Hepatitis C Virus (HCV) Vaccine Development

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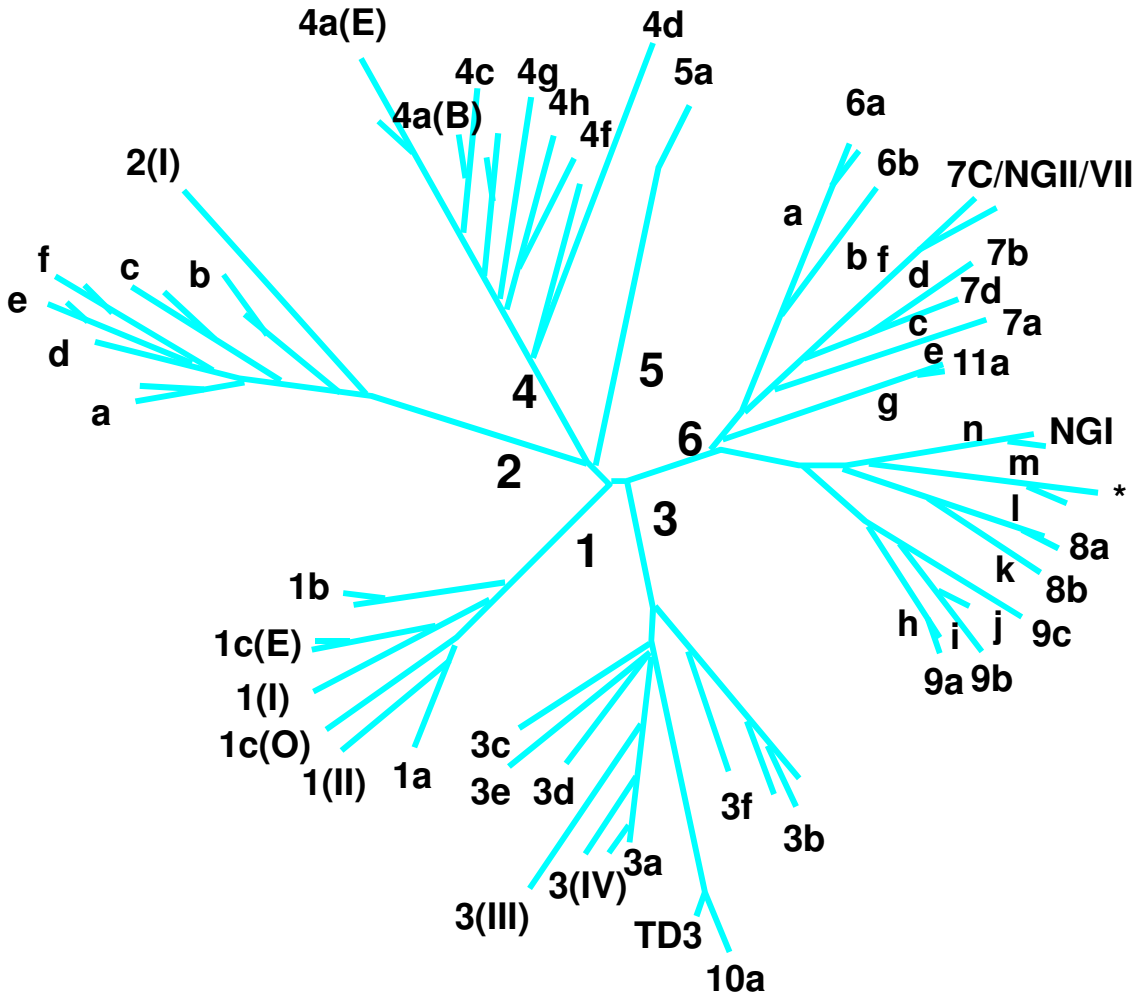
Incidence of HCV Infection

- WHO estimates several million new infections occurring globally p.a.
- USA CDC estimates ~ 20,000 new infections p.a.
- Canadian PHA estimates 2,000-12,000 new infections p.a.

Historical Difficulties

- Lack of a convenient animal model for testing vaccines
  - Chimpanzee is the only immunocompetent animal model
    - endangered species; limited supply, expensive
  - Use is currently prohibited using NIH funds
- Assays for virus-neutralising antibodies only developed in recent years
- Correlates of immunity only emerging recently
- Highly variable RNA virus
  - Hepacivirus genus is more heterogeneous than HIV

Hepacivirus Genus (P. Simmonds 2000)



The immune response can spontaneously resolve a minority of acute HCV infections

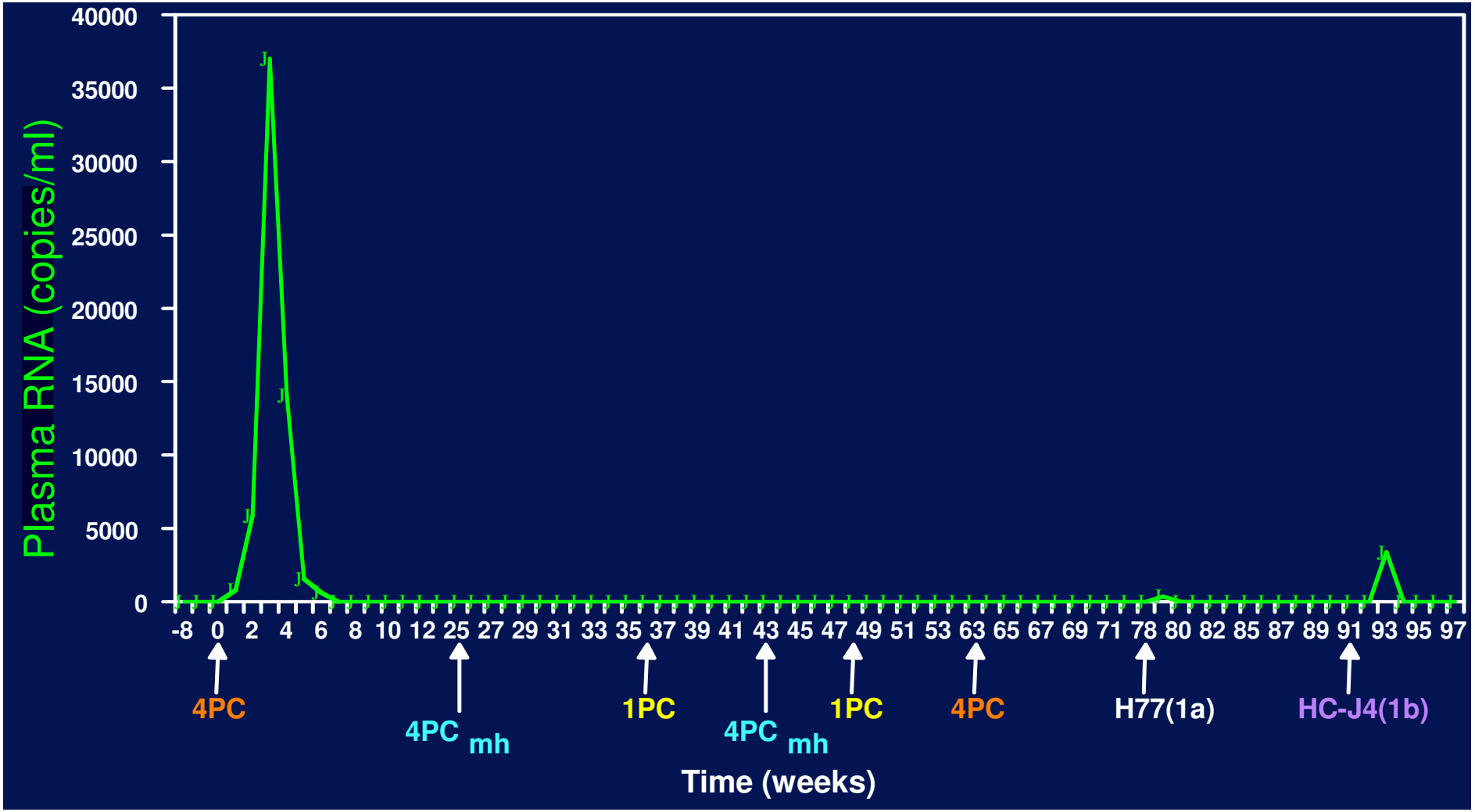
Spontaneous loss of Hepatitis C virus based on anti-HCV seropositivity in the absence of HCV RNA

