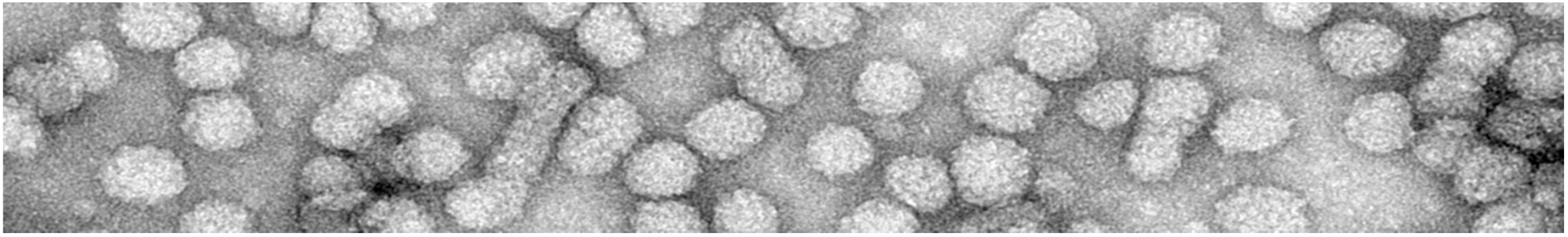
Vers un vaccin bivalent contre les virus des hépatites B et C ?



Philippe Roingeard - INSERM U966 - Tours

roingeard@med.univ-tours.fr

19 mai 2015

Gastroenterology 2014;146:1176–1192

New Hepatitis C Therapies: The Toolbox, Strategies, and Challenges

Jean–Michel Pawlotsky

Therapy for hepatitis C is undergoing a revolution. Several new drugs against the hepatitis C virus (HCV) have reached the market and many others, including direct-acting antivirals and host-targeted agents, are in phase II or III clinical development. All-oral, interferon-free combinations of drugs are expected to cure more than 90% of infections...

Keywords: Direct-Acting Antivirals; Interferon-Free Regimens; Sofosbuvir; Simeprevir; Daclatasvir.

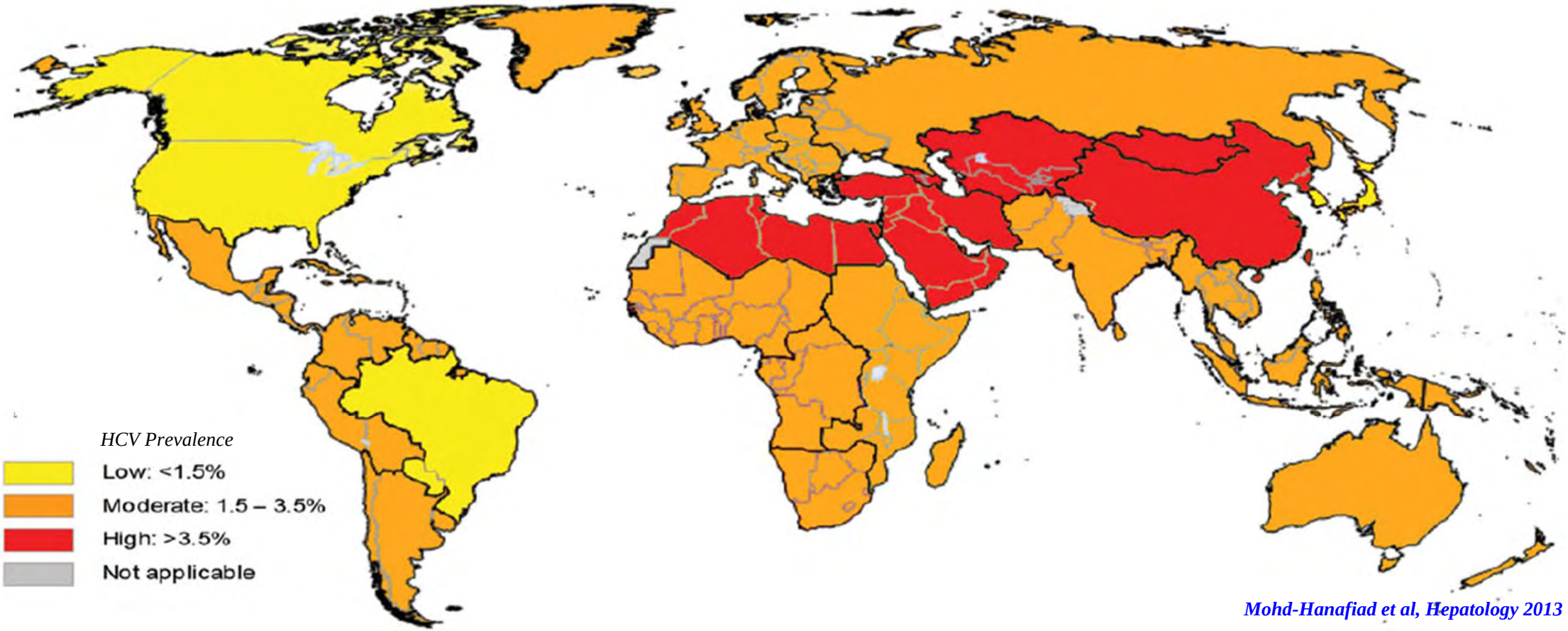
→ **… but DAA therapies are very expensive and therefore unlikely to be adopted universally.**

→ **Low-cost / generic drugs will potentially be available in the futur in low-income countries**

… but most HCV-infected subjects are not aware of their infection,

then the cost of large-scale HCV screening + DAA treatment will remain very high.

→ **≈ 15% of patients display persitent hepatic inflammation and / or cirrhosis despite virological cure.**



Mohd-Hanafiad et al, Hepatology 2013

→ **180 million people currently infected worldwide**

World Health Organization

→ **3-4 million new infections (mostly by blood contact : IVDU, unsafe medical practices, health workers)**

each year

HCV epidemiology in 2015 in the USA

Test and treat this silent killer

The scourge of hepatitis C virus in the United States is woefully underestimated. **Brian R. Edlin** reckons it's time the infection is given the priority it demands.

S18 | NATURE | VOL 474 | 9 JUNE 2011

OPEN ACCESS Freely available online May 2013 | Volume 8 | Issue 5 | e63959 PLOS ONE

Current and Future Disease Progression of the Chronic HCV Population in the United States

Martin Zalesak[1]*, Kevin Francis[1], Alex Gedeon[1], John Gillis[1], Kyle Hvidsten[2], Phyllis Kidder[2], Hong Li[1], Derek Martyn[1], Leslie Orne[1], Amanda Smith[1], Ann Kwong[2¤]

1 Trinity Partners, LLC, Waltham, Massachusetts, United States of America, 2 Vertex Pharmaceuticals Incorporated, Cambridge, Massachusetts, United States of America

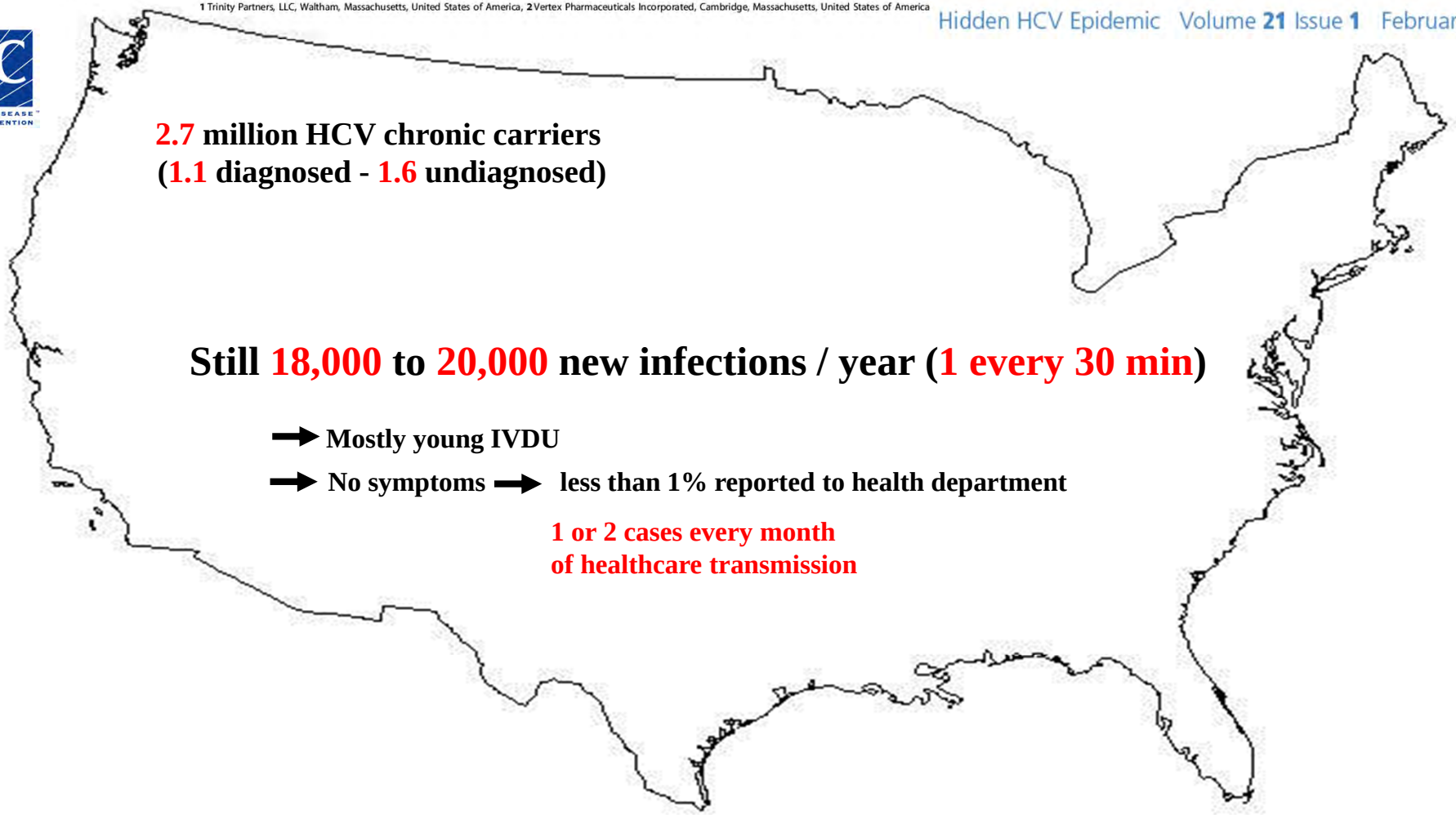
Perspective IAS–USA Topics in Antiviral Medicine

