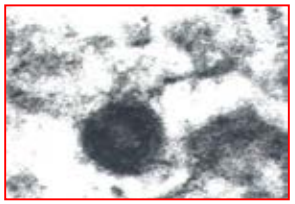


Vaccination contre le virus de l'hépatite C : *où en est la recherche ?*

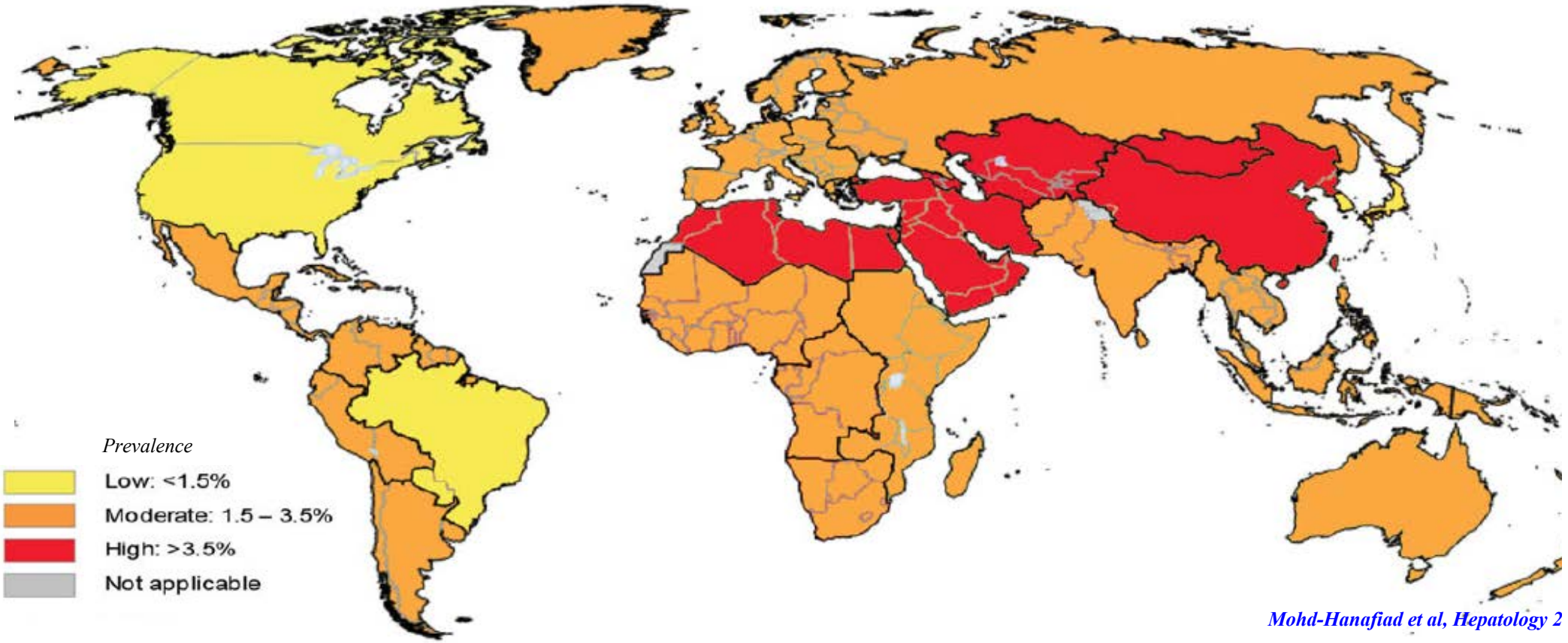
philippe.roingeard@univ-tours.fr

INSERM U966 - Tours

XIV^{ème} Séminaire de Formation et d'Echanges en Virologie Clinique
18 septembre 2014 - Lyon

Organisé avec le concours de Bristol-Myers Squibb

HCV epidemiology in 2013



Mohd-Hanafiad et al, Hepatology 2

➔ **180 million people currently infected worldwide**

World Health Organization

➔ **3-4 million new infections (mostly by blood contact : IVDU, unsafe medical practices, health worker**

each year

HCV epidemiology in 2013 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

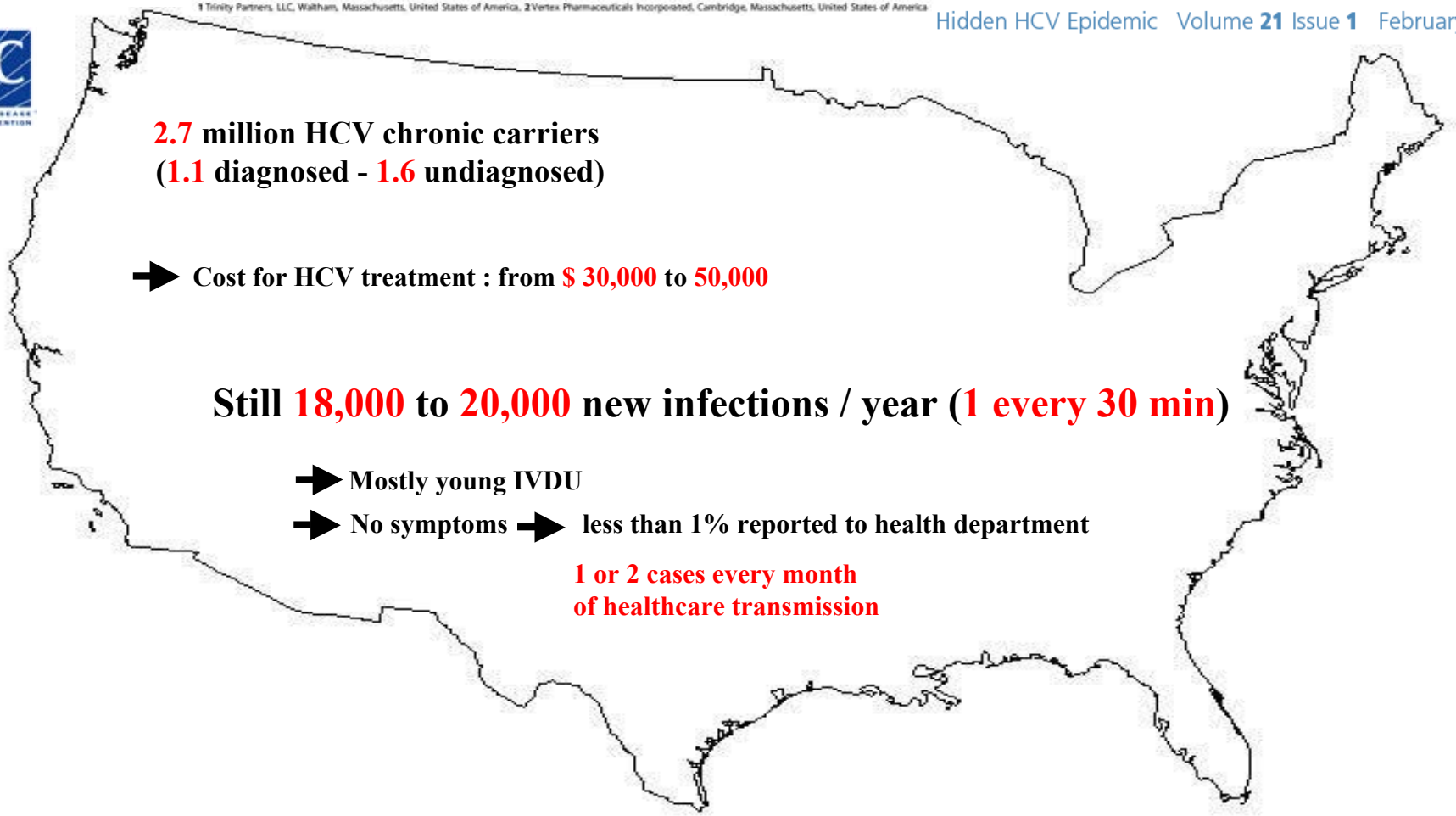
IAS–USA *Topics in Antiviral Medic*

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

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)

→ **Cost for HCV treatment : from $ 30,000 to 50,000**

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 2013 in China

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[1], Rongbin Yu[1*] and Ning Wang[2*]

Liver INTERNATIONAL

Liver International ISSN 1478-3223

Liver International (2011)

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]