Author	Country	% loss	Comments
Alter et al.	USA	26	NHANES III
Kenny-Walsh et al.	Ireland	45	Women receiving immune globulin
Seeff et al.	USA	26	Transfusion hepatitis
Vogt et al.	Germany	45	Children

Seeff et al., Hepatitis C, 2000

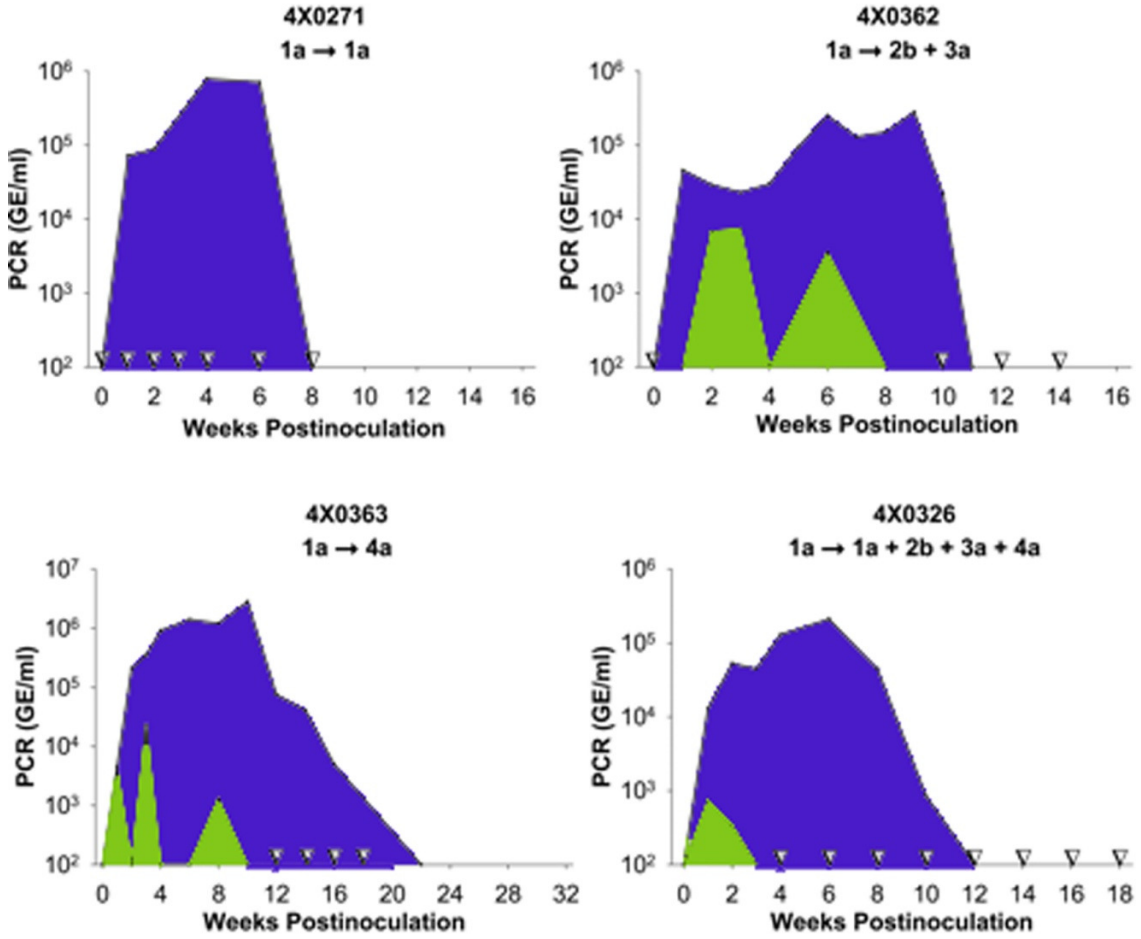
There is natural immunity against HCV – re-infections are usually ameliorated and resolve quickly (*but not always*)

Immunity in chimpanzee 4x0202 infected with HCV-1 RNA and rechallenged with heterologous type 1a and 1b inocula (100 CID50)