The Hidden Epidemic of Hepatitis C Virus Infection in the United States: Occult Transmission and Burden of Disease

Dr Ward is Director of the Division of Viral Hepatitis at the Centers for Disease Control and Prevention in Atlanta, Georgia.

Hidden HCV Epidemic Volume 21 Issue 1 February/March 2013

CDC CENTERS FOR DISEASE CONTROL AND PREVENTION



2.7 million HCV chronic carriers
(1.1 diagnosed - 1.6 undiagnosed)

Still 18,000 to 20,000 new infections / year (1 every 30 min)

- **Mostly young IVDU**
- **No symptoms → less than 1% reported to health department**

1 or 2 cases every month
of healthcare transmission

HCV epidemiology in 2015 in China

Gao et al. BMC Infectious Diseases 2011, 11:88
http://www.biomedcentral.com/1471-2334/11/88

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Prevalence and trend of hepatitis C virus infection among blood donors in Chinese mainland: a systematic review and meta-analysis

Xiaofei Gao[1,2†], Qian Cui[1†], Xiang Shi[1,2†], Jing Su[1], Zhihang Peng[1], Xin Chen[1], Na Lei[1], Keqin Ding[1], Lu Wang[3], Rongbin Yu[1*] and Ning Wang[3*]

Liver INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL ASSOCIATION FOR THE STUDY OF THE LIVER

Liver International (2011)

Liver International ISSN 1478-3223

A systematic review of hepatitis C virus epidemiology in Asia, Australia and Egypt

William Sievert[1], Ibrahim Altraif[2], Homie A. Razavi[3], Ayman Abdo[4], Ezzat Ali Ahmed[5], Ahmed AlOmair[6], Deepak Amarapurkar[7], Chien-Hung Chen[8], Xiaoguang Dou[9], Hisham El Khayat[10], Mohamed elShazly[11], Gamal Esmat[12], Richard Guan[13], Kwang-Hyub Han[14], Kazuhiko Koike[15], Angela Largen[3], Geoff McCaughan[16], Sherif Mogawer[17], Ali Monis[18], Arif Nawaz[19], Teerha Piratvisuth[20], Faisal M. Sanai[21], Ala I. Sharara[22], Scott Sibbel[3], Ajit Sood[23], Dong Jin Suh[24], Carolyn Wallace[3], Kendra Young[3] and Francesco Negro[25]

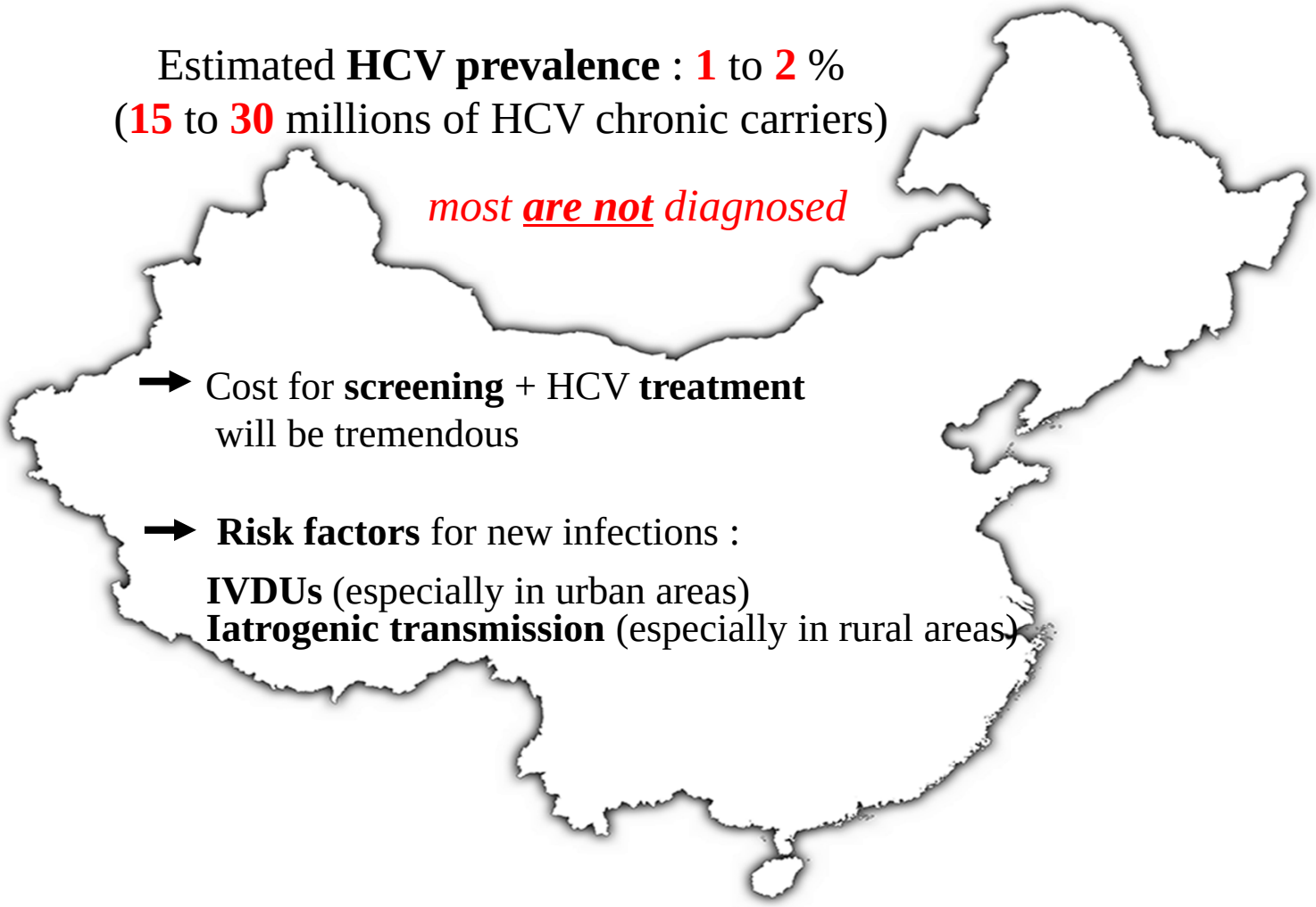
Hepatitis C Seroprevalence and Associated Risk Factors, Anyang, China

Fangfang Liu,[1] Ke Chen,[1] Zhonghu He, Tao Ning, Yaqi Pan, Hong Cai, and Yang Ke

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 15, No. 11, November 2009

Estimated **HCV prevalence** : **1** to **2** %
(**15** to **30** millions of HCV chronic carriers)

*most **<u>are not</u>** diagnosed*



→ Cost for **screening** + HCV **treatment** will be tremendous

→ **Risk factors** for new infections :

IVDUs (especially in urban areas)
Iatrogenic transmission (especially in rural areas)

→ **An HCV prophylactic vaccine is a medical priority** → **best hope of controlling the world epidemic**

→ **opportunity to significantly reduce healthcare cost**
(especially if the HCV vaccine is associated with the HBV vacine)

The HBV vaccine has considerably reduced the incidence of HBV-induced HCC

Will There Be a Vaccine to Protect Against the Hepatitis C Virus?