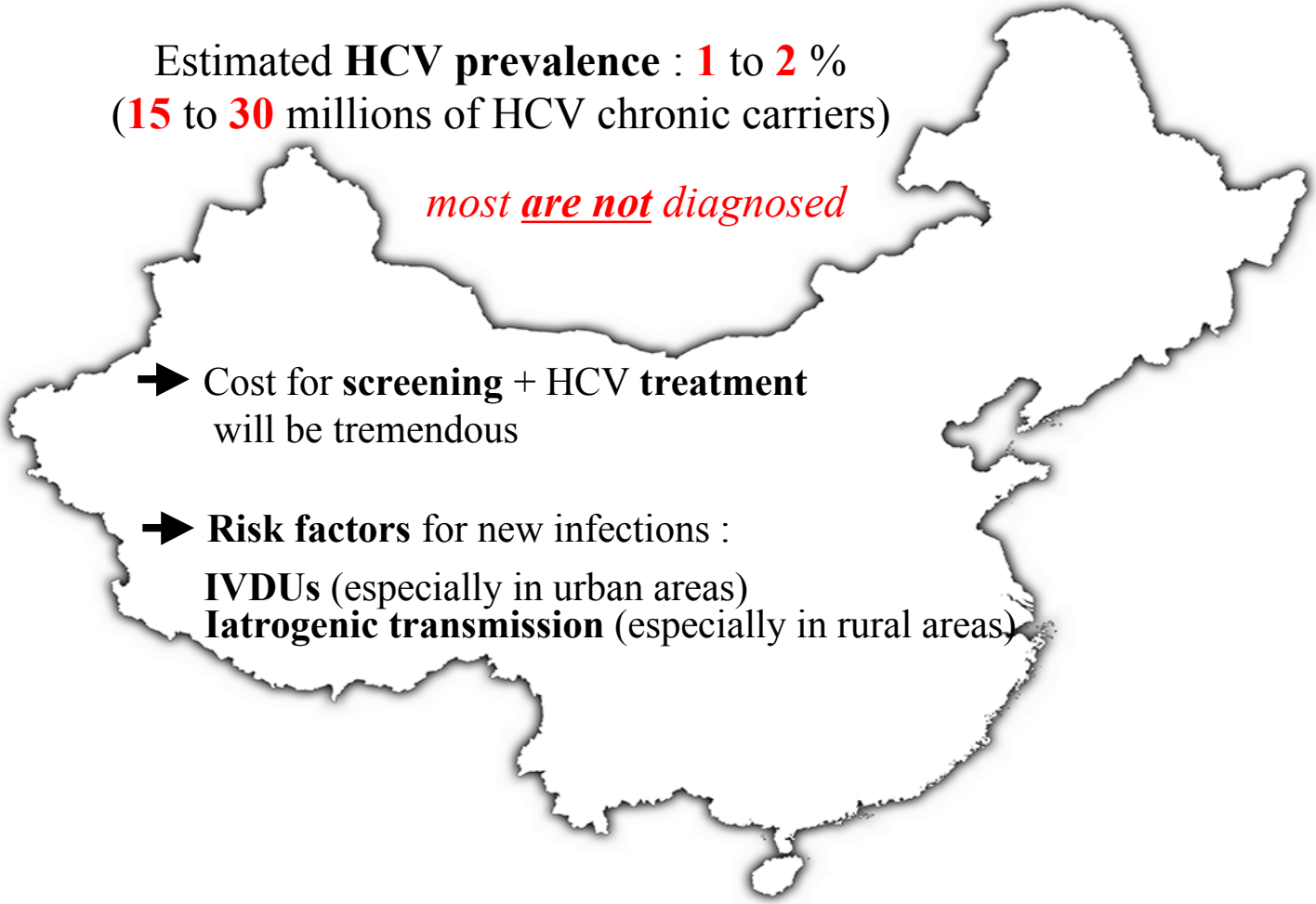
Hepatitis C Seroprevalence and Associated Risk Factors, Anyang, China

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 2

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

*most **are not** diagnosed*

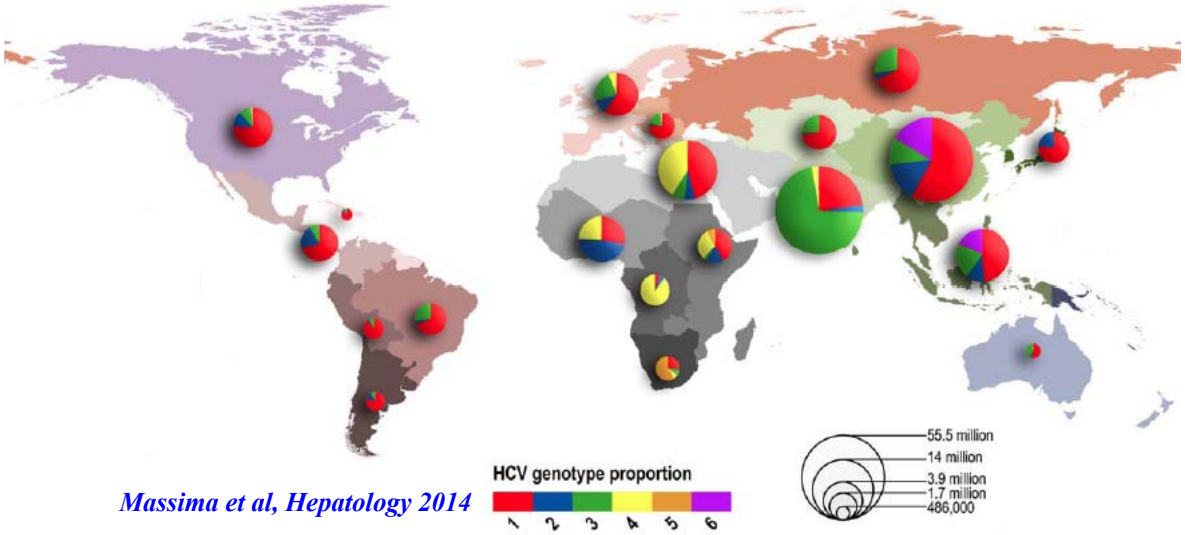


→ Cost for **screening** + HCV **treatment** will be tremendous

→ **Risk factors** for new infections :

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

HCV genetic diversity : global distribution & response to antiviral therapies



Massima et al, Hepatology 2014

➔ **Sustained viral response (SVR) to treatment with pegIFN+RBV : ≈ 80% in gen 2 & 3 *vs* ≈ 45-50% in gen 1**

➔ **Direct Antiviral Agents (DAA) teloprevir & boceprevir ↗ SVR to ≈ 65-75% in gen 1**

➔ **Additionnal DAAs are now / or will be licensed (2nd generation of protease inhibitors, NS5A & NS5B inhibitors, cyclophilin inhibitors) to probably reach ≈ 80-90% SVR for all genotypes in the near future, without IFN**

➔ **However, their high cost and sophisticated bioclinical monitoring makes their universal use unlikely**

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

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

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

Gastroenterology

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

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**

Table 1 Prophylactic HCV vaccine studies in chimpanzees and humans

T Jake Liang - Nat Med 2013

Vaccine		Targeted immunity	Animal testing	Clinical trial
Recombinant protein	gpE1 and gpE2 Adjuvant: MF59 and MF75	Humoral immunity	Immunogenic in small animals; protects chimpanzees from acute or chronic infection	Phase 1a; neutralizing antibodies and $CD4^+$ T cell responses
	Core Adjuvant: Iscomatrix	Cell-mediated immunity	Immunogenic in small animals and rhesus macaques	Phase 1a; $CD4^+$ and $CD8^+$ T cell responses
	gpE1 Adjuvant: alum	Humoral immunity	Immunogenic in small animals; protects chimpanzees from acute or chronic infection	Phase 1a; antibodies and $CD4^+$ T cell responses; no longer in development
	Core, NS3, NS4 and NS5 Adjuvant: Iscomatrix	Cell-mediated immunity	Immunogenic in small animals; no protection from acute or chronic infection	None
	HCV-like particles containing core, gpE1 and gpE2 Adjuvant: AS01B	Humoral and cell-mediated immunity	Immunogenic in small animals; protects chimpanzees from chronic infection	None
DNA and viral vector	DNA prime and adeno expressing core and NS3–NS5	Cell-mediated immunity	Immunogenic in small animals; protects chimpanzees from chronic infection	Phase 1/2 (NS3–NS5); $CD4^+$ and $CD8^+$ T cell responses
	DNA prime and adeno virus expressing core, E1, E2 and NS3–NS5 Adjuvant: IL-12 plasmid	Humoral and cell-mediated immunity	Immunogenic in small animals; protected chimpanzees from chronic infection	None
	DNA prime and MVA expressing core, E1, E2 and NS3, or NS3–NS5	Humoral and cell-mediated immunity	Immunogenic in small animals; reduced peak viremia but did not protect chimpanzees from chronic infection	Phase 1/2 as therapeutic vaccine; $CD4^+$ and $CD8^+$ T cell response
	VV expressing core, E1, E2, p7, NS2 and NS3	Humoral and cell-mediated immunity	Immunogenic in small animals; protected chimpanzees from chronic infection	None
	DNA expressing E2	Humoral and cell-mediated immunity	Immunogenic in small animals; protected chimpanzees from chronic infection	None
DNA/recombinant protein	DNA prime and protein boost (core, E1, E2 and NS3) Adjuvant: alum	Humoral and cell-mediated immunity	Immunogenic in small animals; protected chimpanzees from chronic infection	None

Only chimpanzee studies with two or more chimpanzees are listed.