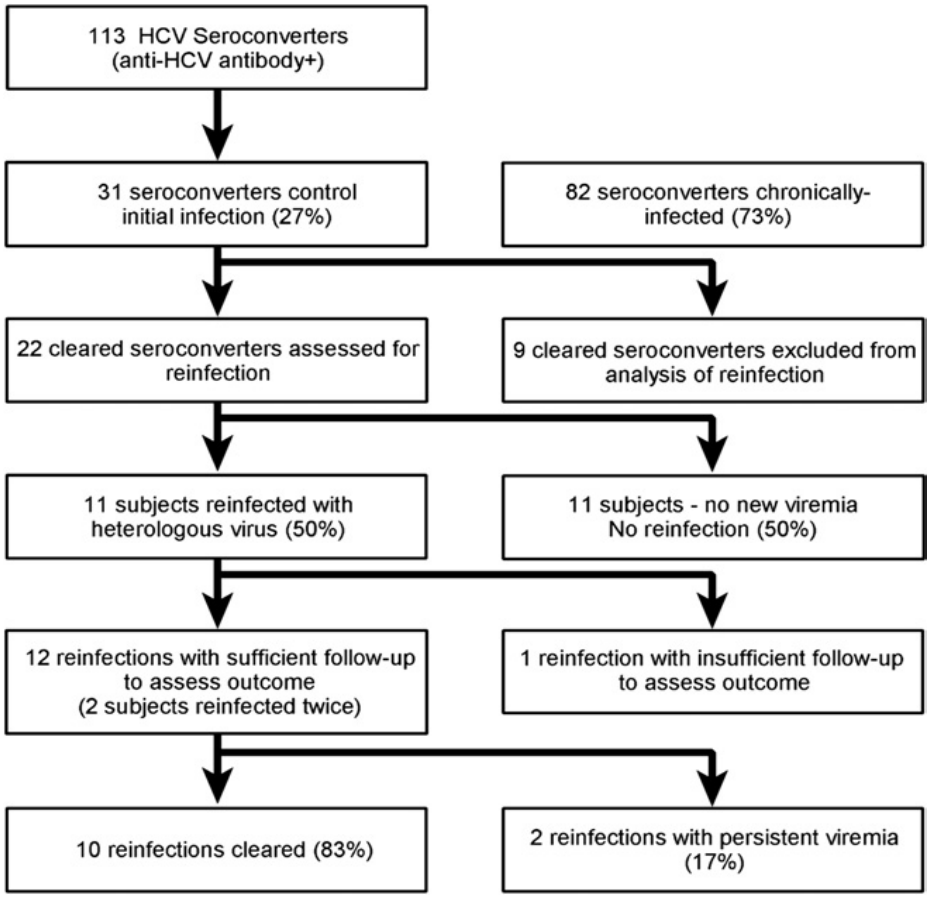
Weiner et al. J.Virol 2001

Cross-genotype protective immunity in the chimpanzee (R.Lanford et al, 2004)



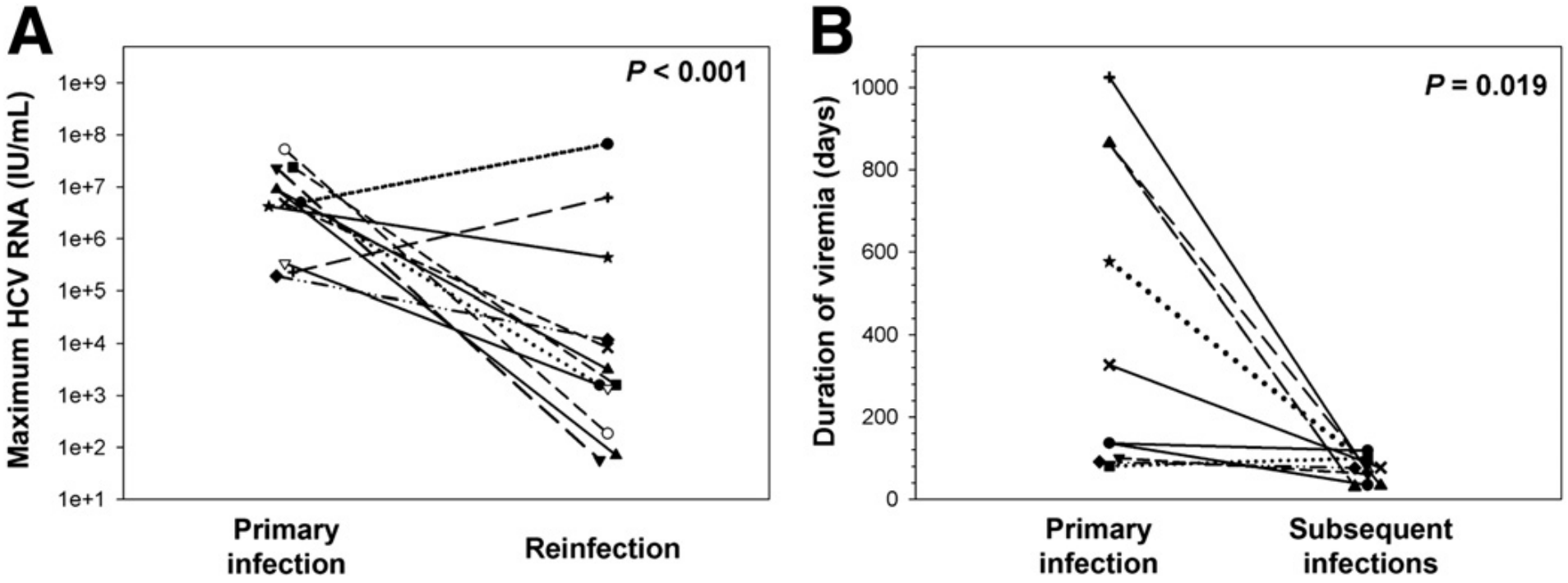
Outcome of re-infection in ivdu's

(W.Osburn et al 2010)



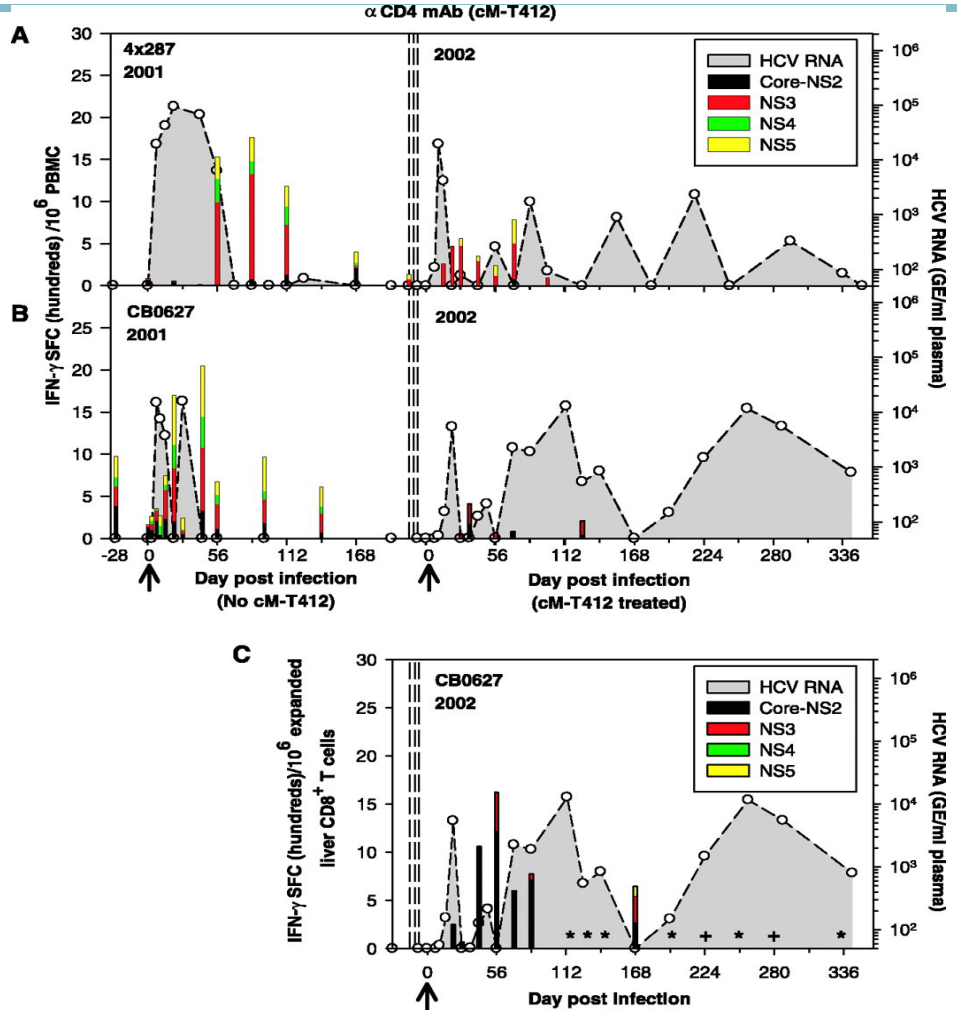
*The ratio of cleared to persistent subjects during reinfection was significantly greater than during primary infection (P = 0.001) (but **not** in HCV/HIV coinfections !)*

