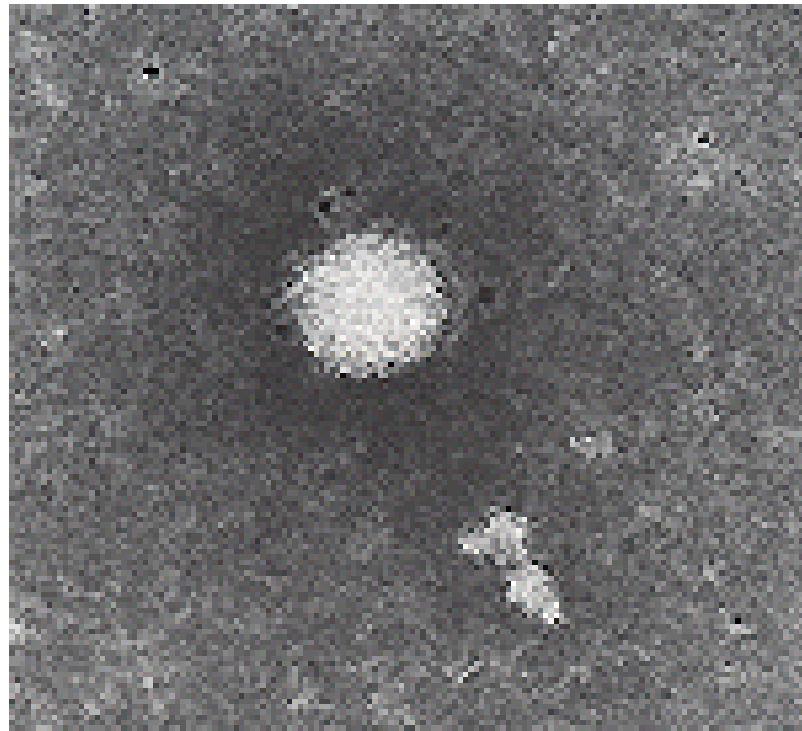


# **Western Management Of Hepatitis C Virus Infection**

**Stewart Cooper MD**

*Hepatitis C Caring Ambassadors Program  
California Pacific Medical Center, San Francisco  
CPMC Research Institute  
UCSF Liver Center*

# HCV: Western Medical Therapy

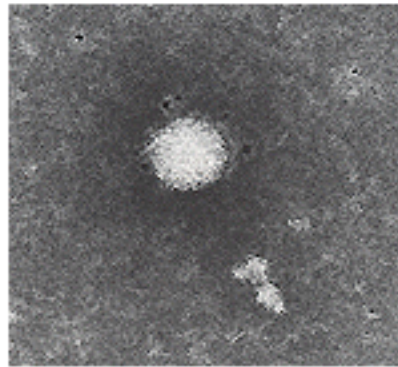


# HCV: Western Medical Therapy

## ▪ Empirical Therapies

Based on:

experience  
anecdote  
safety profile



## ▪ Logical Therapies

Based on:

research  
teleology  
safety profile

WHICH REALLY WORK  
AND ARE SAFE?



**CLINICAL TRIALS**

**The Result of HCV-based Clinical Trials:**

**Current Western Therapy for HCV:**

**Interferon alpha + Ribavirin**

# Interferon (IFN)

- Discovered by Isaacs and Lindemann 1957
- Naturally occurring
- 3 related but distinct structural groups:
  - *ALPHA*
  - *BETA*
  - *GAMMA*
- Interferon alpha:  
(15 Types)
  - IFN alpha 2a
  - IFN alpha 2b

***HCV Rx***

# Interferon-alfa: Mechanisms of Action

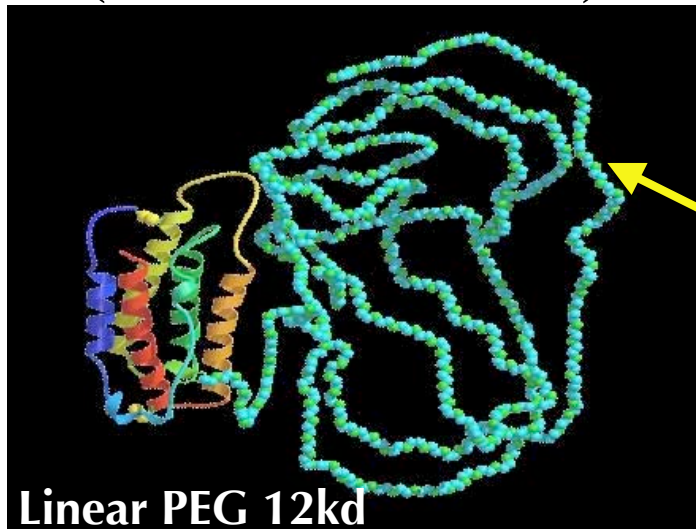
- *Anti-viral actions*
  - multiple sites
- *Augmented Cellular Immunity*
  - Increased T cell-mediated (“Th1”) immunity
  - HLA Class I (-A,B,C) and II (-DR,DP,DQ) upregulation
  - Enhanced innate immunity (NK cells)
- *Anti-proliferative effects* (↓Fibrosis)