Benoît Callendret, Christopher M. Walker
The Research Institute at Nationwide Children's Hospital and Department of Pediatrics, College of Medicine, The Ohio State University

Gastroenterology
Volume 142, Issue 6, May 2012, Pages 1384–1387

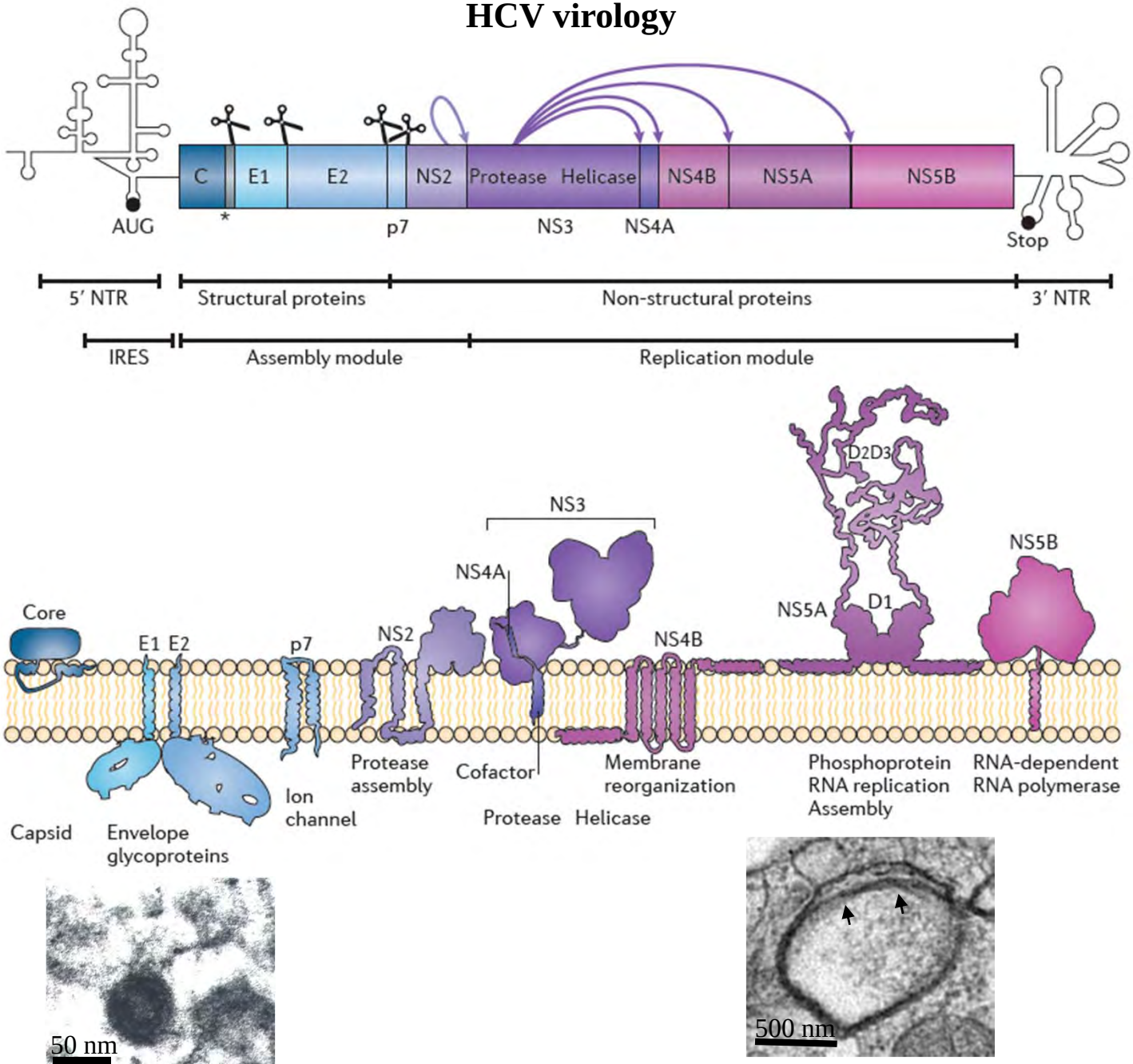
After many years of controversy, a partially-effective HCV vaccine (≈ 60-80% efficacy) appears to be a feasible goal based on :

→ **Natural immunity demonstrated in re-exposed humans & chimpanzees**

→ **Natural immunity linked with viral-specific CD4+ & CD8+ T cell responses & cross-neutralising antibodies**

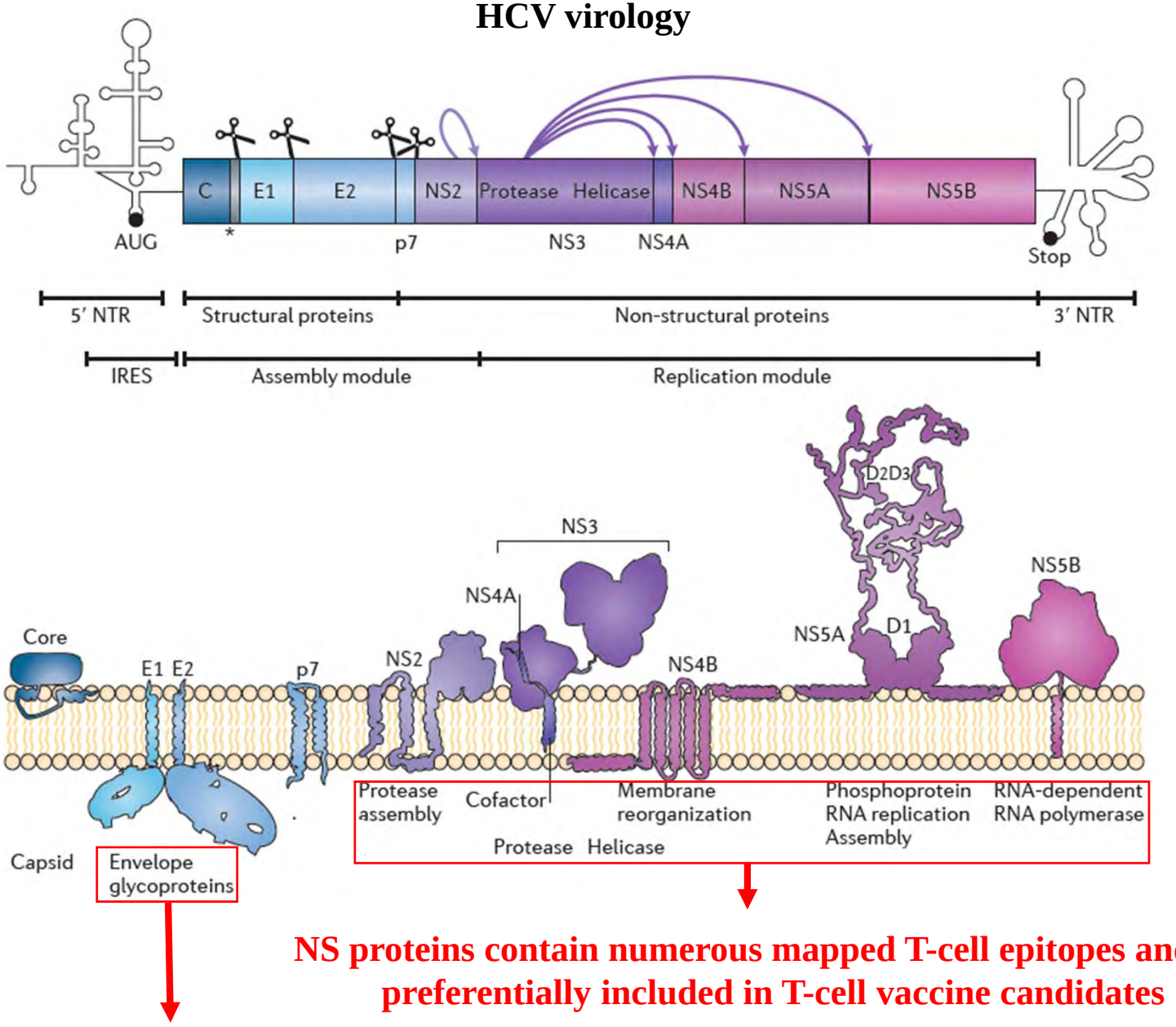
→ **Chimpanzee studies demonstrating that vaccinated animals are protected against the development of the carrier state**