Amelioration of viremia during reinfection consistent with immune memory responses (W. Osburn et al 2010)



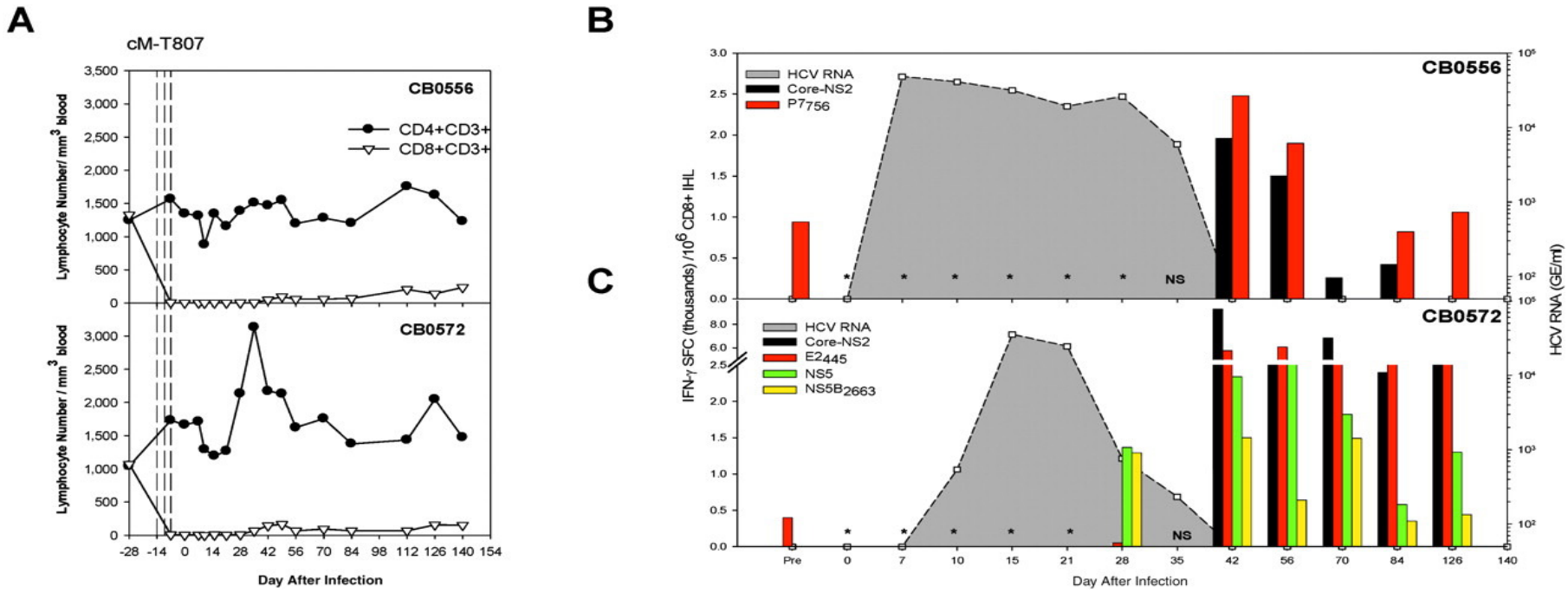
Adaptive immune responses correlate with recovery from acute HCV infection

Depletion of CD4+ T cells in convalescent chimpanzees leads to viral persistence following re-challenge



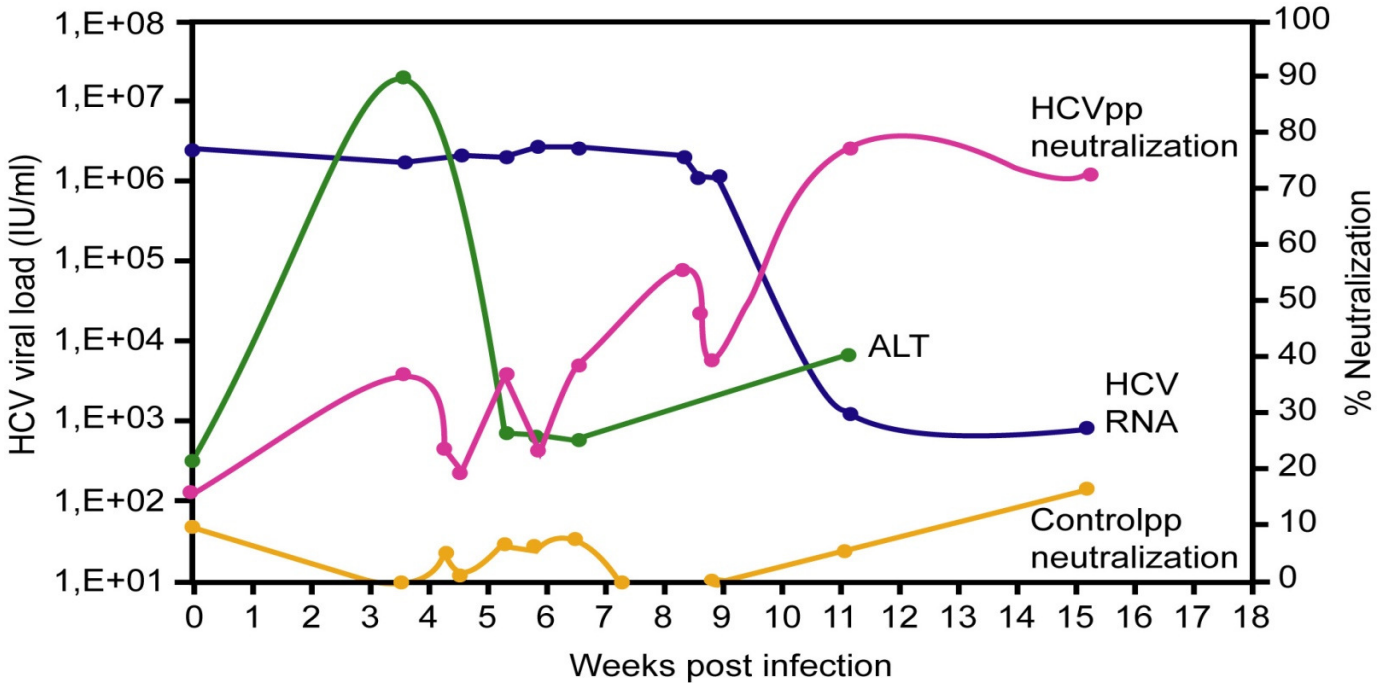
A Grakoui et al. Science 2003;302:659-662