Table 1 Prophylactic HCV vaccine studies in chimpanzees and humans *T Jake Liang - Nat Med 2013*

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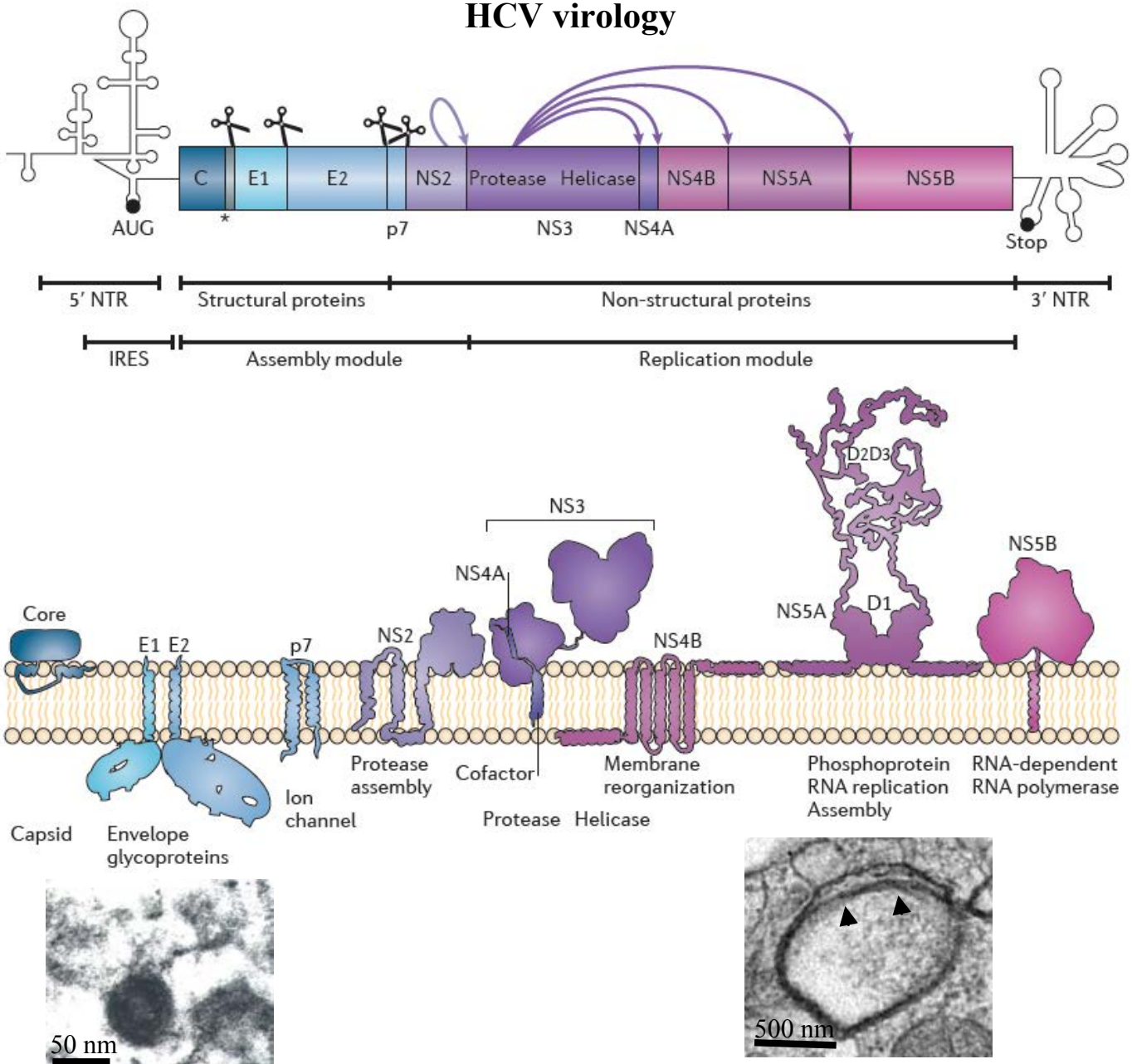
	DNA expressing E2	Humoral and cell-mediated immunity	Immunogenic in small animals; protected chimpanzees from chronic infection	None
DNA/recombinant protein	DNA prime and protein boost (core, E1, E2 and NS3) Adjuvant: alum	Humoral and cell-mediated immunity	Immunogenic in small animals; protected chimpanzees from chronic infection	None

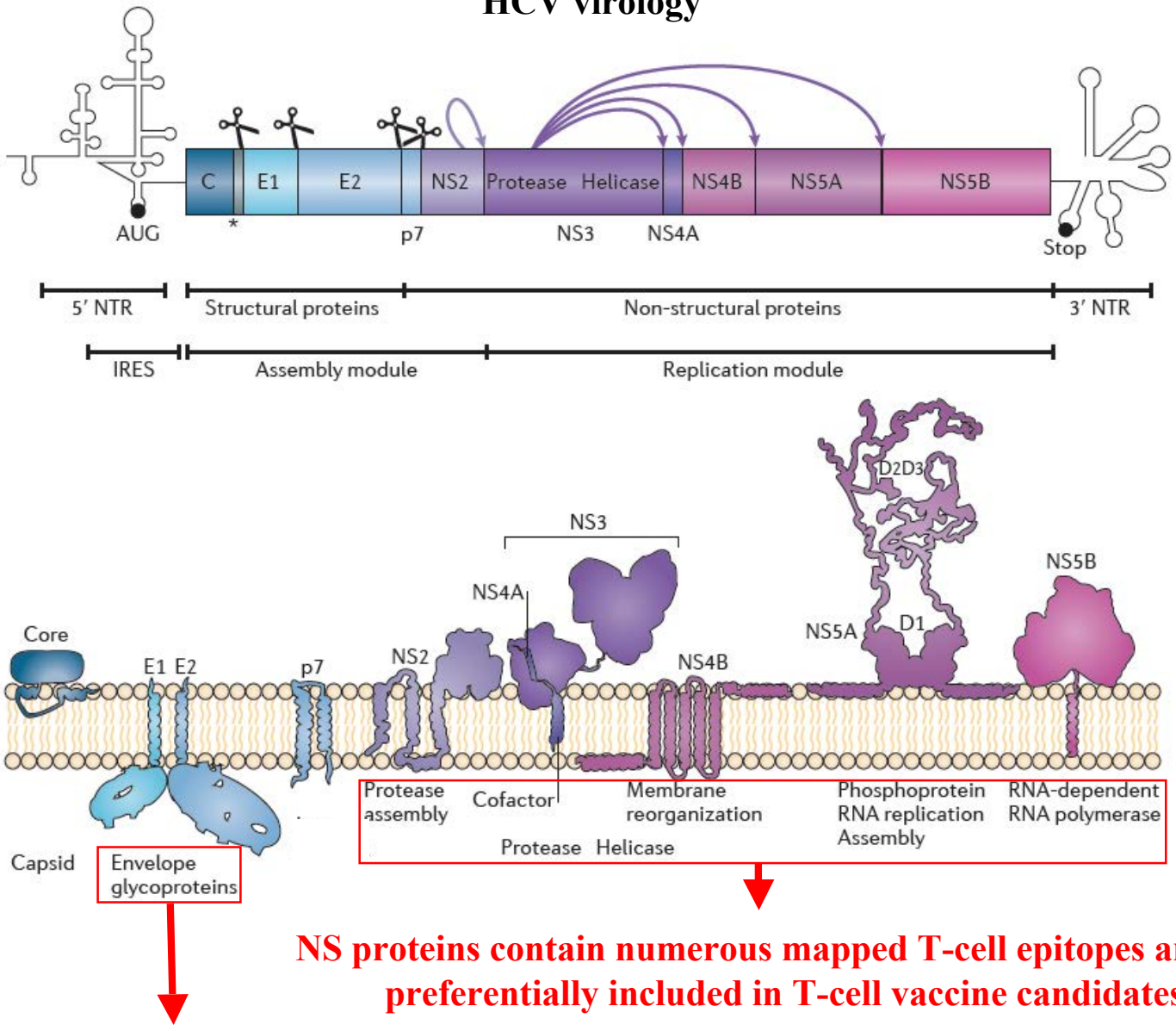
Only chimpanzee studies with two or more chimpanzees are listed.

HCV virology



Adapted from Bartenschlager et al, Nat Rev Microbiol

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)

HCV vaccines based on viral vectors to elicit a T-cell response

➔ **The most promising are Poxviruses & Adenoviruses encoding the NS proteins**

➔ **Clinical trials are currently evaluating a Modified Vaccinia Ankara (MVA) vector for therapeutic use (TG4040)**

transgene

Reports in the last EASL meeting (April 2013) showed an improved therapeutic response in patients treated with TG4040 as compared to PegIFN/RBV alone