HCV virology



Adapted from Bartenschlager et al, Nat Rev Microbiol 2013

HCV virology

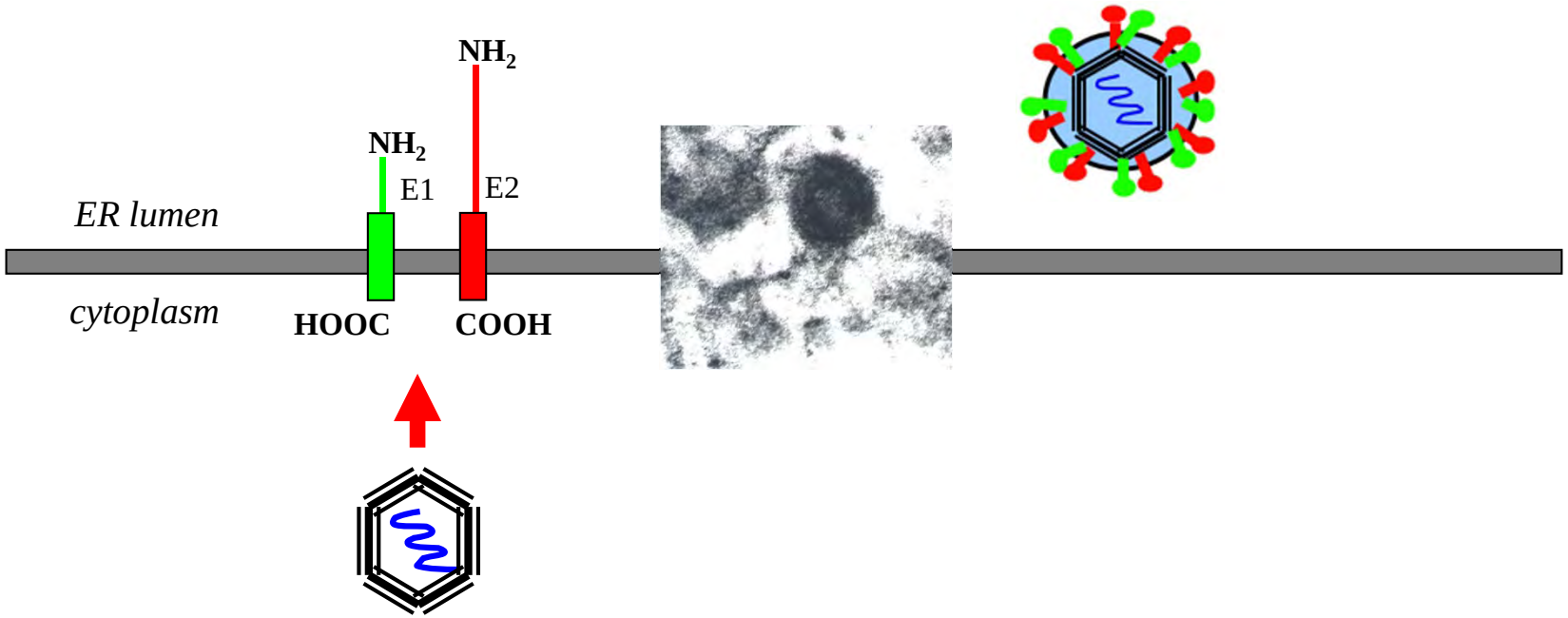


NS proteins contain numerous mapped T-cell epitopes and are preferentially included in T-cell vaccine candidates

E1&E2 proteins can induce neutralizing antibodies (nAbs)

okairos
from genes to vaccines

Recombinant E1-E2 vaccine



- **Native heterodimer complex comprising both full lenght envelope glycoproteins E1 (33KDa) & E2 (17KDa)**
- **Produced in CHO or Hela cell lines**
- **E1-E2 retained in the ER via transmembrane domain (TMD)**
- **Primes the induction of viral nAbs a CD4+ T-cell response**

Dr M. Houghton & collaborators

CHIRON

NOVARTIS

Recombinant E1-E2 vaccine

Combined HCV vaccine preclinical data in the chimpanzee model

(combined results from homologous HCV 1a & heterologous HCV 1a challenges)

		number that developed:	
	number	acute infection	chronic infection
Vaccinees	31	26 (84%)	5 (16%)
Controls	24	24 (100%)	15 (62%)

P < 0.001

Houghton & Abrignani, Nature 2005 ; Houghton Immunol Reviews 2011

Chimpanzee studies performed at CHIRON / NOVARTIS *over the course of 15 years (1994-2009) with various adjuvants and recombinant E1-E2 of varying purities*

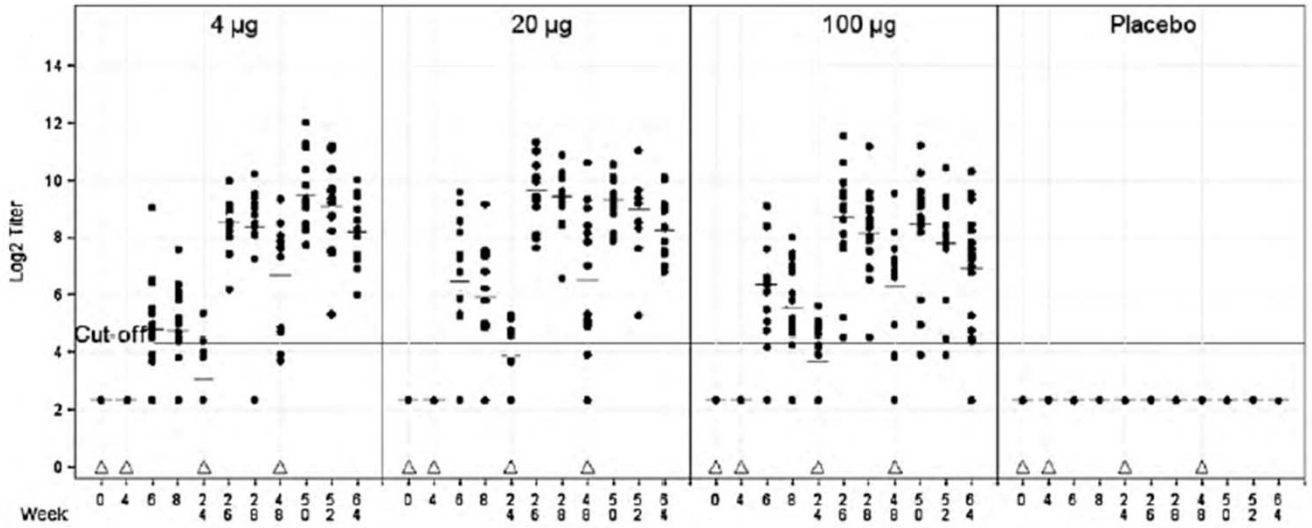
Phase I trial with E1-E2 recombinant vaccine (gen 1a) + MF59 as adjuvant

Safety and immunogenicity of HCV E1E2 vaccine adjuvanted with MF59 administered to healthy adults☆

Sharon E. Frey[a,*], Michael Houghton[b], Stephen Coates[c], Sergio Abrignani[d], David Chien[c], Domenico Rosa[e], Piero Pileri[e], Ranjit Ray[a], Adrian M. Di Bisceglie[f], Paola Rinella[e], Heather Hill[g], Mark C. Wolff[g], Viola Schultze[h], Jang H. Han[c], Bruce Scharschmidt[i], Robert B. Belshe[a]

Vaccine 28 (2010) 6367–6373

Anti-E1-E2 (ELISA)



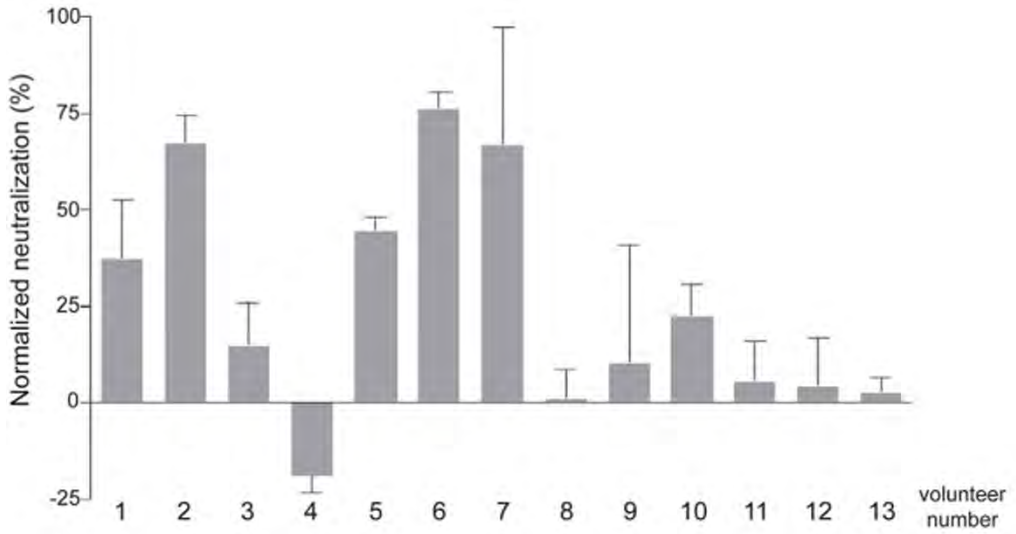
- **60 healthy volunteers (4 groups of 15 individuals with 4x injections of 4, 20 or 100 µg)**
- **Vaccine safe & well-tolerated**
- **Elicits anti-E1-E2 titers in the same range as in protected chimpanzees**
- **Induces a strong lymphoproliferative response to E1-E2**
- **20 µg E1-E2 dose administered on month 0, 1 & 6 appears optimal**
  (100% of subjects developped a humoral response after the 3rd vaccination)

Phase I trial with E1-E2 recombinant vaccine (gen 1a) + MF59 as adjuvant
(neutralization assays with sera collected 2 weeks post-3rd vaccination with 100 μg)