# Pegylated Interferons

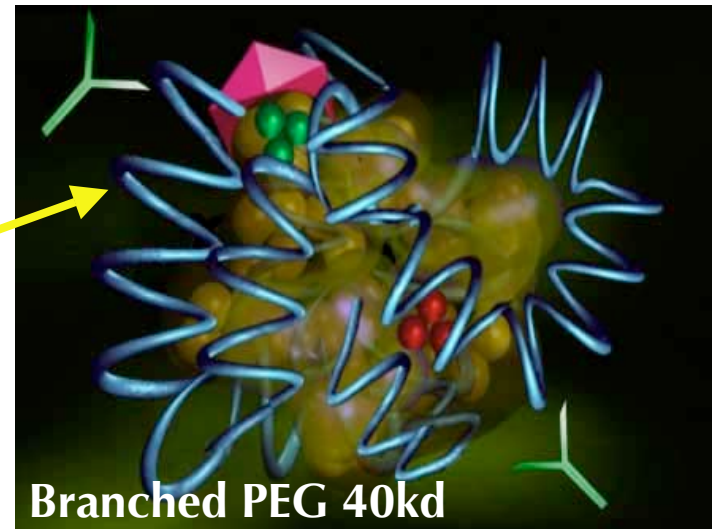
IFN- $\alpha$



**PEG-INTRON** Schering Plough  
(Interferon-alfa2b)

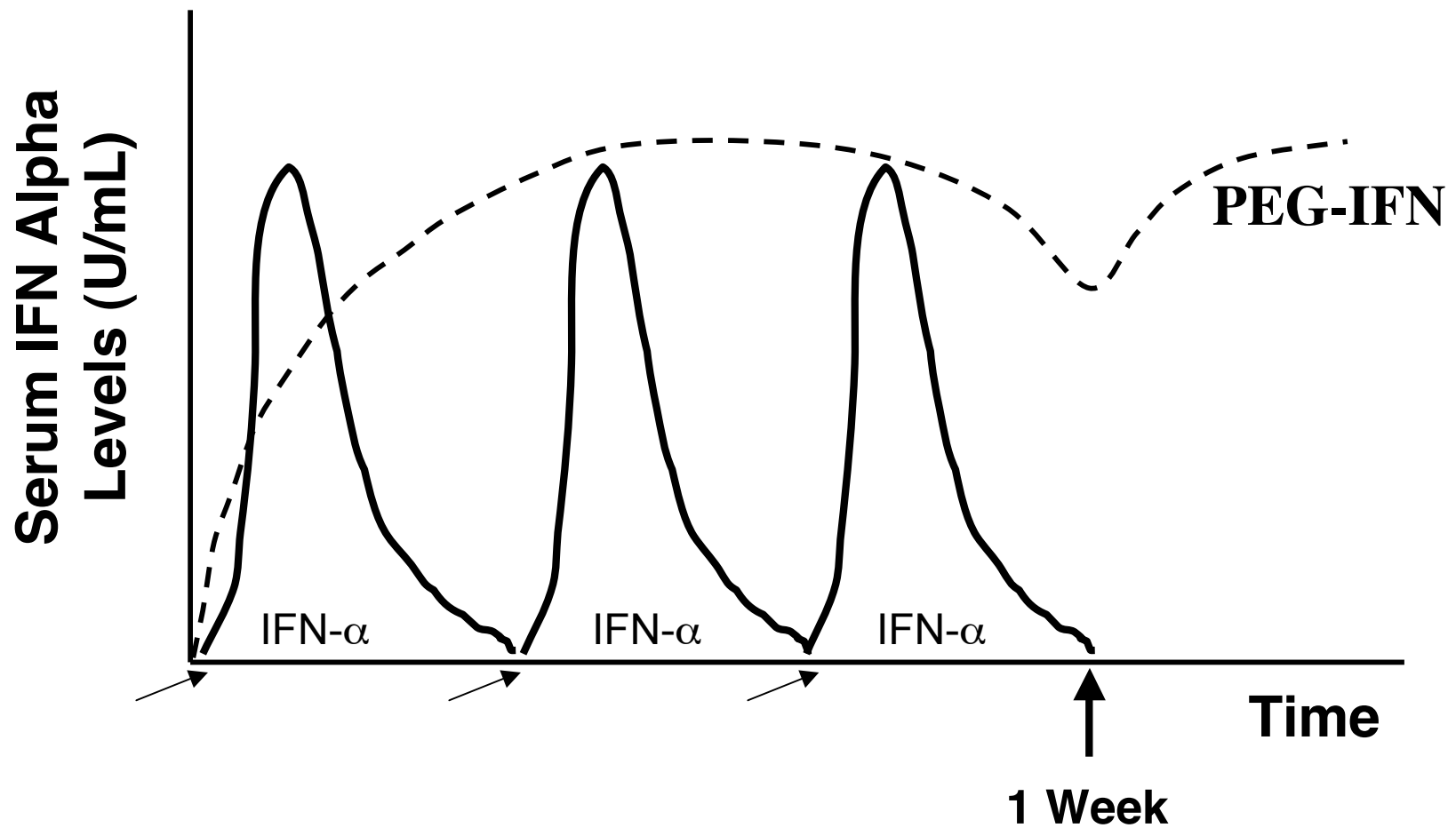


**PEGASYS** Roche  
(Interferon-alfa2a)



PEG

# Interferon Levels: Pegylated vs. Standard Interferon-alpha



Modi MW et al. *Hepatology*. 2000;32(4 pt 2):394A  
Xu Z-X et al. *Hepatology*. 1998;28(4 pt 2):702A.

# Ribavirin: Mechanism of Action

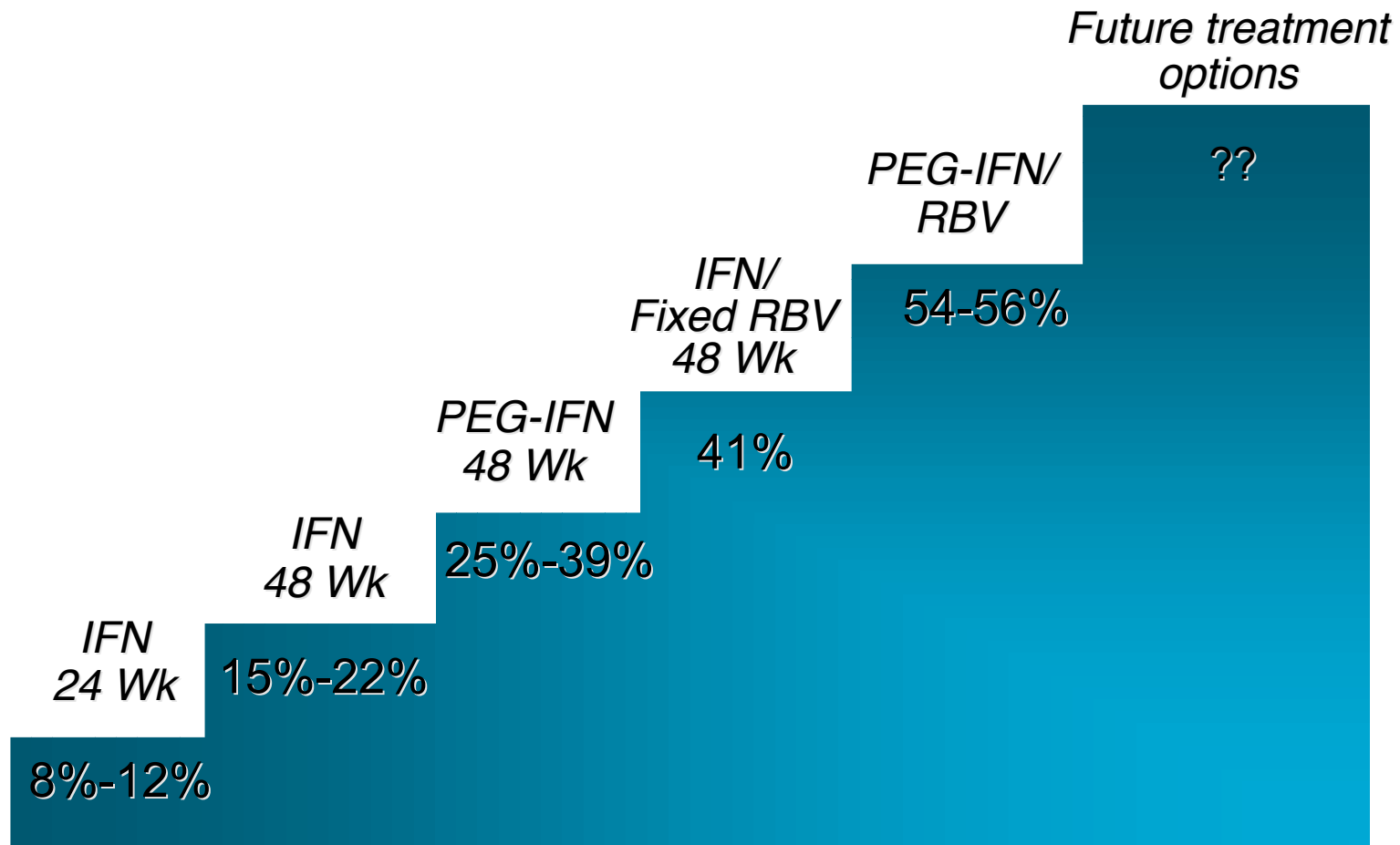
- Synthetic Guanosine analogue:
  - Inhibits IMPDH (Inosine-5'-monophosphate dehydrogenase)
  - Inhibits RNA and DNA synthesis
  - Activity against some RNA and DNA viruses
- Weak if any inhibitory effect on HCV replication/VL
- Significant adjunctive therapeutic effect with Interferon
  - Enhances Antiviral Responses
  - Reduces Relapse Rates
- Principal action may be its immune stimulating effect.