➔ **Okairos has developed a strategy based on Adenoviruses (Ad) encoding gen 1b NS-3-4A-4B-5A-5B for both therapeutic and prophylactic use**

okairos
from genes to vaccines
gsk GlaxoSmithKline

➔ **Since Ad are highly immunogenic and common, pre-existing antibodies may interfere with the vaccine ➔ Strategy based on rare human serotypes (Ad6) and chimpanzee adenovirus 3 (ChAd3**

okairos
from genes to vaccines

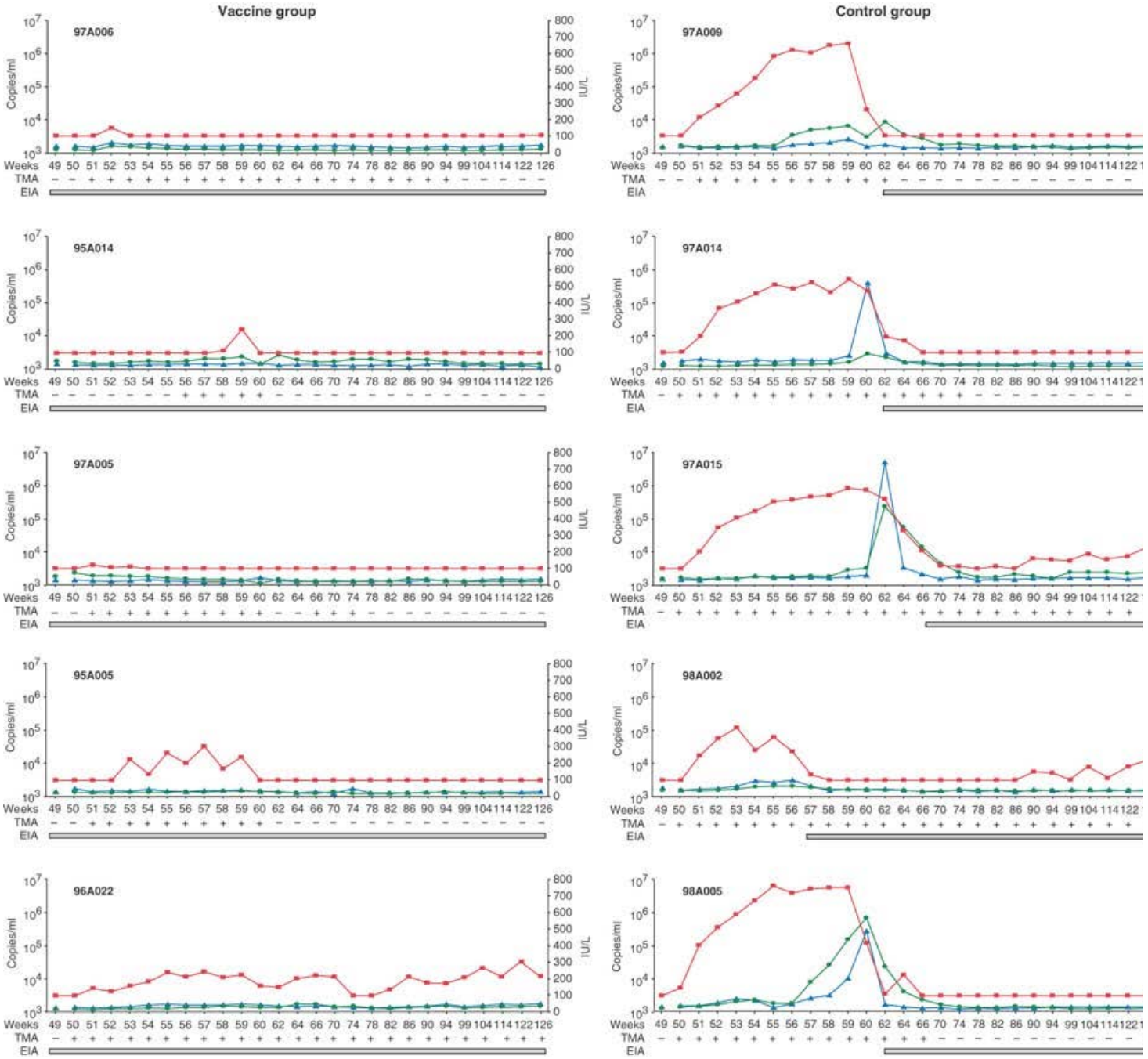
A T-cell HCV vaccine eliciting effective immunity against heterologous virus challenge in chimpanzees

Antonella Folgori, Stefania Capone, Lionello Ruggeri, Annalisa Meola, Elisabetta Sporeno, Bruno Bruni Ercole, Monica Pezzanera, Rosalba Tafi, Mirko Arcuri, Elena Fattori, Armin Lahm, Alessandra Luzzago, Alessandra Vitelli, Stefano Colloca, Riccardo Cortese & Alfredo Nicosia

VOLUME 12 | NUMBER 2 | FEBRUARY 2006 NATURE MEDICINE

- Induction of a broad CD4+ CD8+ T-cell response in vaccinated animals (multiple primes with the 2 Ad + boost with electroporated plasmid DNA)

- After challenge with heterologous 1a virus, all animals became infected but vaccinees presented :
  - 100 x lower peak of viremia (average)
  - short duration of viremia
  - no increase in liver enzymes



HCV RNA ALT GGT

Novel Adenovirus-Based Vaccines Induce Broad and Sustained T Cell Responses to HCV in Man

Eleanor Barnes,[1,2]* Antonella Folgori,[3]* Stefania Capone,[3] Leo Swadling,[1] Stephen Aston,[1] Ayako Kurioka,[1] Joel Meyer,[1] Rachel Huddart,[1] Kira Smith,[1] Rachel Townsend,[1] Anthony Brown,[1] Richard Antrobus,[1] Virginia Ammendola,[3] Mariarosaria Naddeo,[3] Geraldine O'Hara,[1] Chris Willberg,[1] Abby Harrison,[1] Fabiana Grazioli,[4] Maria Luisa Esposito,[4] Loredana Siani,[3] Cinzia Traboni,[3] Ye Oo,[5] David Adams,[5] Adrian Hill,[1,2] Stefano Colloca,[3] Alfredo Nicosia,[3] Riccardo Cortese,[3] Paul Klenerman[1,2†]

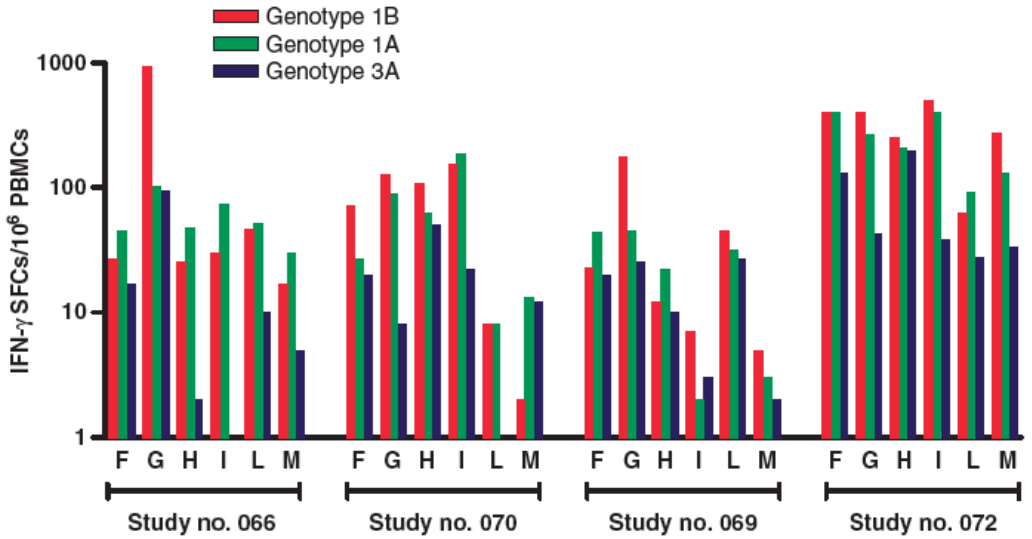
Science Translational Medicine
AAAS
4 January 2012 Vol 4 Issue 115 115ra1

➔ **Phase I trial on 40 healthy volunteers with both Ad6 & ChAd3 encoding gen 1b NS-3-4A-4B-5A-5B**

➔ **Induction of specific CD4+ & CD8+ cells secreting multiples cytokines (IL2, IFNγ, TNFα)**

➔ **HCV specific T cells response targeted multiple epitopes and recognized hererologous 1a or 3a HCV strain (although to a lesser extent than for 1b)**

Cross reactivity measured by IFNγ ELISpot *ex vivo* against peptides from different genotype



➔ **After 1 year, a polyfunctional and proliferative long-term memory population was still observed**

Okairos Announces Initiation of Phase I/II Clinical Trial for Potential First-in-Class Hepatitis C Vaccine