Control of acute viremia by HCV-specific CD8+ T cells

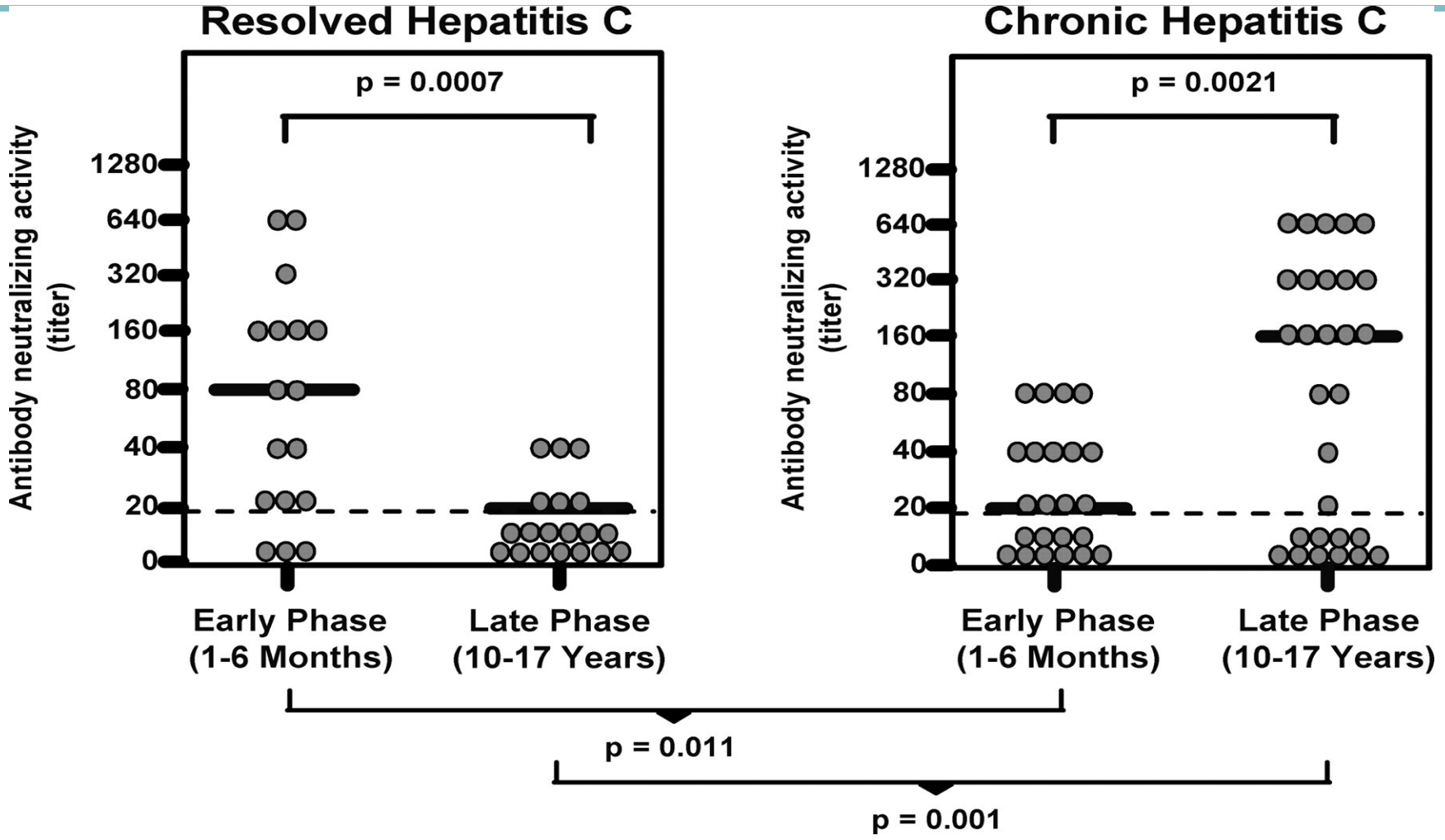


Shoukry N H et al. J Exp Med 2003;197:1645-1655

Association between control of acute HCV viremia and cross-neutralising Ab (J-M Pawlotsky et al 2005)