# Pegylated Interferon-alfa + Ribavirin combination therapy

- Two Peg-Interferons:
  - Interferon- $\alpha$ 2a (Pegasys : Roche) 40kd PEG (*K23*)
    - Dose: 180ug/week sc (“Flat dose”)
  - Interferon- $\alpha$ 2b (Pegintron : Schering) 12kd PEG (*R23*)
    - Dose: 1.5ug/kg/week sc (“Wt-based” dosing)
- Two Proprietary Ribavirin formulations: Copegus (Roche) and Rebetol (Schering)
  - **HCV genotypes 1, 4:** Wt-based Dosing:  
Copegus  $\geq 75\text{kg}$   $\rightarrow$  1200mg/d //  $< 75\text{kg}$   $\rightarrow$  1000mg/d (75kg  $\approx$  165lbs)  
Rebetol: 15mg/kg/d
  - **HCV genotypes 2, 3:** 800mg/d po
- **Rx Duration:** Genotypes 1, 4 = 48 weeks  
Genotypes 2, 3 = 24 weeks

# Treatment Evolution of Hepatitis C:

## *Associated SVR %*



# Peg-IFN + Ribavirin SVR Rates in HCV Infection

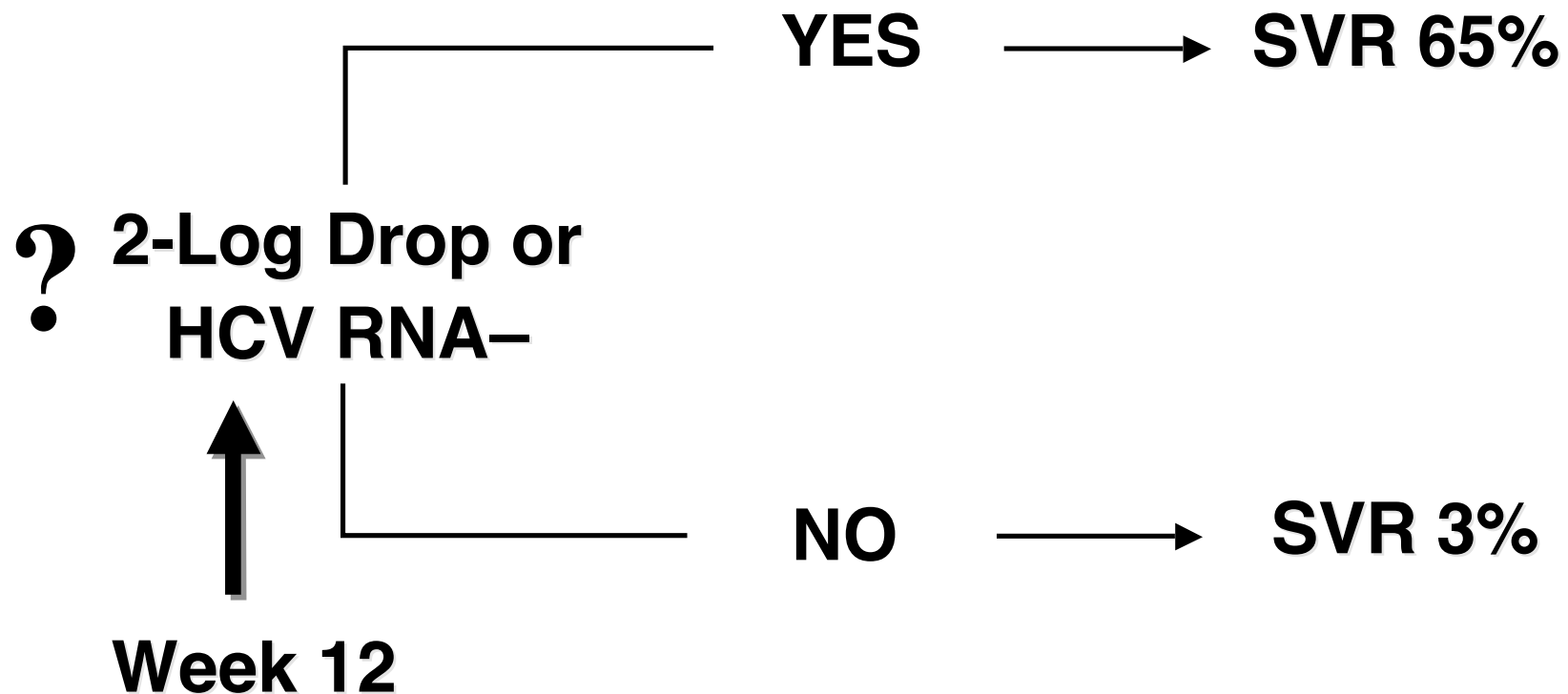
| <b>Genotype</b> | <b>High VL<br/>&gt;800k iu/ml</b> | <b>Low VL<br/>≤800k iu/ml</b> |     |
|-----------------|-----------------------------------|-------------------------------|-----|
| I               | ~47%                              | ~65%                          | SVR |
| II/III          | ~85%                              | ~84%                          | SVR |