okairos

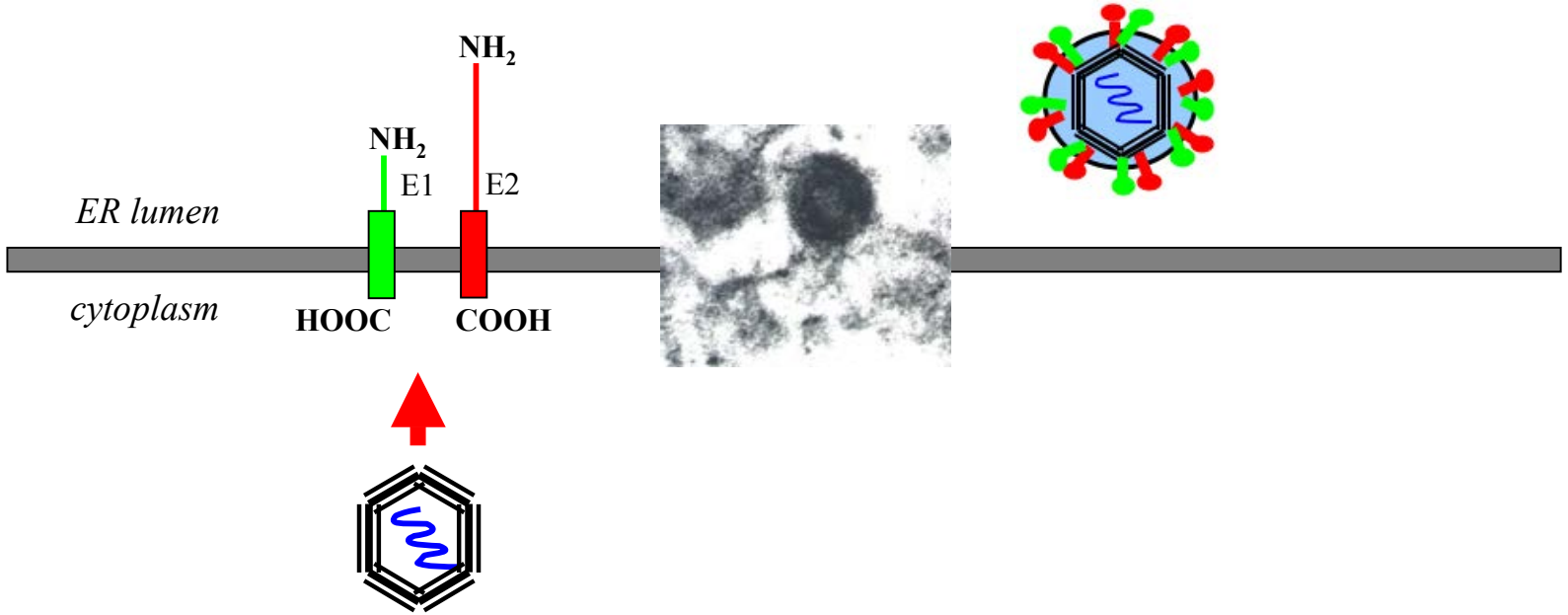
Basel, Switzerland – 14 March 2012 – Okairos today announced the initiation of a Phase I/II clinical trial evaluating its vaccine against the hepatitis C virus (HCV). This is the first multi-center, double blinded, randomized, placebo-controlled trial of a vaccine to prevent HCV infection, and represents a major milestone in the collaboration between Okairos and the National Institute of Allergy and Infectious Diseases (NIAID), which is part of the US National Institutes of Health (NIH). The NIH-funded trial will be conducted by co-principal investigators from Johns Hopkins University and the University of California San Francisco (UCSF).

➔ **As antibodies & T-cell response against Ad6 were detected after the priming and limited the boosting effect of the 2nd immunization with ChAd3, the trial is now performed with MVA+ChAd3**

➔ **≈ 350 subjects will be enrolled**

➔ **Results expected in 2015/2016**

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 201

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

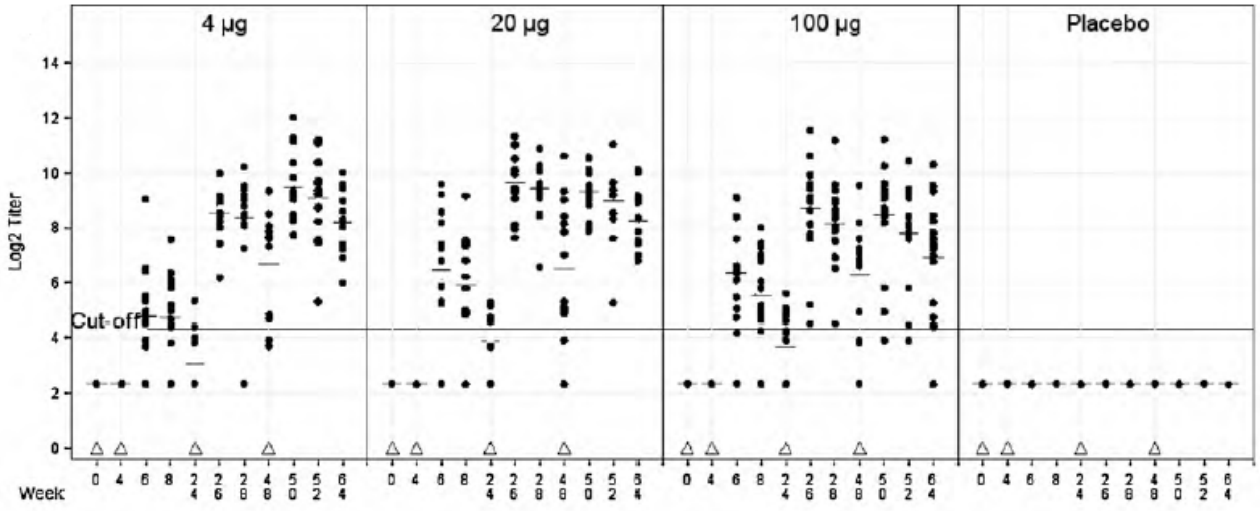
Phase I trial with E1-E2 recombinant vaccine (gen 1a) + MF59 as adjuvant

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)



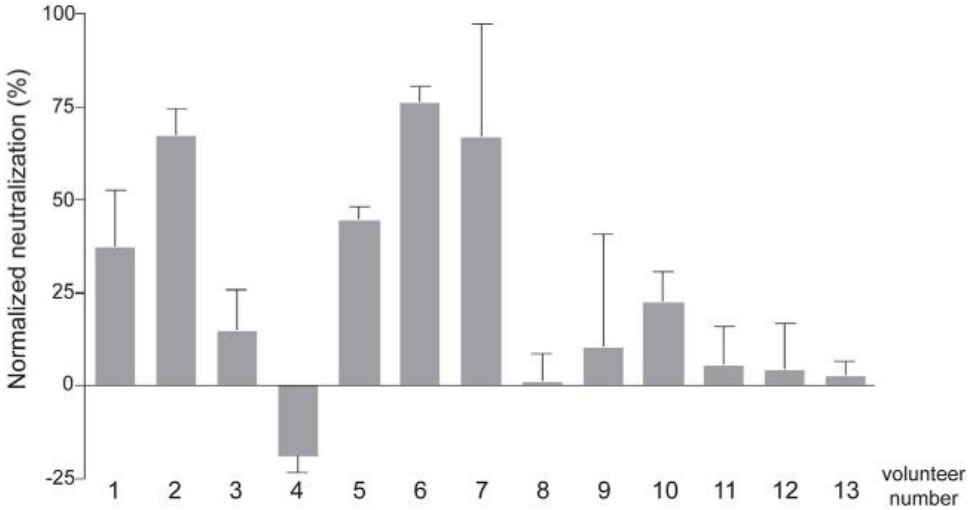
- **60 healthy volunteers (4 groups of 15 individuals with 4x injections of 4, 20 or 100 µg)**
- **Vaccine safe & well-tolerated**
- **Elicits anti-E1-E2 titers in the same range as in protected chimpanzees**
- **Induces a strong lymphoproliferative response to E1-E2**
- **20 µg E1-E2 dose administered 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)

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)

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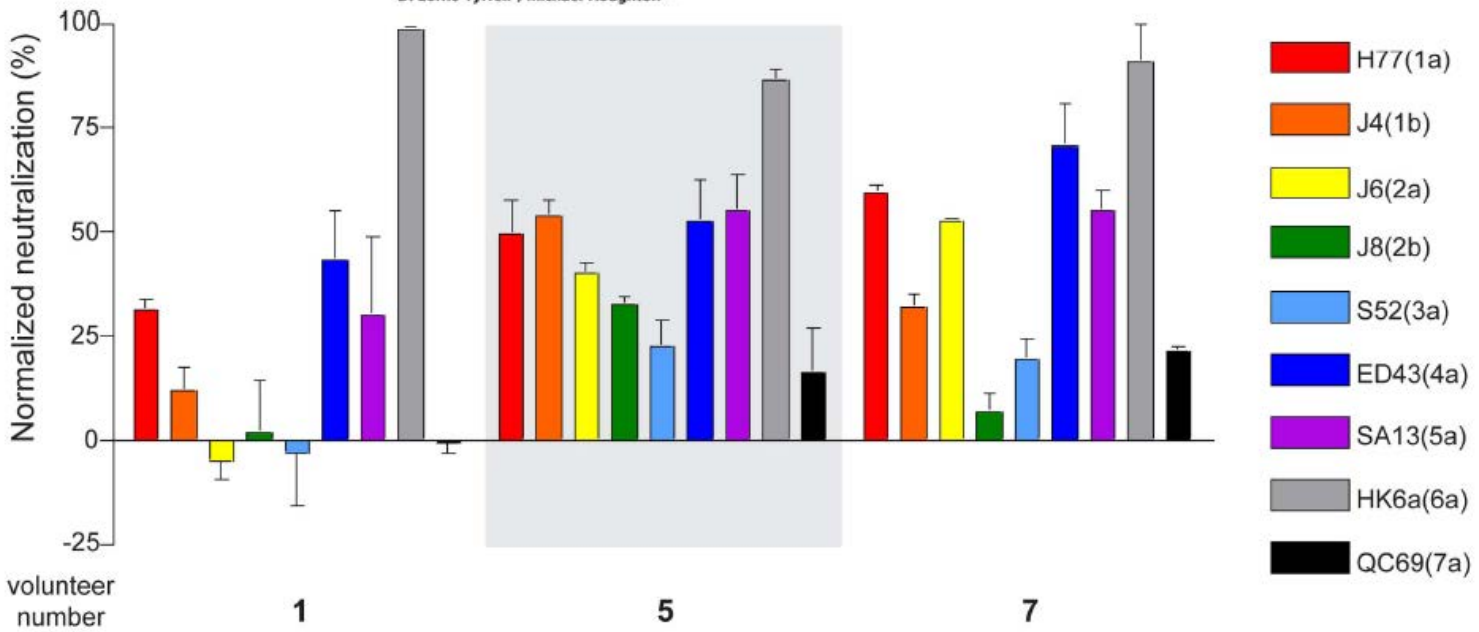