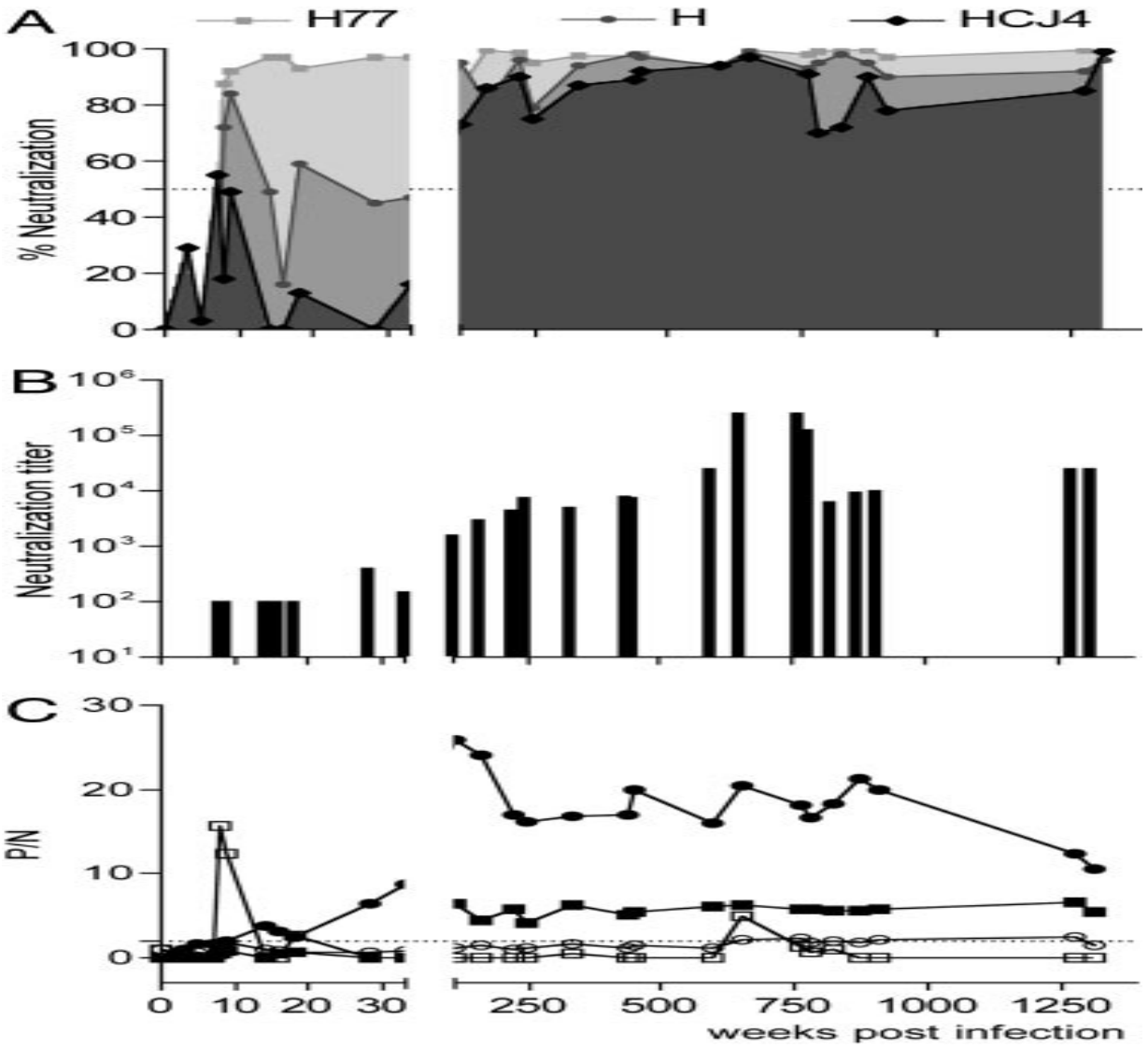


Neutralizing antibodies in patients with resolved or chronic hepatitis C.



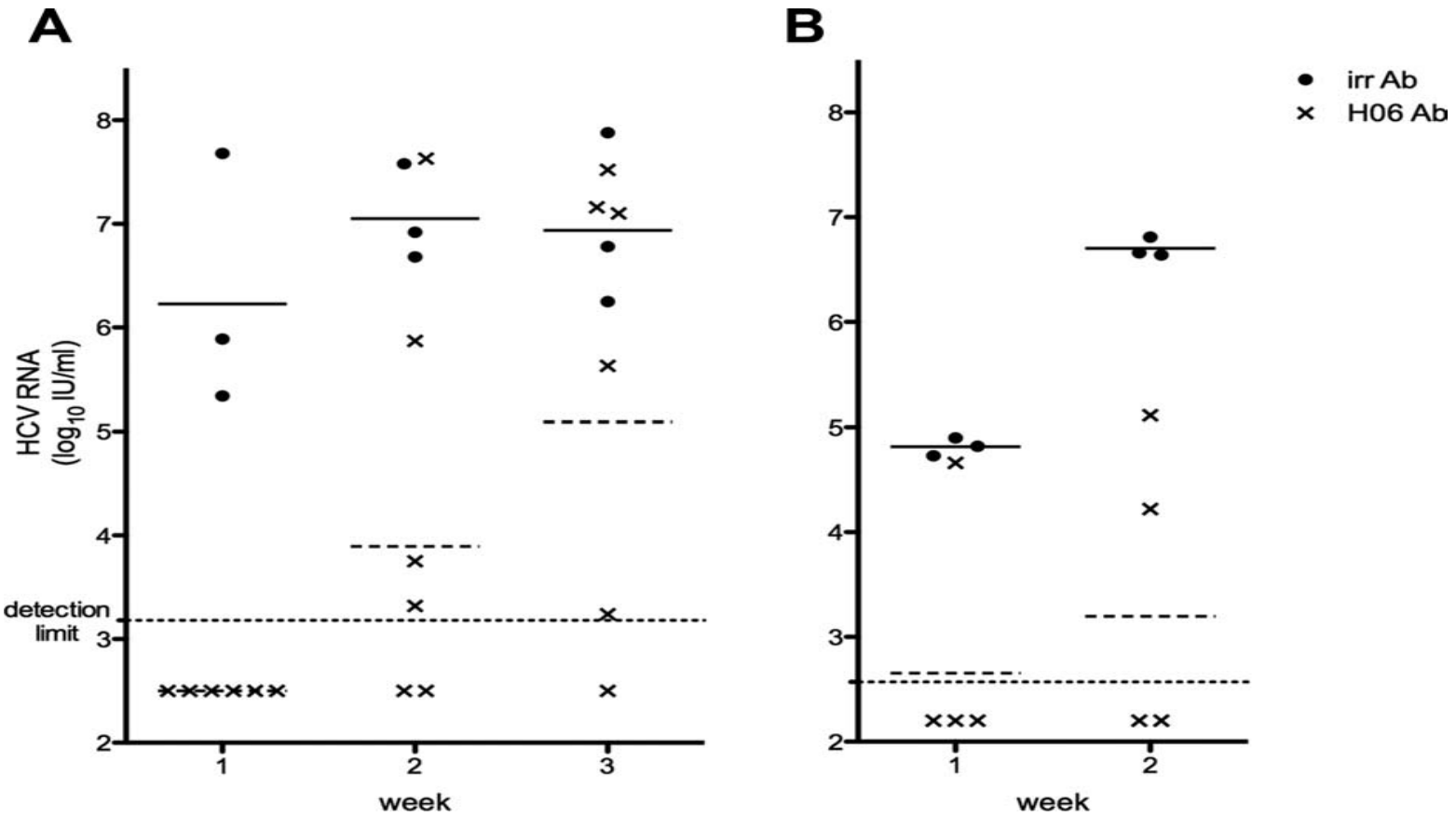
Pestka J M et al. PNAS 2007;104:6025-6030

Slow induction of neutralising antibodies in acutely-infected patient H (Logvinoff et al 2004)



Ig from chronic HCV patient H prevents or delays viremia in the SCID/uPA humanised mouse following heterologous challenge

(P.Meuleman et al Hepatol 2011)



Viral load in treated and nontreated chimeric mice challenged with HCV of **genotype 4a strain mED43 (A)** or **genotype 6a strain mHK6a (B).** Chimeric mice were injected with either irrelevant control IgG (I) or H06-antibodies (). Three days later all animals were injected with the minimal dose needed to establish a robust infection in all animals. HCV RNA (IU/mL) present in mouse plasma was quantified weekly and all individual levels are shown. Horizontal lines represent the geometric mean within the group (solid line: control challenge group; dashed line: H06-treated challenge group).