*Hadziyannis et al Ann Int Med 2004;140:346-55*

*Other Outcome-influencing Variables: Race, BMI, Advanced Fibrosis, Alcohol*

# Early Viral Response: Prognostic Relevance

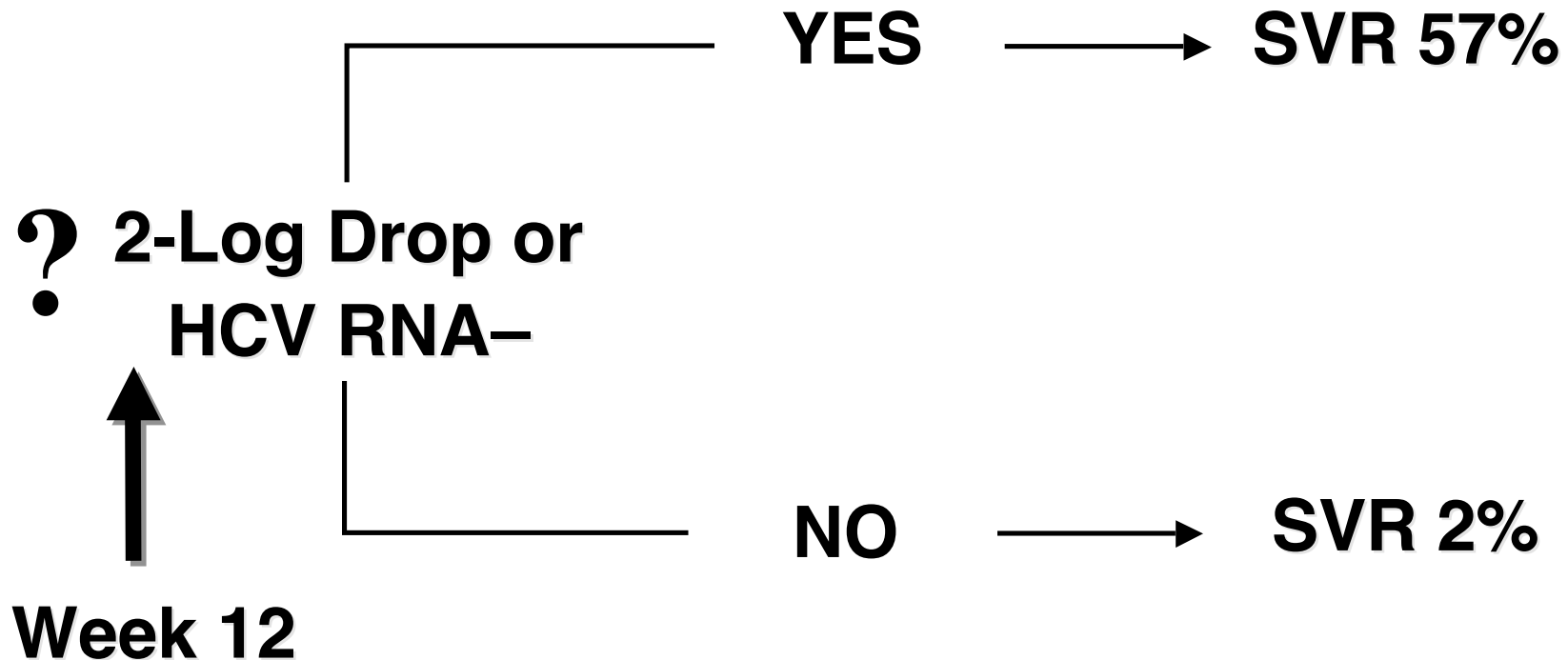
**EVR defined by change in VL after 12 weeks therapy**



*Pegasys+Ribavirin*

Fried MW, et al. *N Engl J Med.* 2002;347:975.

# Early Viral Response: Genotype 1 Rx: Pegasys+Ribavirin



# Pegylated Interferon Comparisons

- Are Pegylated Interferons equally effective?
- EASL 2004 poster#490: Genotype 1: Luise et al:

| <b>WEEK POST Rx</b>   | <b>12</b> | <b>EOT (48)</b> |
|---|-----------|-----------------|
| <b>Peg-Intron</b><br>1.5mcg/kg/wk +<br>Ribavirin 15mg/kg/d<br><b>N=52</b> | 60%       | 76%             |
| <b>Pegasys</b><br>180mcg/wk<br>Ribavirin 1000 - 1200mg/d<br><b>N=23</b>   | 30%       | 55%             |

*Caveats: Small numbers; Non-randomized; Assymmetric Rx groups  
Needed: Randomized “head to head” study.*

# Recent Treatment Considerations

- Genotype 1 infection:
  - Is shorter Rx duration possible?
    - Rapidity of VR: What if EVR achieved by 4 weeks (RVR)?
  - What if VR delayed?
    - Can SVR be improved by longer Rx duration?
    - Is duration of viral suppression critical?
- Genotype 2/3 infection:
  - Same Rx responsiveness?
  - Is even shorter Rx duration possible?

# Genotype 1 with RVR-Can we treat for shorter duration?

- *Zeuzem et al., J Hepatol 2006*
  - Genotype 1 (n=235)
  - Low pre-tx viremia (<600,000 IU)
  - Peg-IFN alpha 2b + Rib 800-1400 mg/day for 24 wks
  - 50% SVR lower than 48 week historical control rate of 71%
- Subset with RVR
  - 89% SVR similar to 48 week historical control rate of 85%

# Recent Rx Considerations: G1

- Is shorter Rx duration possible?
  - 24hr VR predicts Rx response: Jessner et al Lancet 2001
  - 4 week EVR (“Super Responders”) predicts very high SVR  
Ferenci et al. J Hepatol 2006
    - Retrospective analysis of Fried’s cohort: 100% of Super Responders (91/240) achieved SVRs.
  - Super Responder SVRs following 24wk Rx
    - 86.7%
    - 78.2% (ITT)  
Ferenci et al. Shanghai-Hong Kong Intl Liver Congress 2006 Poster (N=372)
    - 89% {G1 LVL (<600k iu/ml)} Peg-intron+RVN  
Zeuzem et al. J Hepatol 44(1): 97-103;2006