OPEN ACCESS Freely available online March 2013 | Volume 8 | Issue 3 | e59776 PLOS ONE

A Hepatitis C Virus (HCV) Vaccine Comprising Envelope Glycoproteins gpE1/gpE2 Derived from a Single Isolate Elicits Broad Cross-Genotype Neutralizing Antibodies in Humans

John Lok Man Law[1]*, Chao Chen[1], Jason Wong[1], Darren Hockman[1], Deanna M. Santer[1], Sharon E. Frey[2], Robert B. Belshe[2], Takaji Wakita[3], Jens Bukh[4], Christopher T. Jones[5], Charles M. Rice[5], Sergio Abrignani[6], D. Lorne Tyrrell[1], Michael Houghton[1]*



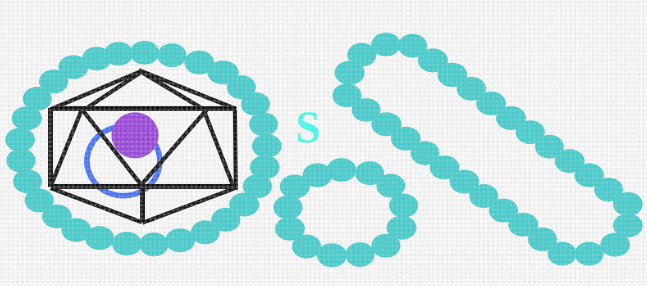
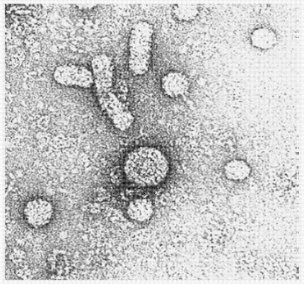
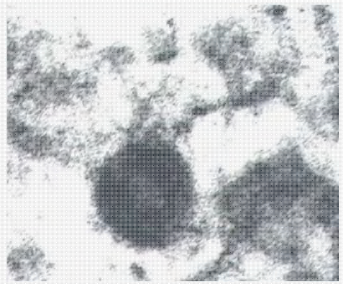
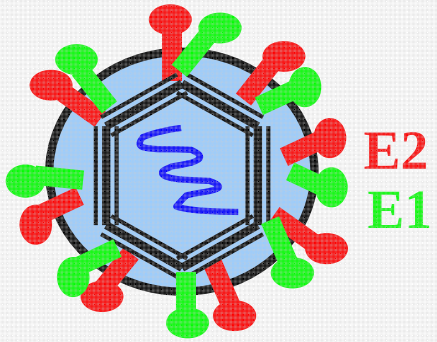
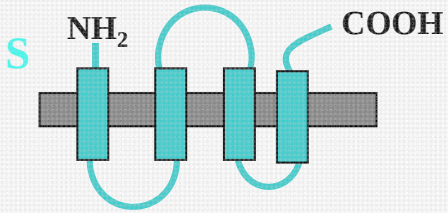
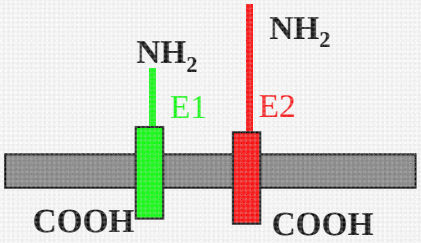
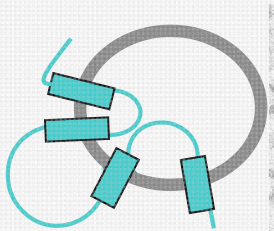
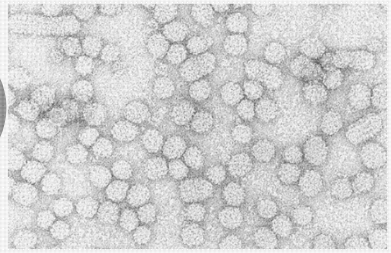
Neutralization normalized using the pre-vaccination sera of the same individual

→ **5/13 human sera neutralized over 50% of heterologous HCVcc 1a**
(2 of which neutralized up to 80% of viral infectivity)

Li Ka Shing Institute of Virology

(Dr Houghton) is planning to test the efficacy of an improved recombinant E1-E2 vaccine in Canadian IVDUs

Hepatitis B & hepatitis C viruses

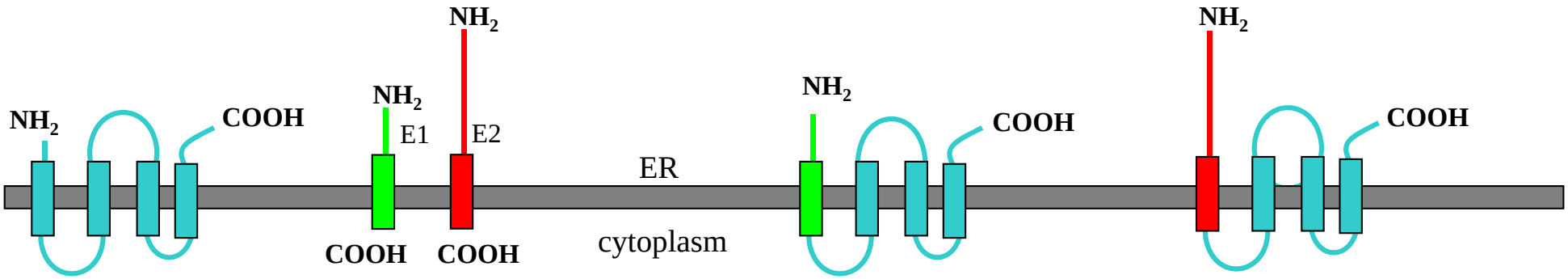
HBV		HCV
Hepadnavirus / DNA	Family / genome	Flavivirus / RNA
 	Structure	 
	Envelope	
 	Prophylactic vaccine	

Chimeric Hepatitis B Virus/Hepatitis C Virus Envelope Proteins Elicit Broadly Neutralizing Antibodies and Constitute a Potential Bivalent Prophylactic Vaccine

Elodie Beaumont,[1] Romuald Patient,[1] Christophe Hourioux,[1]
Isabelle Dimier-Poisson,[2] and Philippe Roingeard[1]

HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases
(HEPATOLOGY 2013;57:1303-1313)

Patent : N− 08/03377 (June 17, 2008)
N− PCT/FR2009/051142 (June 15, 2009)



HBV S

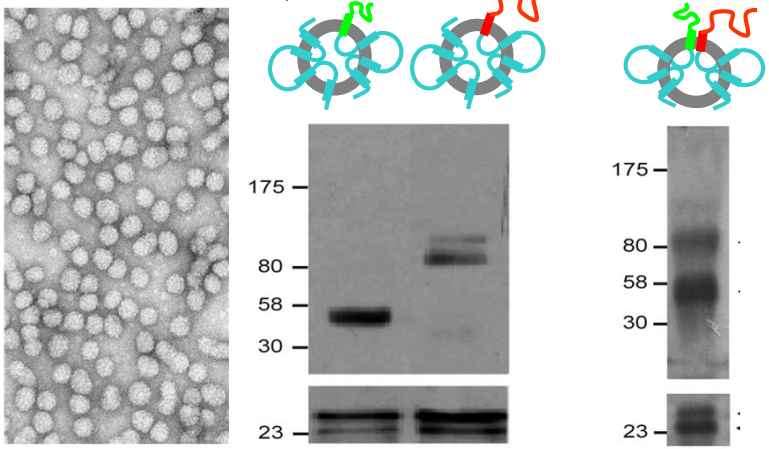
HCV E1 & E2

E1-S chimeric protein

E2-S chimeric protein

subviral particles are secreted and used for the HBV vaccine

(no particle) proteins are not secreted and extremely difficult to purify



anti-E1 + anti-E2

anti-S

Stable production of ≈ 10 µg/ml HBs Ag in the supernatant of CHO clones

Productive folding and heterodimerization of the HCV envelope proteins in the context of the fusion proteins