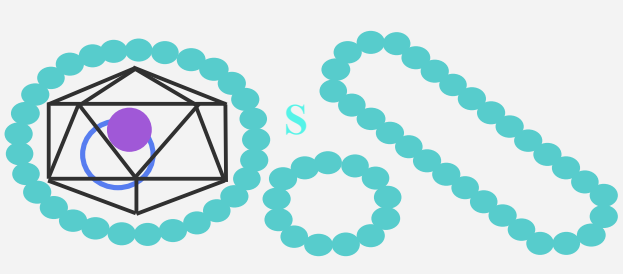
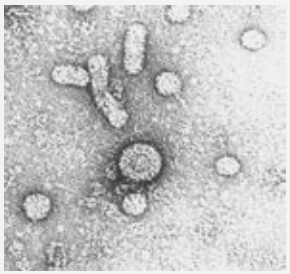
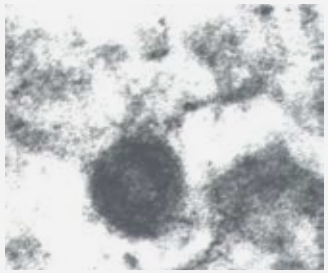
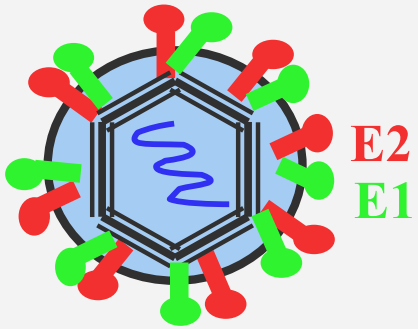
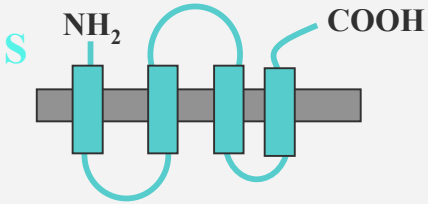
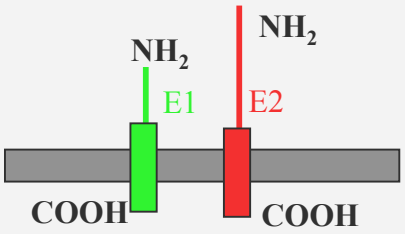
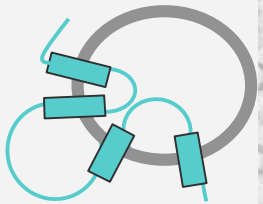
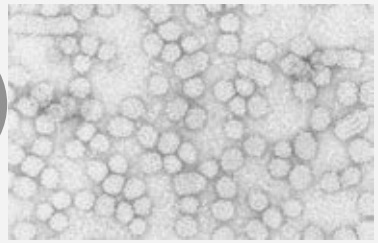
➔ **3 sera with high neutralization properties were choosen for further analysis**

➔ **2/3 sera presented a broad range of neutralization against HCVcc of all 7 genotypes**

(the lowest efficiency being observed in genotypes 2, 3 & 7)

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, 200

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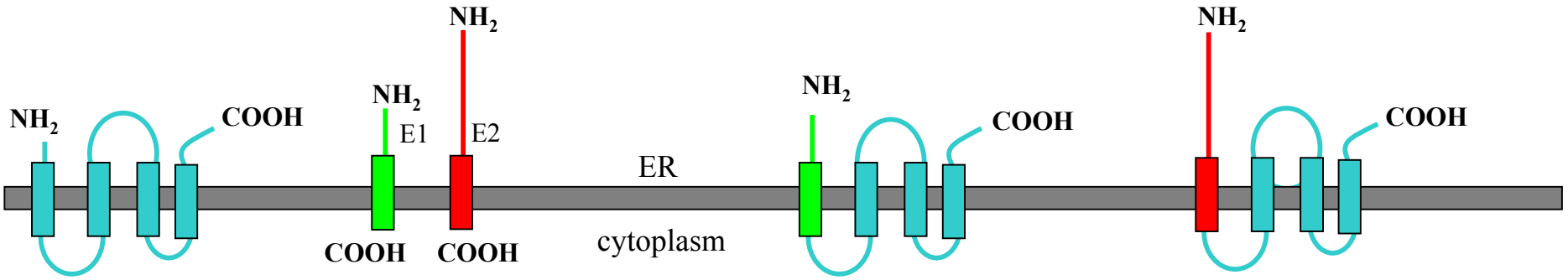
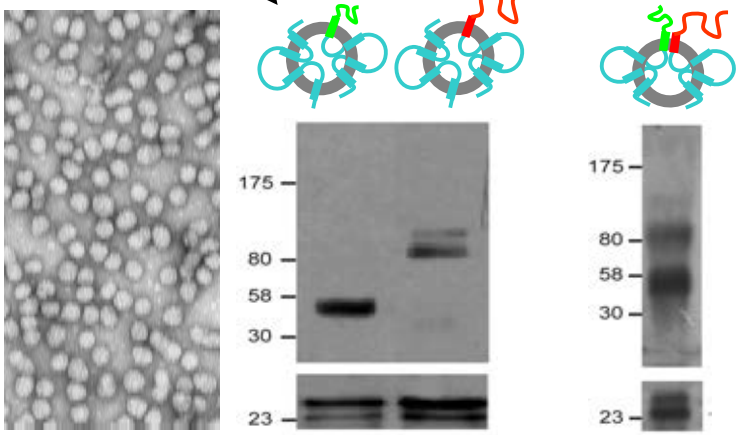
Inserm



subviral particles are secreted and used for the HBV vaccine

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

Chimeric HBV-HCV envelope proteins containing the complete HCV E1 and/or E2 protein sequence (HCV 1a genotype) self assemble into subviral particles resembling to the HBV vaccine



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

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

(rabbits & mice data, with different adjuvants)

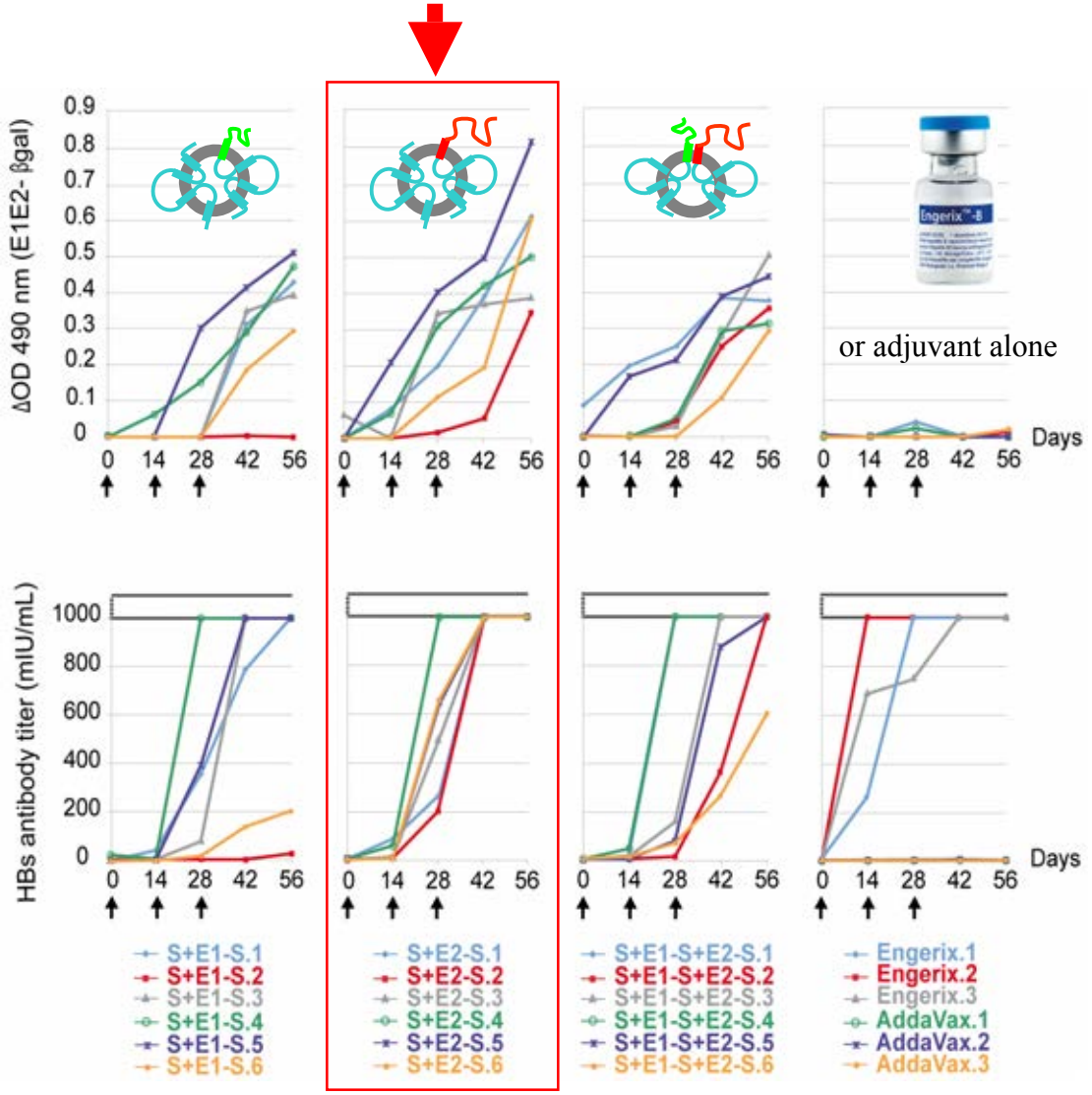
3 x 15 µg (week 0, 2, 4)
of particles
serum collected week 6