# Recent Rx Considerations: G1

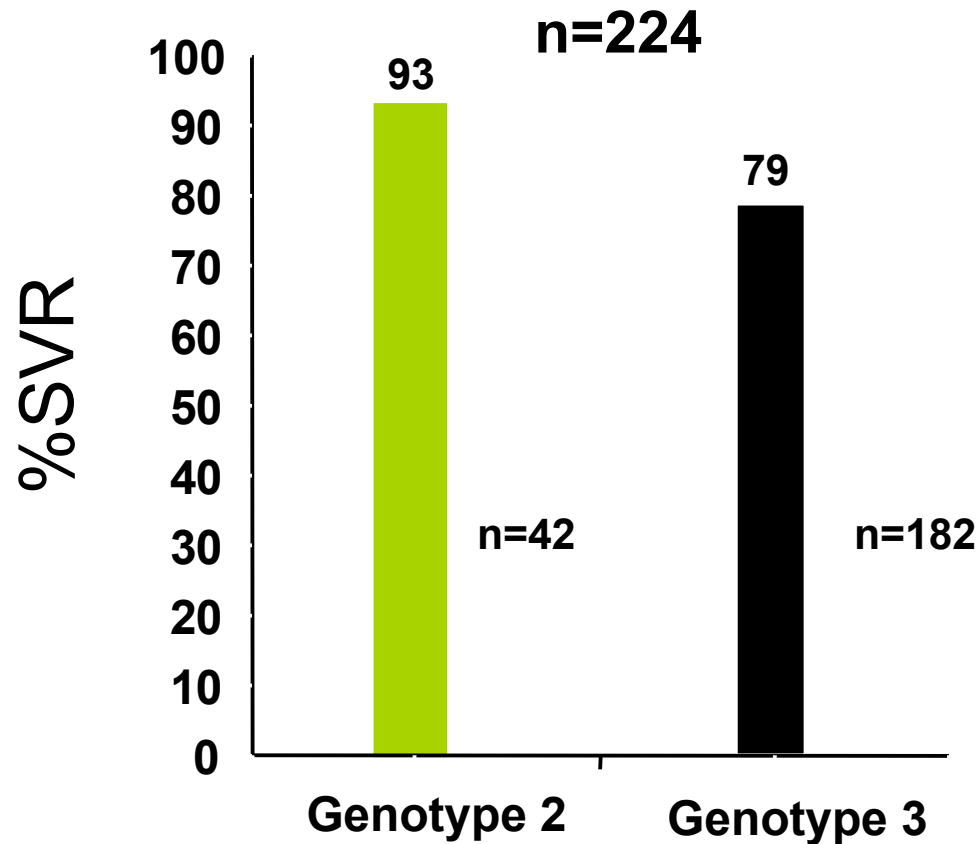
- What if VR is slow (week 12+ week 24 neg)?
  - Can SVR be improved by longer Rx duration?

*Gastroenterology. 2006 Apr;130(4):1357-62 Pegasys + RVN 800mg*

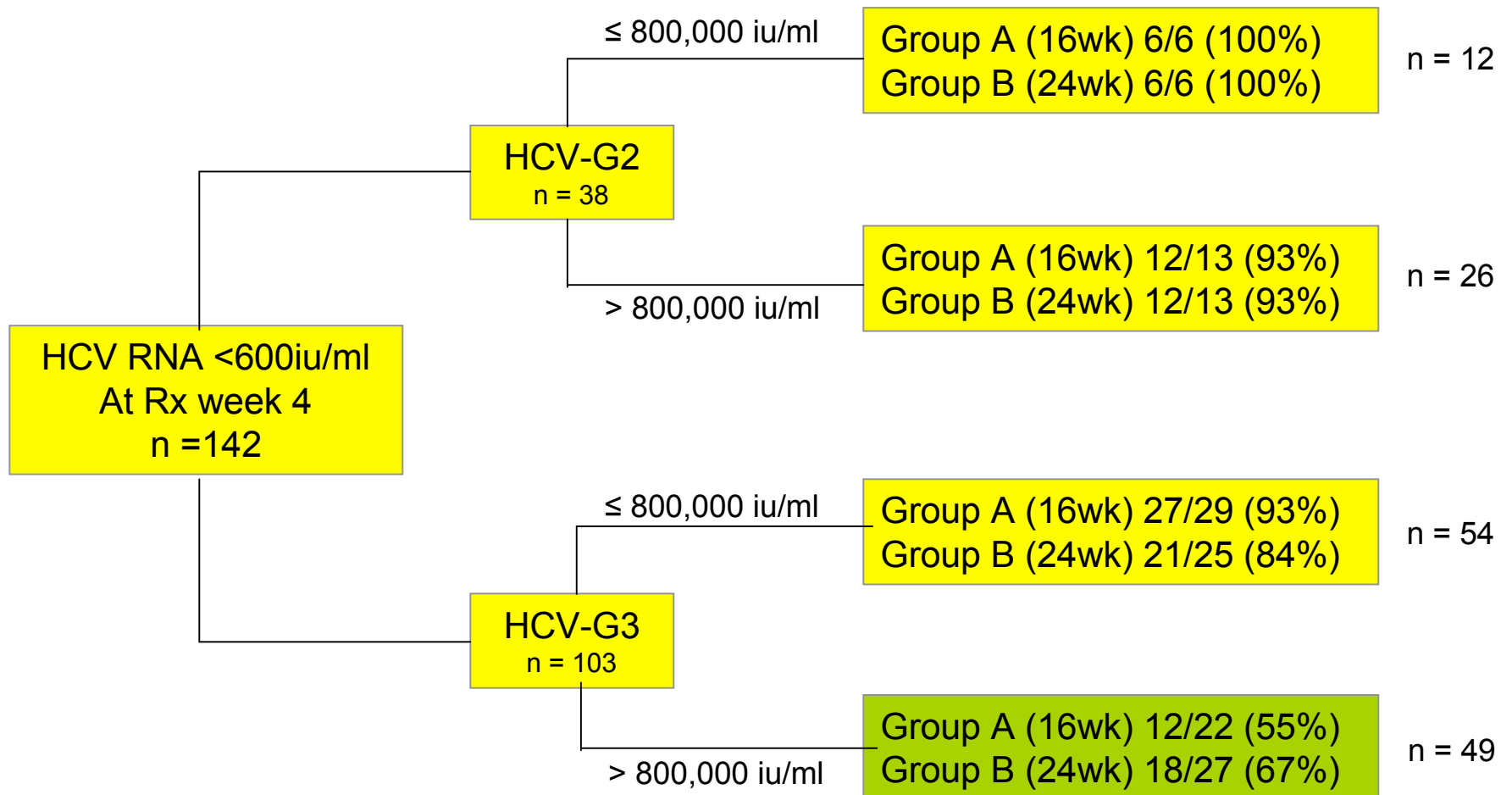
| <b>WEEK 12<br/>HCV RNA</b> | <b>SVR<br/>(48wk)</b> | <b>SVR<br/>(72wk)</b> |       |
|----------------------------|-----------------------|-----------------------|-------|
| NEGATIVE                   | 63%                   | 54%                   | P=ns  |
| POSITIVE                   | 17%                   | 29%                   | P=.04 |

- Therefore is duration of viral suppression critical?