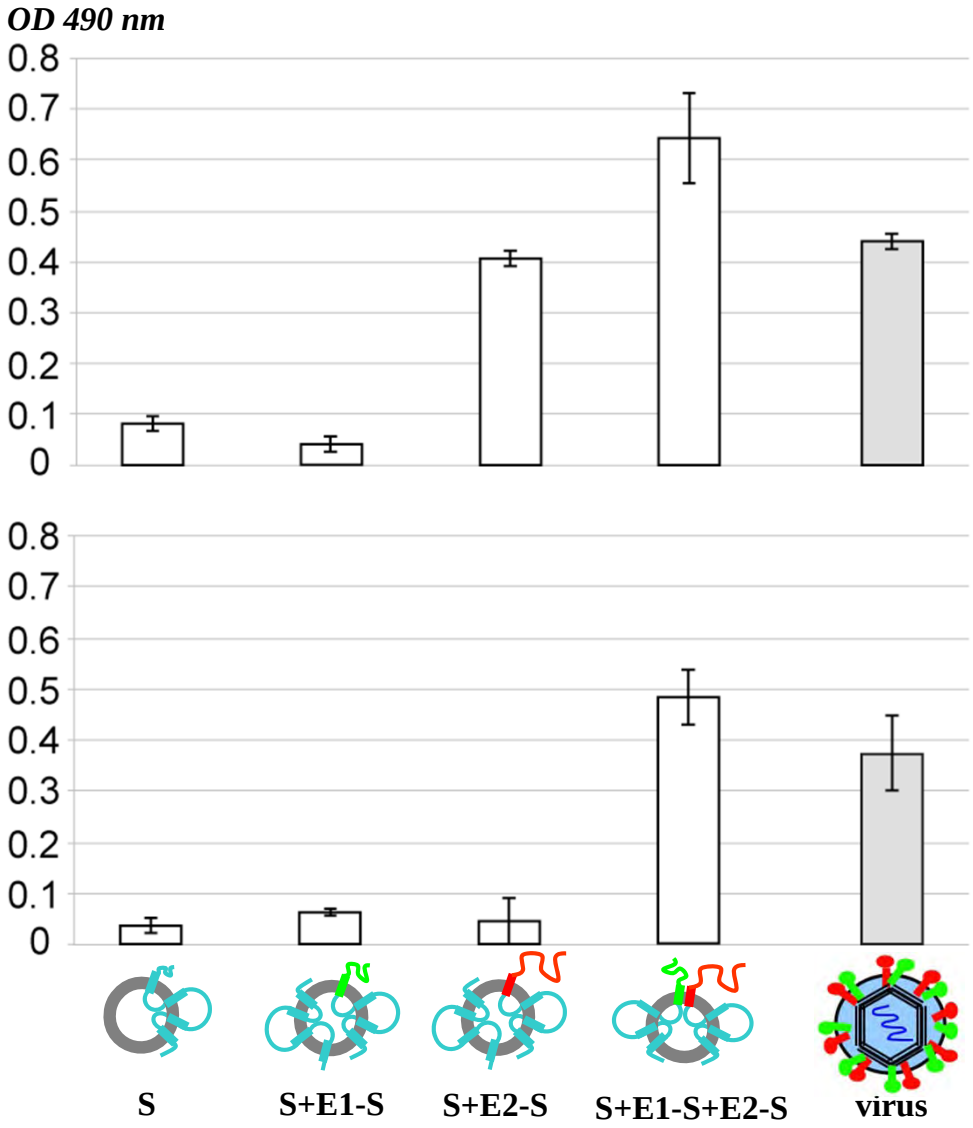
mAb AR3A

recognize a conformation-dependent discontinuous epitope on E2

neutralize different HCV genotypes *in vitro*

mAb AR5A

recognize the folded E1-E2 heterodimer



Beaumont et al, Hepatology 2013

➞ **The best immunogen for anti-HCV response is the subviral particle containing the E2-S chimeric protein**

(rabbits & mice data, with different adjuvants)

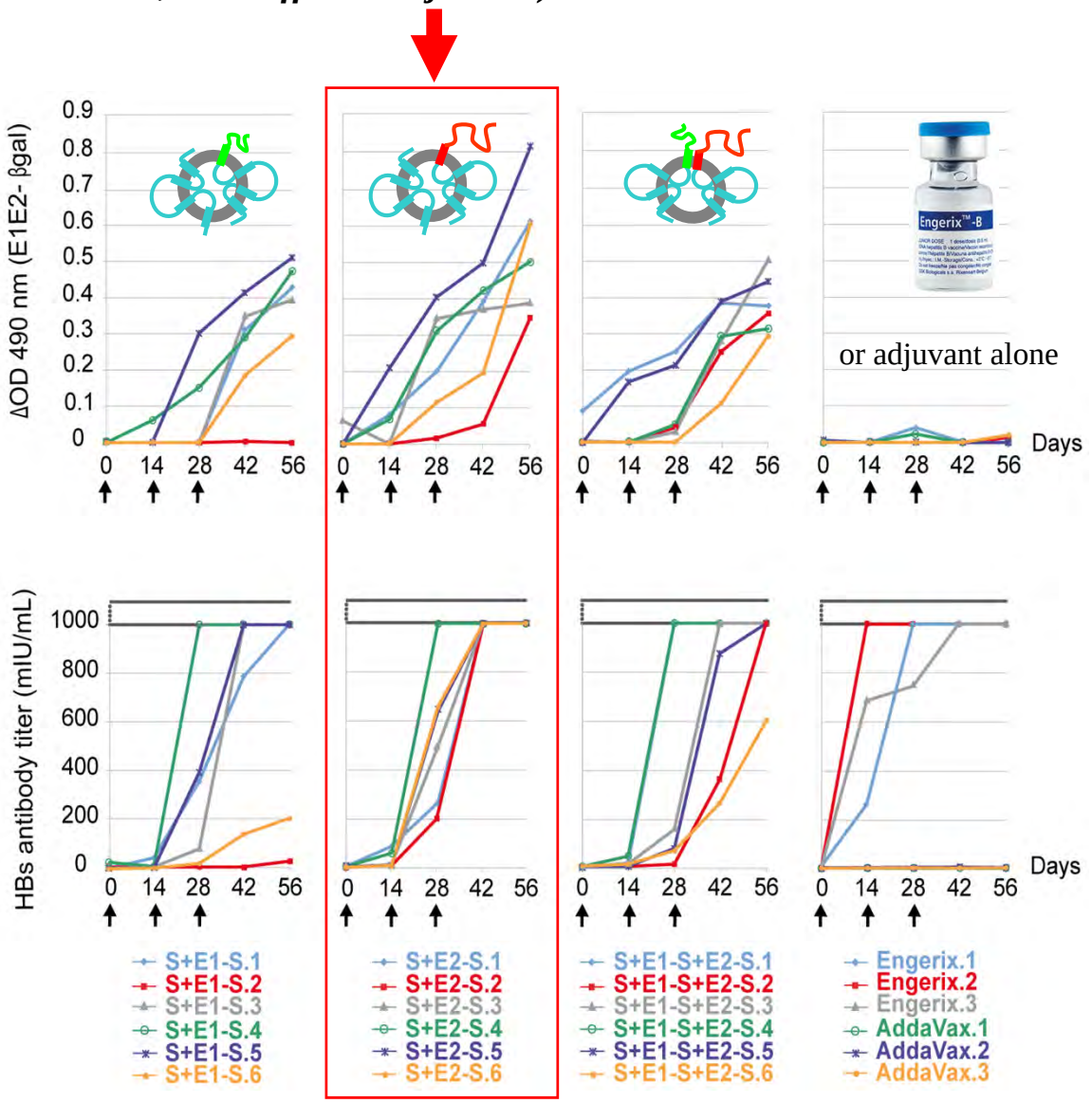
3 x 15 µg (week 0, 2, 4)
of particles
serum collected week 6

+ controls with Engerix

+ controls with adjuvant alone (MF 59 Addavax ®)

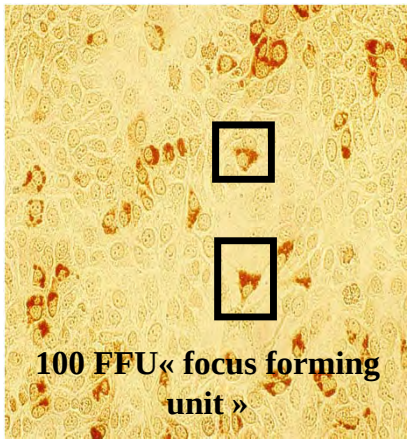
anti-E1 or E2

anti-HBs



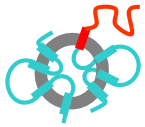
➞ **The anti-HBs response is equivalent to the response induced by a commercial HBV vaccine, suggesting that the chimeric particles could replace existing HBV vaccines whilst providing the additional benefit of protection against HCV.**

Evaluation of the neutralizing response in the HCVcc chimeric viruses Huh7.5 model