Note : Half-life of human Ig only ~ 5-7 days in SCID/uPA mouse model

Correlates of Immunity : Conclusions

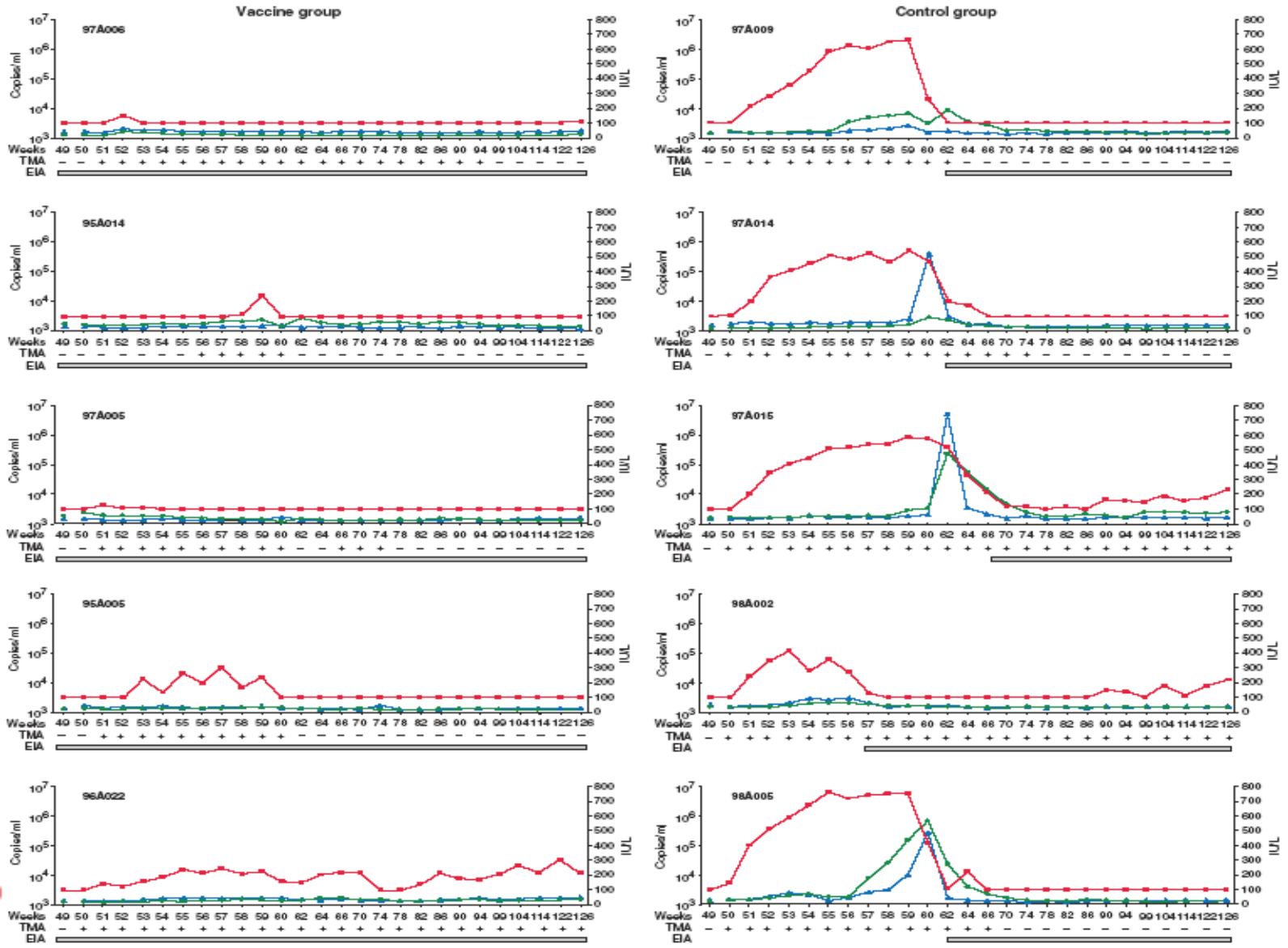
- T cell depletion studies in the chimpanzee model demonstrate the *requirement* of HCV-specific CD4+ and CD8+ T cell responses in the eradication of acute viremia
- HCV neutralising Ab is associated with eradication of acute viremia in humans and modulates infection in animal models
- Therefore, an optimal HCV vaccine probably needs to elicit broad cross-reactive cellular immune responses *and* cross-neutralising antibodies
  - *Note : All approved viral vaccines elicit neutralising antibodies*

Status of HCV Vaccine Development

Prophylactic HCV "T cell vaccine" in phase 2 efficacy testing (A.Folgori et al. (Okairos & NIH))

- Prime/boost immunisation regimen using a chimpanzee adenovirus & modified vaccinia ankora expressing HCV genotype1b non-structural (NS) 3,4 & 5 genes
  - NS proteins encode large number of CD4+ and CD8+ epitopes
  - Both replication-defective viral vectors
  - Relies on multi-specific CD4+ & CD8+ T cell responses without any neutralising antibody
- ***Prototype*** vaccine tested in 5 chimpanzees
  - Evidence for amelioration of acute hepatitis and acute viremia in vaccinees after experimental challenge with heterologous 1a virus
    - *But no significant difference in carrier rates*
    - *~10% population have antibodies vs chimp adenovirus*
- Efficacy data anticipated in 2015
  - Earliest approval estimated ~ 2018/9/20

Hepatitis C virus T cell vaccine (Multiple Primes with 2 Adenoviruses expressing 1b NS3,4,5 + Multiple Boosts with Electroporated 1b DNA-NS3,4,5) *Heterologous 1a challenge in chimpanzees*