# **SVR Genotype 2/3 Dissection: PEG-IFN- $\alpha$ 2b + RVN 800-1400 mg (24 wk)**



# SVRs in Early Responders Stratified by Genotype and Pre-Rx Viral Loads



# Who Should *Not* Be Treated?

- Allergy or hypersensitivity to IFN or ribavirin
- Unstable severe neuropsychiatric disease
- Uncontrolled Coronary disease, Diabetes
- Active Autoimmune / Connective tissue Disease
- Unwilling to practice reliable birth control
- Pregnancy (breast feeding)
- Severe Anemia and/or Low Platelets

# Relative Contraindications To Therapy

- Active alcohol or drug use
- Decompensated Liver Disease
- Following (non-liver) Organ Transplantation

# **Interferon and Ribavirin**

**How can we maximize Rx  
Responses?**

# Interferon: Common Side Effects

## Rarely dose limiting

- Flu-like symptoms
  - Headache
  - Fatigue
  - Muscle and Joint aches
  - Fever, Chills
- Nausea
- Diarrhea
- Hair Loss
- Injection site reaction

## Commonly dose limiting

- Psychiatric symptoms
  - depression
  - insomnia
- Low Neutrophils (white cells)
- Low Platelets
- Autoimmunity

# Interferon-associated Depression

- incidence of depression/irritability during interferon therapy:
  - 24% depressive symptoms and 12% with major depression on 3MU TIW<sup>1</sup>
  - 29-31% developed depression with pegylated interferon<sup>2</sup>
  - 33-47%<sup>3,4</sup> anxiety, emotional lability, irritability
  - 10-17%<sup>3,4</sup> concentration impairment

<sup>1</sup> Castera et al, Hepatology 2002;35:978

<sup>2</sup> Manns et al, Lancet 2001;358:958

<sup>3</sup> Pegasys PI. Nutley, NJ: Roche Pharmaceuticals; 2002

<sup>4</sup> PEG-Intron PI. Kenilworth, NJ: Schering Corp; 2001.

# Ribavirin: Side Effects

- Serious adverse events:
  - hemolytic anemia
  - birth defects
- Milder symptoms
  - Cough
  - Shortness of breath
  - Skin rash, Itching
  - Reduced appetite

# Anemia Associated with Combination Therapy

- anemia occurs to some degree in every patient treated with combination antiviral therapy<sup>1</sup>
- hemoglobin decreases 2-3 g/dL within the first 4 weeks of peg-IFN/ribavirin<sup>2</sup>
- 9%-22% of patients require dose modification due to changes in hemoglobin <sup>1,3</sup>
- 36% of treatment discontinuations are secondary to anemia<sup>4</sup>

<sup>1</sup> Russo MW, et al. *Gastroenterology*. 2003;124:1711.

<sup>2</sup> De Franceschi, et al. *Hepatology*. 2000;31:997.

<sup>3</sup> Rebetol PI. Kenilworth, NJ: Schering Corp; 2001.

<sup>4</sup> Gaeta GB, et al. *Aliment Pharmacol Ther*. 2002;16:1633.

# Consequences of Side Effects

- Anemia
  - fatigue, impaired QoL and reduced adherence
  - risk of coronary insufficiency

BUT ↓RBV dose = ↓ SVR!
- Neutropenia (↓ANC)
  - ↓ peg-IFN dose
  - risk of infection
- Thrombocytopenia (↓Platelets)
  - ↓ peg-IFN dose
  - risk of bleeding

# Improving Peg-IFN/RVN Responses

- The Patient
  - Depression or substance abuse addressed in advance
  - Education – consequences of non-adherence or f/u

≥80% Expected Ribavirin dose

≥80% Expected IFN dose

≥80% Expected Rx Duration

**Improves SVR**

- Education – weight loss/exercise program
- support systems – family/peers/professional

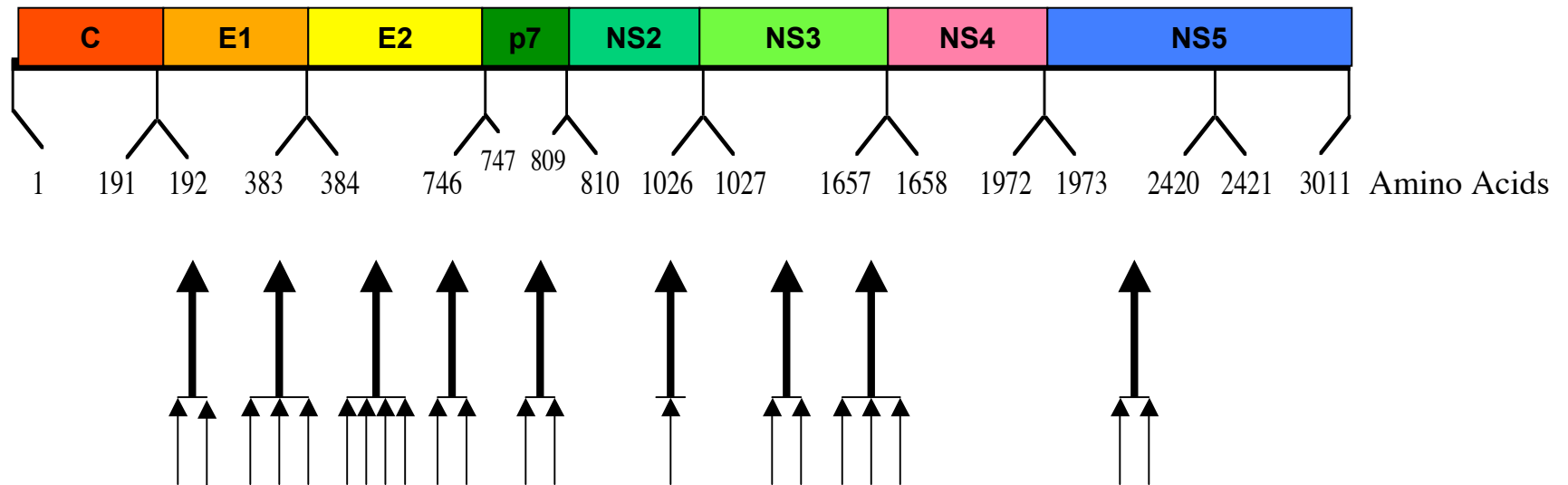
# Improving Peg-IFN/RVN Responses

- The Side Effects
  - educate
  - access to healthcare staff (*attentive monitoring*)
  - Antidepressants
  - Erythropoietin (? Iron)
  - GCSF (Neupogen)

