 wk	8 wk	No	12 wk	12 wk (HCV RNA ≤800,000 IU/ml)	No
	Treatment-experienced	12 wk	8 wk	No	No	No	No
Genotype 5	Treatment-naïve	12 wk	8 wk	No	12 wk	No	No
	Treatment-experienced	12 wk	8 wk	No	No	No	No
Genotype 6	Treatment-naïve	12 wk	8 wk	No	12 wk	No	No
	Treatment-experienced	12 wk	8 wk	No	No	No	No

DAA, direct-acting antiviral; DSV, dasabuvir; EBR, elbasvir; GLE, glecaprevir; GZR, grazoprevir; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LDV, ledipasvir; OBV, ombitasvir; PIB, pibrentasvir; PTV, paritaprevir; r, ritonavir; SOF, sofosbuvir; VEL, velpatasvir; VOX: voxilaprevir.

Journal of Hepatology 2018 vol. 69 j 461–511

Treatment recommendations for HCV patients with chronic hepatitis C with compensated (Child-Pugh A) cirrhosis

Patients	Prior treatment experience	SOF/VEL	GLE/PIB	SOF/VEL/VOX	SOF/LDV	GZR/EBR	OBV/PTV/r + DSV
Genotype 1a	Treatment-naïve	12 wk	12 wk	No	12 wk	12 wk (HCV RNA ≤800,000 IU/ml)	No
	Treatment-experienced	12 wk	12 wk	No	No	12 wk (HCV RNA ≤800,000 IU/ml)	No
Genotype 1b	Treatment-naïve	12 wk	12 wk	No	12 wk	12 wk	12 wk
	Treatment-experienced	12 wk	12 wk	No	12 wk	12 wk	12 wk
Genotype 2	Treatment-naïve	12 wk	12 wk	No	No	No	No
	Treatment-experienced	12 wk	12 wk	No	No	No	No
Genotype 3	Treatment-naïve	No	12 wk	12 wk	No	No	No
	Treatment-experienced	No	16 wk	12 wk	No	No	No
Genotype 4	Treatment-naïve	12 wk	12 wk	No	12 wk	12 wk (HCV RNA ≤800,000 IU/ml)	No
	Treatment-experienced	12 wk	12 wk	No	No	No	No
Genotype 5	Treatment-naïve	12 wk	12 wk	No	12 wk	No	No
	Treatment-experienced	12 wk	12 wk	No	No	No	No
Genotype 6	Treatment-naïve	12 wk	12 wk	No	12 wk	No	No
	Treatment-experienced	12 wk	12 wk	No	No	No	No

DAA, direct-acting antiviral; DSV, dasabuvir; EBR, elbasvir; GLE, glecaprevir; GZR, grazoprevir; HCV, hepatitis C virus; HIV, human immunodeficiency virus; LDV, ledipasvir; OBV, ombitasvir; PIB, pibrentasvir; PTV, paritaprevir; r, ritonavir; SOF, sofosbuvir; VEL, velpatasvir; VOX: voxilaprevir.

Journal of Hepatology 2018 vol. 69 j 461–511

LEDIPASVIR/SOFosbuvir

- Ledipasvir (LDV)/SOF (Harvoni,Fosvaldi Plus,..) is FDA approved for the treatment of HCV genotypes 1 and 4 through 6
- Ribavirin may be required in combination with LDV/SOF for patients with decompensated cirrhosis or for patients who have received a liver transplant.
- Food intake minimally affects LDV/SOF concentrations

LEDIPASVIR/SOF

- Acid-suppression medications have been shown to decrease LDV concentrations
- LDV/SOF can be used in patients with any degree of hepatic impairment
- The duration of therapy is always 12 weeks unless the patient has HCV genotype 1, is treatment naïve, is not cirrhotic, is not co-infected with HIV, and has a pretreatment HCV RNA less than 6 million IU/mL; 8 weeks of therapy is sufficient in these populations.

Durg-drug interaction

- Proton pump inhibitors(PPIs),Histamin 2 Receptor Antagonist
  - Result in substantially decreased absorption of ledipasvir and velpatasvir
  - should be held for a week before and during the treatment period.
  - famotidine ≤40 mg/day or omeprazole 20 mg/day or equivalent can be provided
  - Ledipasvir or velpatasvir should be dosed >8 hours after famotidine, with orange juice.
  - Patients who are unable to wean off of higher-dose PPIs should be considered for a non-ledipasvir- or velpatasvir-containing treatment protocol.

Durg-drug interaction

- Amiodarone
  - have been associated with symptomatic bradycardia when coadministered with sofosbuvir
    and, in one case, fatal cardiac arrest.
  - Amiodarone should be stopped for a minimum of 4 weeks prior to initiating sofosbuvir.
- Rosuvastatin should not be co-administered with ledipasvir (↑ Statin;contraindicated)

Conclusions

- Vast majority of HCV infections curable
- Multiple regimens highly effective and safe across HCV genotypes
  - Outcomes confirmed in “real-world” studies
  - Most historically difficult-to-treat populations are now routinely treated


Thank You..
Raed Abouhaib