+ controls with Engerix

+ controls with adjuvant alone (MF 59 Addavax ®)

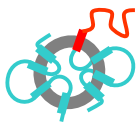
anti-E1 or E2

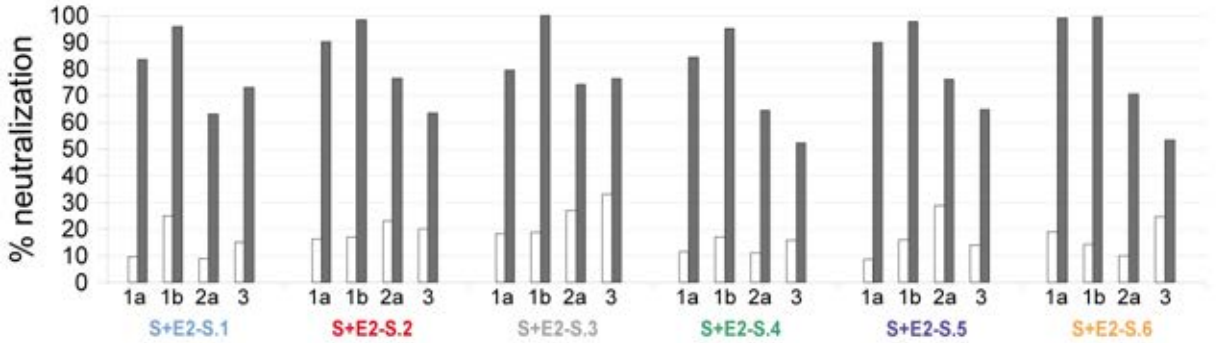
anti-HBs



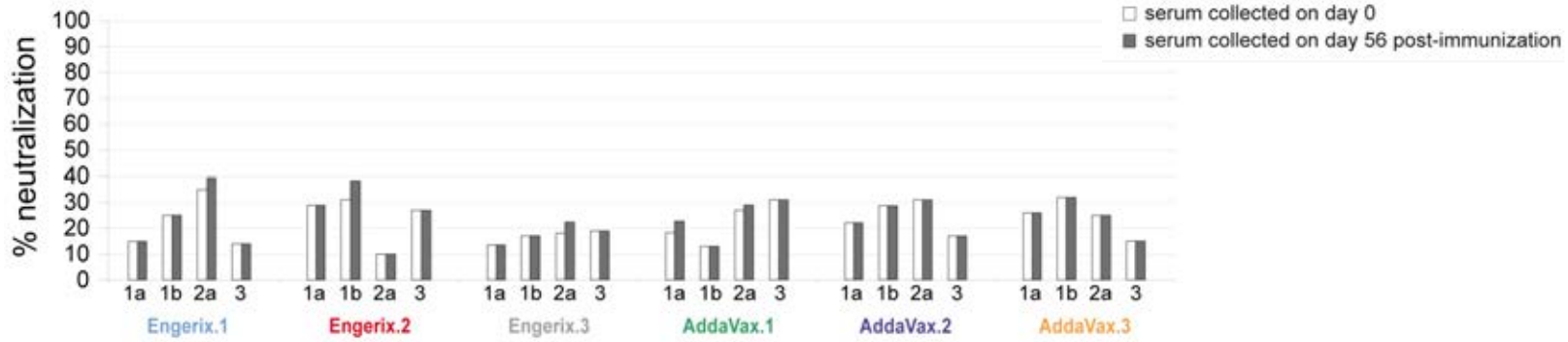
➔ **The anti-HBs response is equivalent to the response induced by a commercial HBV vaccine, suggesting that the chime particles could replace existing HBV vaccines whilst providing the additional benefit of protection against HCV.**

Evaluation of the neutralizing response against HCVcc genotypes 1a, 1b, 2 and 3 *in vitro*



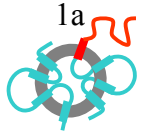


or adjuvant alone

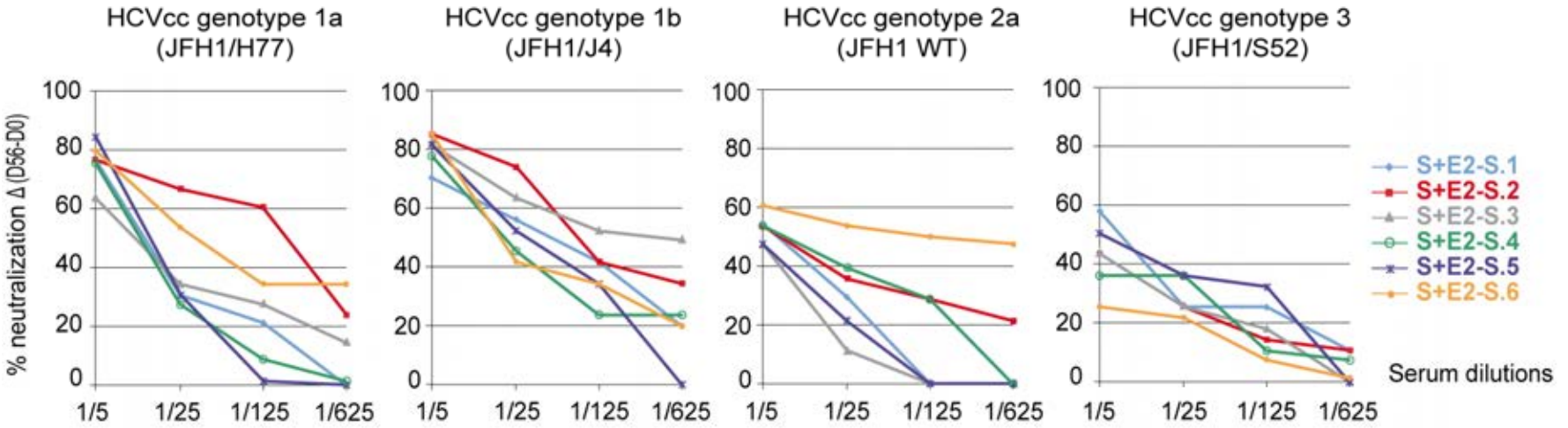


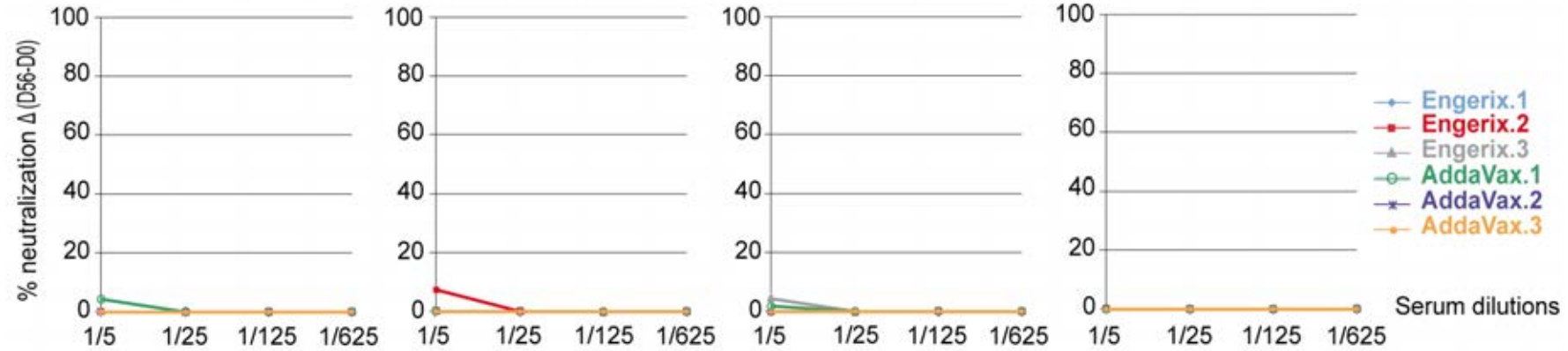
➔ **Sera containing anti-E2 elicited by the chimeric HBV-HCV (genotype 1a) particles neutralize infections with HCVcc from different heterologous strains of various genotypes : 1a = 1b > 2a > 3.**