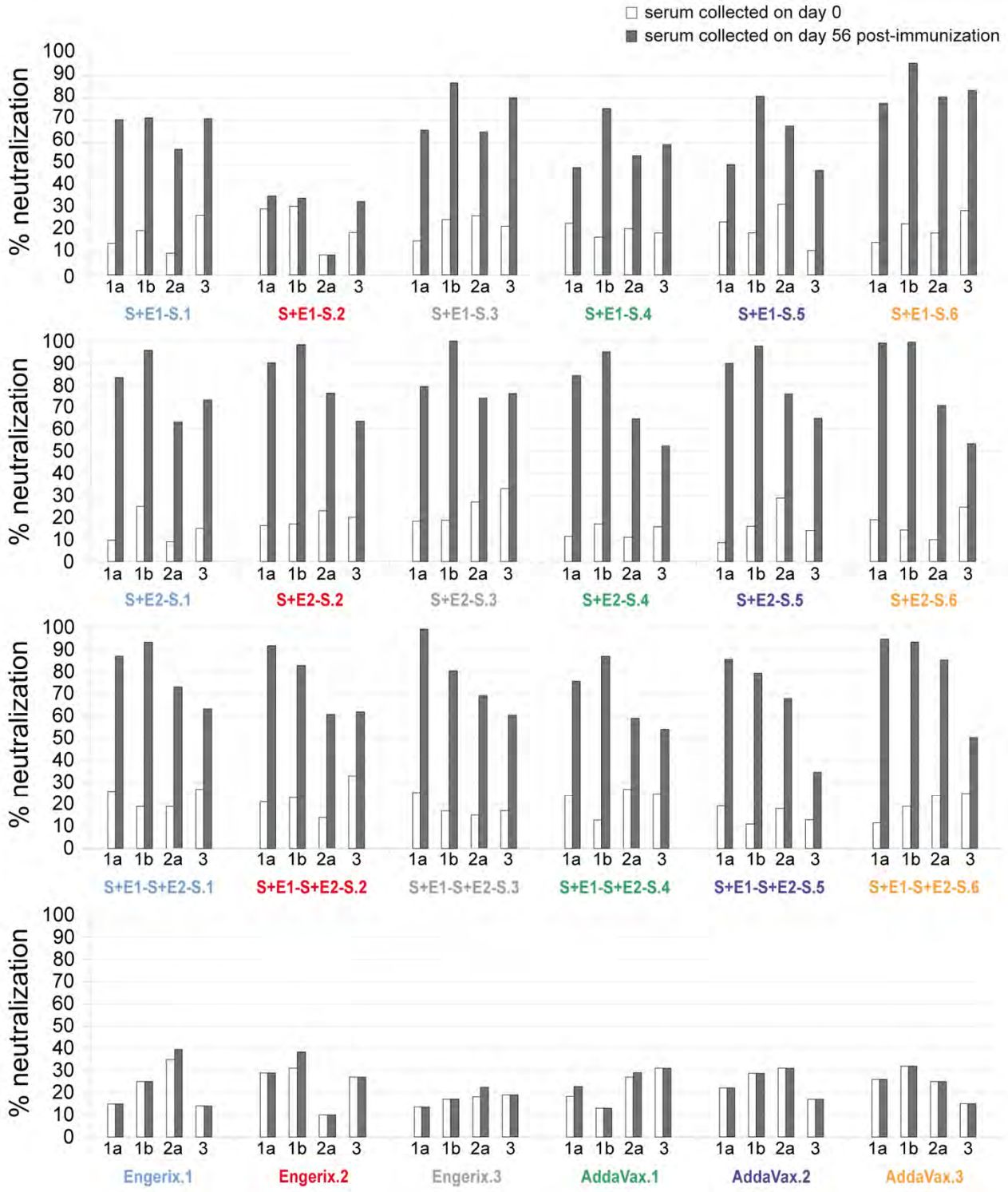


100 FFU« focus forming unit »

Genotypes 1a, 1b, 2a & 3



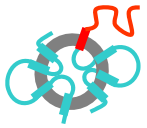
or adjuvant alone



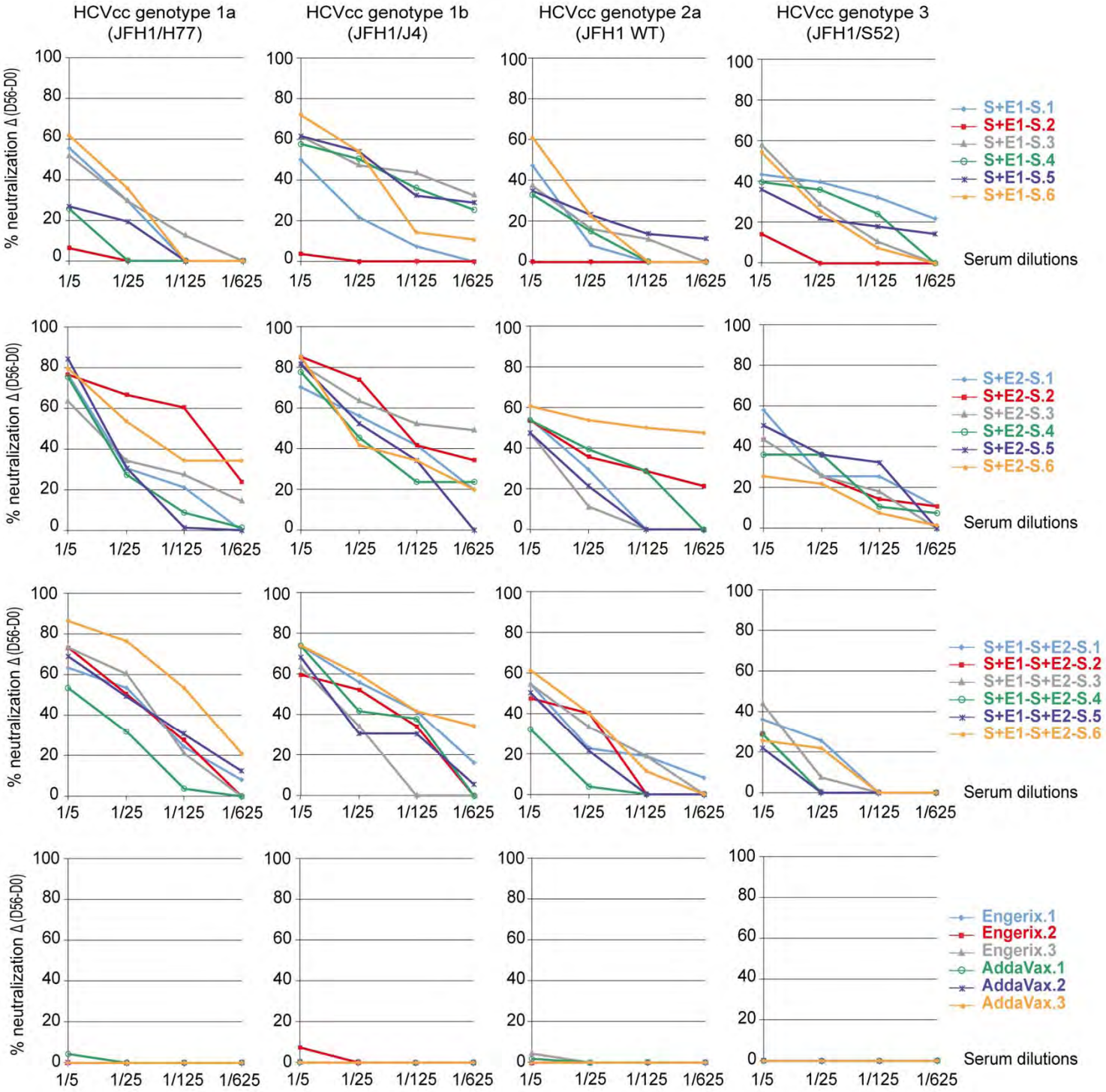
Beaumont et al, Hepatology 2013

Evaluation of the neutralizing response in the HCVcc chimeric viruses Huh7.5 model

Serum dilutions



or adjuvant alone

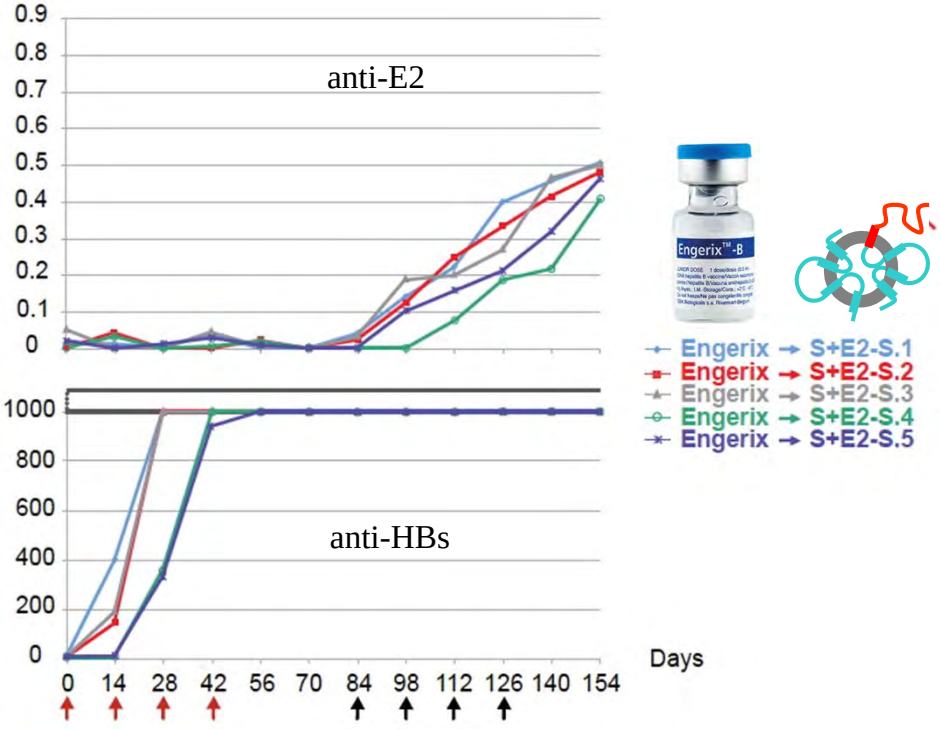


Beaumont et al, Hepatology 2013

Chimeric hepatitis B virus (HBV)/hepatitis C virus (HCV) subviral envelope particles induce efficient anti-HCV antibody production in animals pre-immunized with HBV vaccine