# **WINNING THE STRUGGLE AGAINST HCV MUTATION**

# Studies of Natural Immune Clearance of HCV

## Map of HCV Structure



### 21 HCV-specific Cytotoxic T Lymphocytes

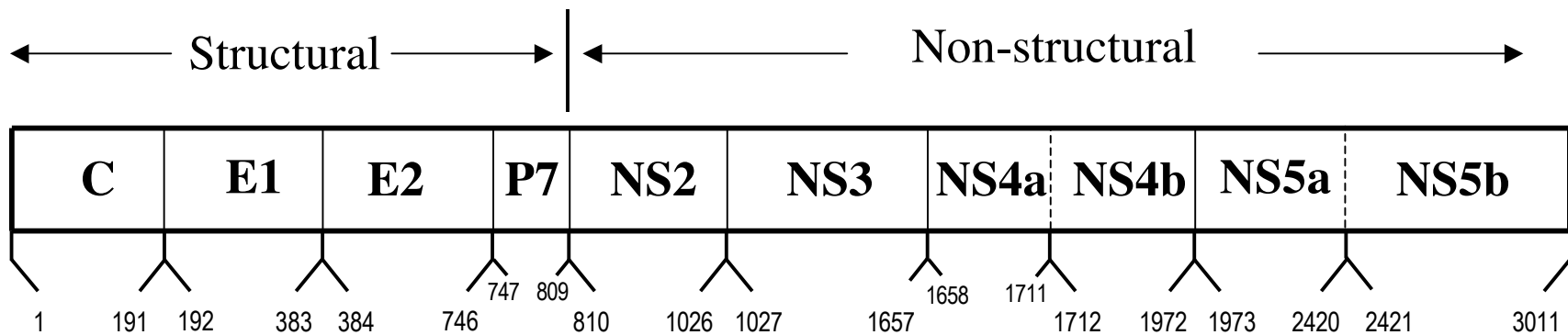
- Cytotoxic T cells simultaneously target many HCV proteins
- Many CTL even attack the same target

# Can We Achieve Higher Rates of HCV Clearance?

- Successful immune responses and HIV ART may be showing us how
- Probably by exerting “selection pressure” at multiple points simultaneously
- A combination of therapies likely to emerge, as in HIV infection

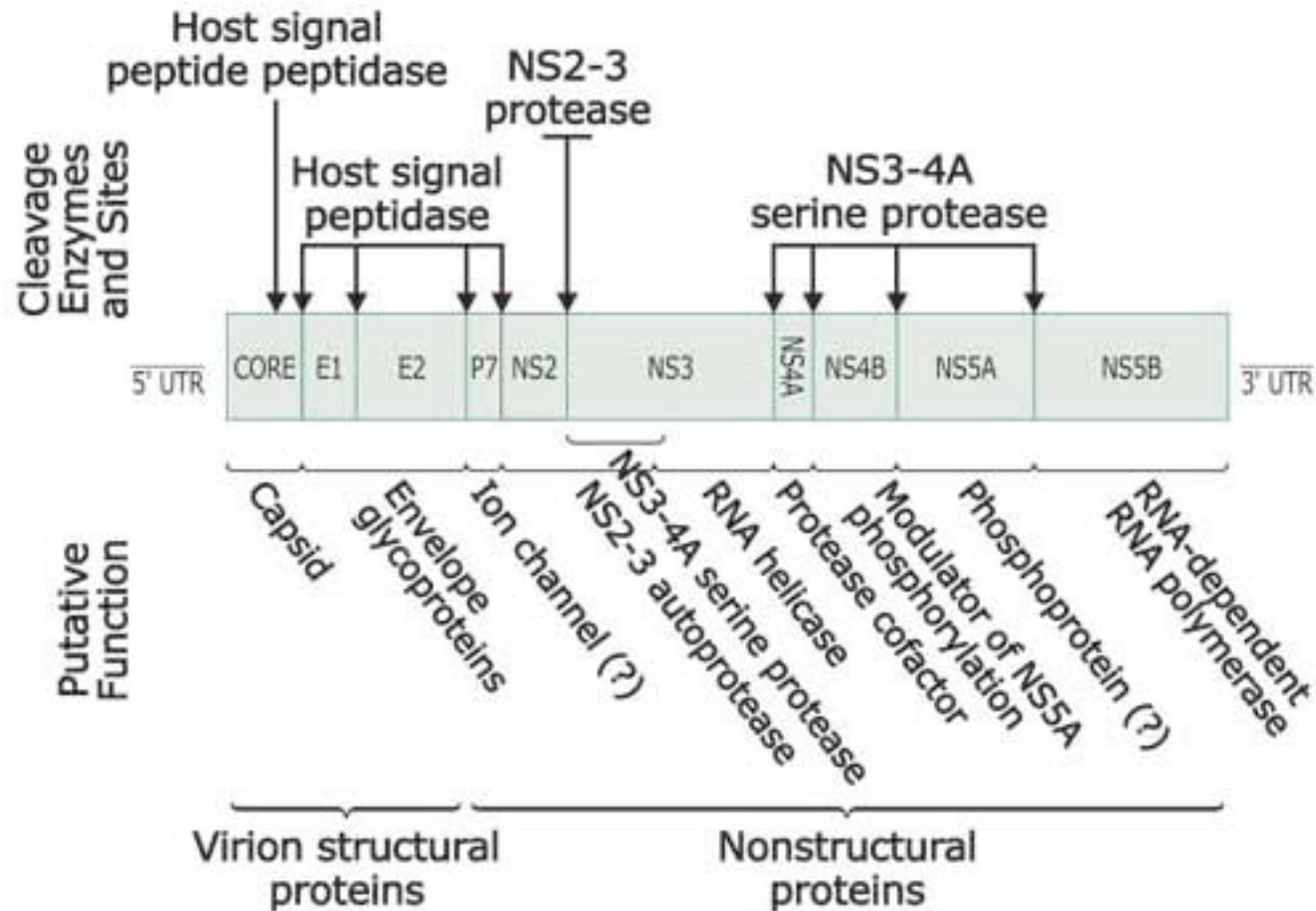
# **NEW ANTIVIRAL AGENTS**

# HCV-1 Protein Structure



- **9.6 kb + RNA Open Reading Frame**
- **3010-3033 Amino Acid Polyprotein Precursor (HCV-1= 3011)**
- **10 Proteins: Structural and Nonstructural**