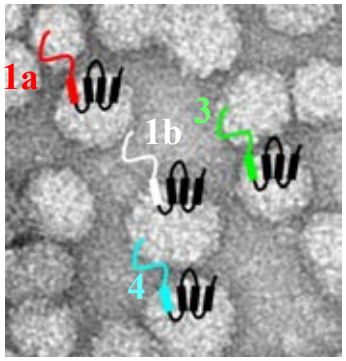
Evaluation of the neutralizing antibodies titers

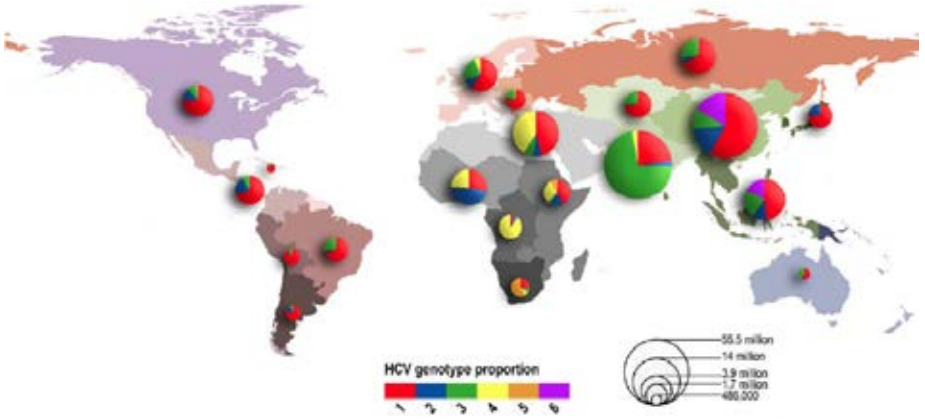


or adjuvant alone

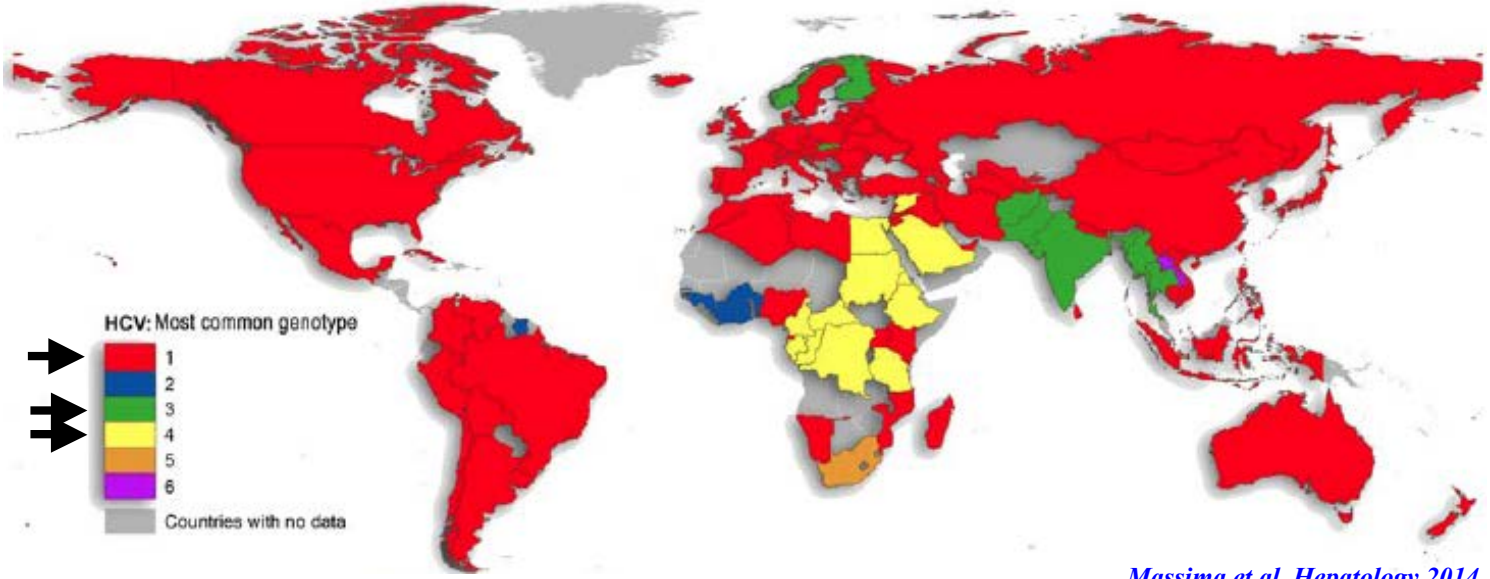






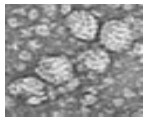


Production of subviral particles containing HCV envelope from different genotypes is in process in Tours to immunize with a mix of particles and increase the cross-neutralizing properties of this vaccine candidate

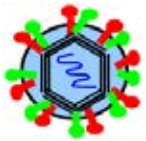


Massima et al, Hepatology 2014

Conclusions



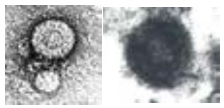
The entire HCV E1 and/or E2 env proteins, are incorporated in secreted subviral particles resembling the HBV vaccine.



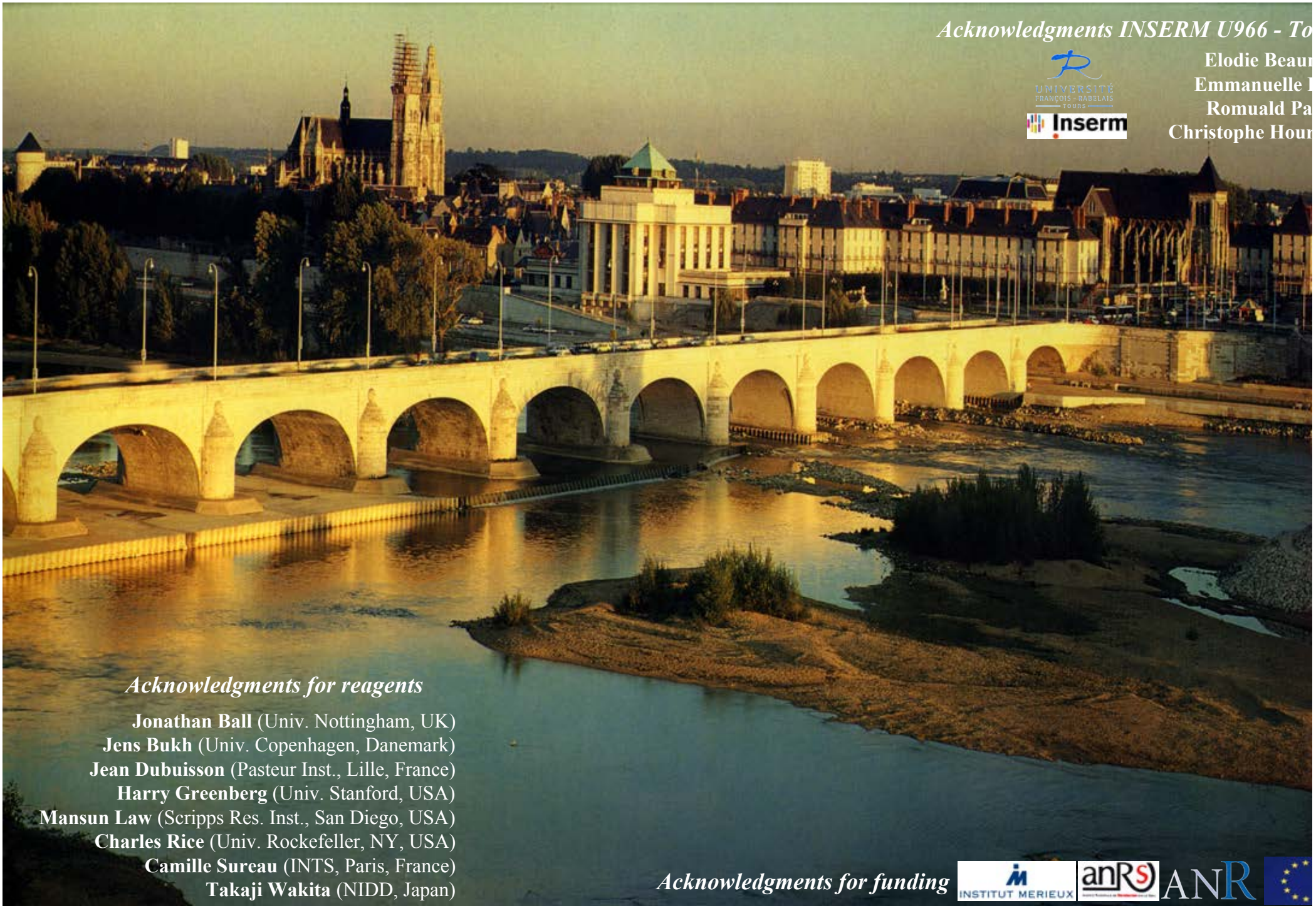
Sera containing anti-E1 and anti-E2 elicited by the chimeric HBV-HCV (genotype 1a) particles neutralize different HCV heterologous strains of various genotypes (1a, 1b, 2a and 3).

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.



A bivalent HBV-HCV prophylactic vaccine is of potential interest as the population at risk of infecti with these two viruses are essentially the same (persons exposed to infected blood).



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