Elodie Beaumont, Philippe Roingeard*

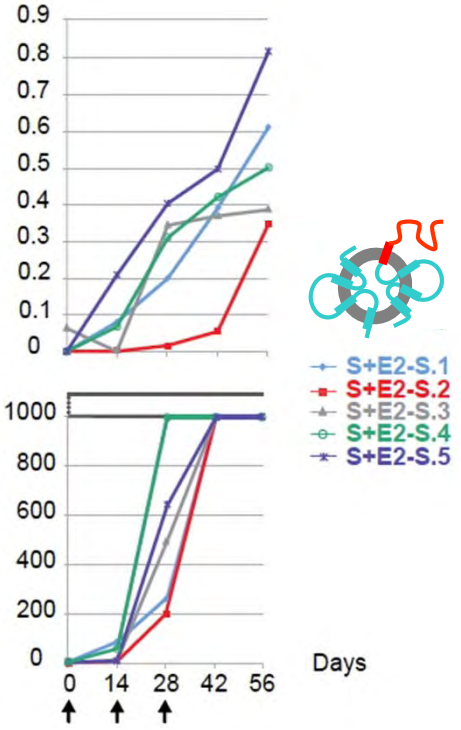
Vaccine 33 (2015) 973–976



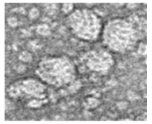
➞ **Chimeric HBV-HCV particles could be used in two different strategies:**

➞ **In primary vaccination, to induce protective immunity to both HBV & HCV**

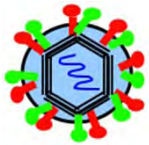
➞ **As booster doses in individuals previously vaccinated against HBV, to ensure full protection against HBV and induce protective immunity to HCV**



Conclusions



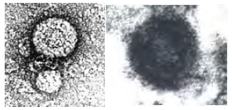
The **entire** HCV **E1** and/or **E2** env proteins, are incorporated in secreted subviral particles resembling the HBV vaccine.



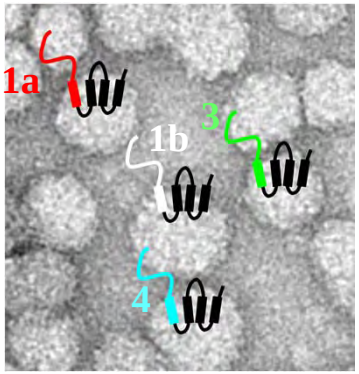
Sera containing anti-E1 and anti-E2 elicited by the chimeric HBV-HCV (genotype 1a) particles **neutralize** different HCV **heterologous strains** of **various genotypes (1a = 1b > 2 & 3).**

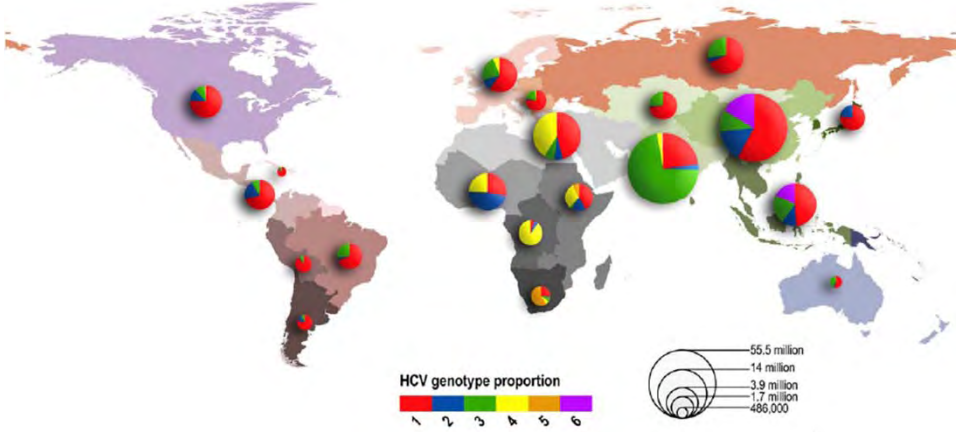
This vaccine candidate could be produced by the same **procedures** established for **HBV vaccines,** reducing the time and cost of its industrial development.

The **anti-HBs response** induced by the chimeric particles is **equivalent** to the response induced by a **commercial HBV vaccine**, suggesting that this vaccine could replace existing HBV vaccines whilst providing the additional benefit of protection against HCV.

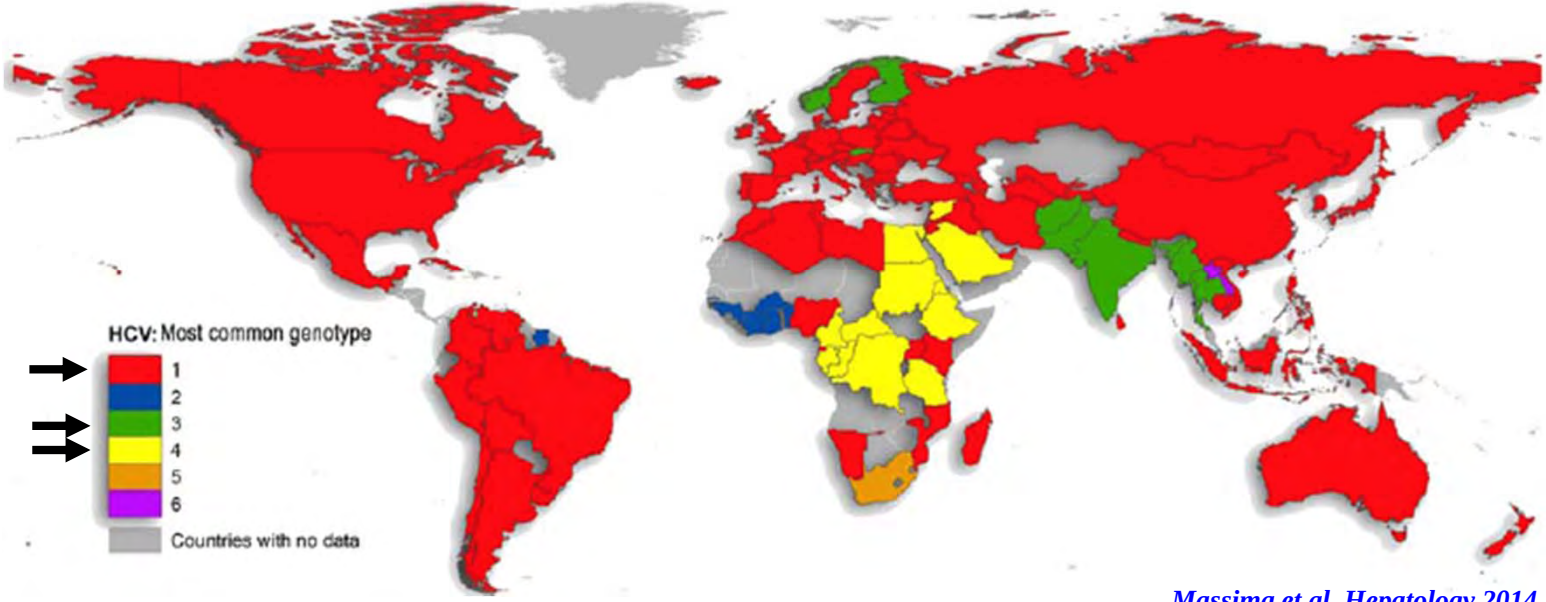


This **bivalent HBV-HCV prophylactic vaccine** could be used in primary vaccination for both viruses or as booster doses in individuals previously vaccinated against HCV.





Perspective 1 : Production of subviral particles containing HCV envelope from different genotypes to immunize with a mix of particles and increase the cross-neutralizing properties of this vaccine candidate



Massima et al, Hepatology 2014

Perspective 2 : Preclinical assay in a primate model

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- Compare HBV vaccine with the HBV-HCV chimeric particles
- Tolerability
- T-cell response (ELISPOT)
- Humoral immune response (anti-HBs & anti-E1-E2)
- Various HCV genotypes neutralization

Acknowledgments INSERM U966 - Tours

Elodie Beaumont
Emmanuelle Roch
Lucie Chopin
Romuald Patient
Christophe Hourioux

Acknowledgments for reagents

Jonathan Ball (Univ. Nottingham, UK)
Jens Bukh (Univ. Copenhagen, Danemark)
Jean Dubuisson (Pasteur Inst., Lille, France)
Harry Greenberg (Univ. Stanford, USA)
Mansun Law (Scripps Res. Inst., San Diego, USA)
Charles Rice (Univ. Rockefeller, NY, USA)
Camille Sureau (INTS, Paris, France)
Takaji Wakita (NIDD, Japan)

Acknowledgments for funding