# Known Functions of the HCV Polyprotein



# Translational Relevance of Basic HCV Viral Studies: Strategic Approaches

## 1. Design of Inhibitors of the HCV-encoded enzymes:

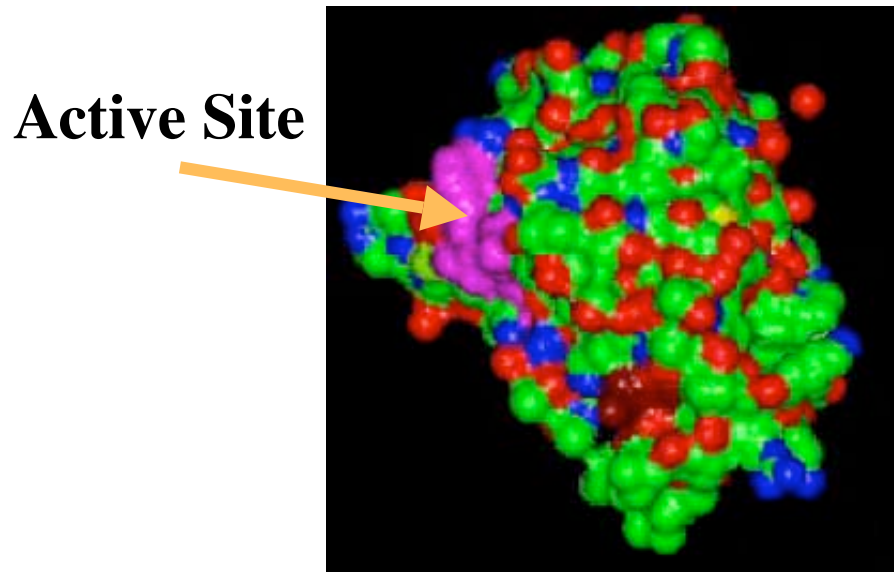
NS2-3 Protease

NS3-4A Protease

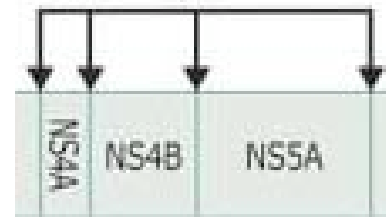
NS3 Helicase

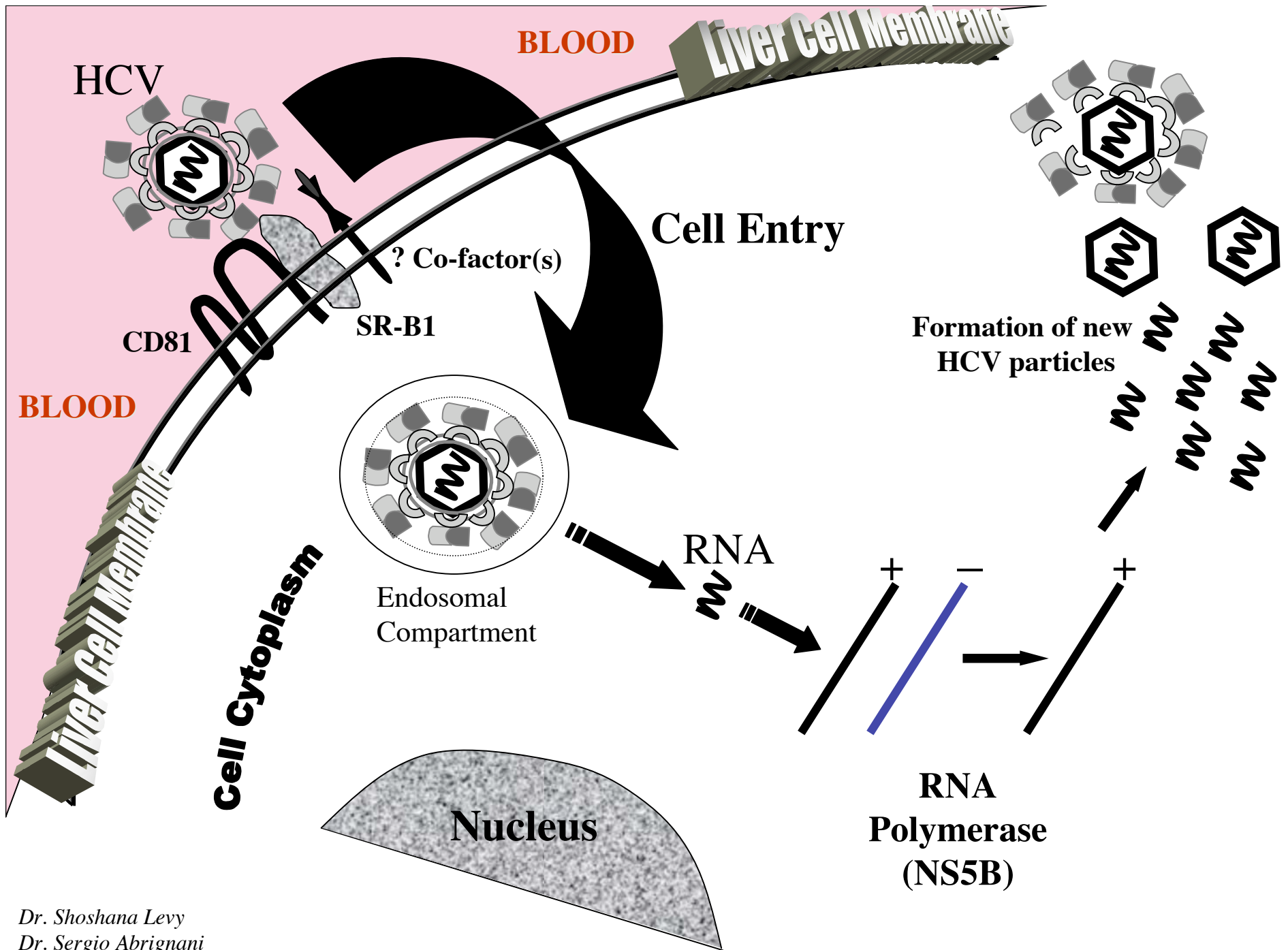
NS5 RNA-directed RNA Polymerase

NS3-4A Protease Crystal Structure



NS3-4A Protease Enzyme  
Cleavage Sites





Dr. Shoshana Levy  
 Dr. Sergio Abrignani  
 Dr. François-Loïc Cosset

# New HCV Antiviral Agents

## 2. Development of drugs that specifically disrupt HCV life cycle:

- **Targets:** multiple -- Cell entry to egress.

## 3. Development of other/more potent immune stimulators:

### – **Other IFNs:**

- Infergen & Peg-Infergen
- Interferon gamma 1b
- Albuferon-alpha
- Omega Interferon

### – **Less toxic versions of Ribavirin:**

- Viramidine: a RVN prodrug which is activated in the liver resulting in reduced ribavirin accumulation in red blood cells.

### – **Drugs Promoting Other Mechanisms:**

#### • **TLR agonists:**

- TLR-7: ISATORIBINE
- TLR-9: ACTILON

# New HCV Antiviral Agents

- **Obstacles**

- Delivery
- Inactivation: eg. by host nucleases.
- Interactions
- Toxicity: eg. BILN2061 cardiotoxicity in animals.
- Resistance.

- **In Human Trials**

- SCH7:
- VX-950:

- **5-year Expectations**

- Interferon-based combination therapies.
- Lower doses IFN/RVN (or RVN replacements) may be achievable with newer combination therapies.