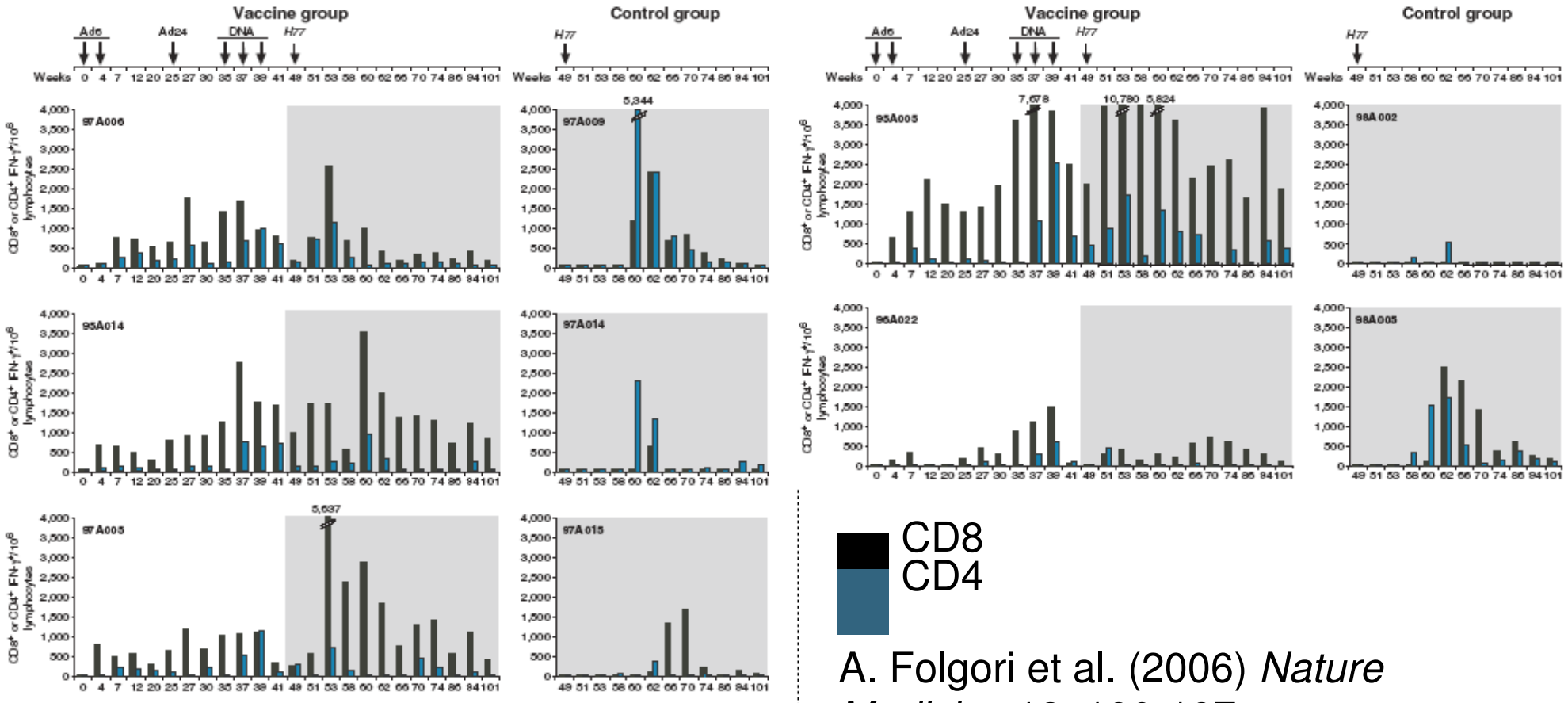


bDNA
GGT
ALT
Anti-HCV+ve

A. Folgori (2006)
Nature Medicine
12, 190-197

Hepatitis C virus T cell vaccine (Prime with Adenovirus expressing 1b NS3,4,5 + boost with Electroporated 1b DNA-NS3,4,5) – circulating T cell responses

Heterologous 1a challenge in chimpanzees

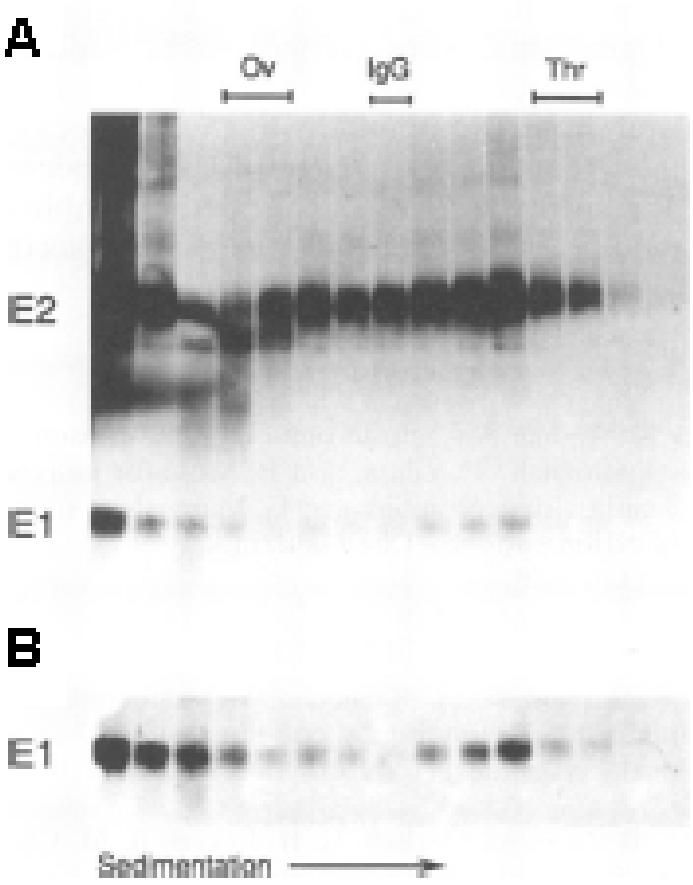


A. Folgori et al. (2006) *Nature Medicine* 12, 190-197

A vaccine based on recombinant gpE1/gpE2 envelope glycoproteins (Novartis ; M.Houghton Immunol Rev 2011)

- Native heterodimer complex comprising both full-length envelope glycoproteins gpE1 (33KDa) + gpE2 (72KDa)
- Produced in CHO or HeLa cell-lines
- gpE1/gpE2 retained in lumen of endoplasmic reticulum via C-terminal transmembrane anchor regions
- Purified to homogeneity under native conditions

Oligomeric recombinant gpE1/gpE2 purified from CHO cells
(R.Ralston et al)

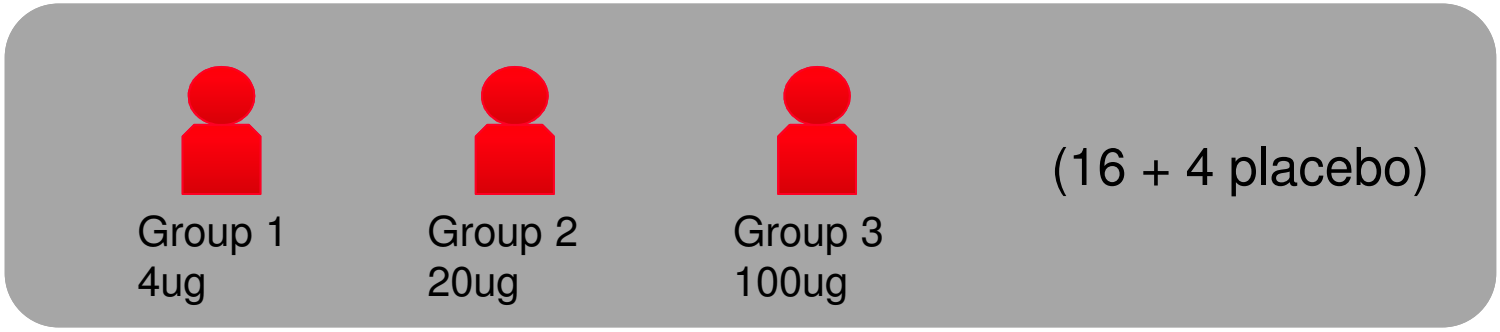


Prophylactic efficacy in chimpanzee model

Viral challenge	Group	Total	Acute infections	Chronic infection (%)	
Homologous	gpE1/gpE2	12	7	2(17)	P=0.003
HCV-1	Unimmunized	10	10	7(10)	
Heterologous	gpE1/gpE2	19	19	3(16)	P=0.02
H77	Unimmunized	14	14	8(57)	
Total	gpE1/gpE2	31	26	5(16)	P=<0.001
	Unimmunized	24	24	15(63)	

Adapted from Houghton, Immunological Review 2011

Phase I trial design



Vaccine: **recombinant E1E2+ MC59C.1 adjuvant**

4 rounds at 0, 4, 24, 48 wks

Serum collected every 2 wks twice after each dose
(4,6,8 wks; 24, 26, 28 wks…)

Frey *et al.* , Vaccine 2010

Phase I trial conducted

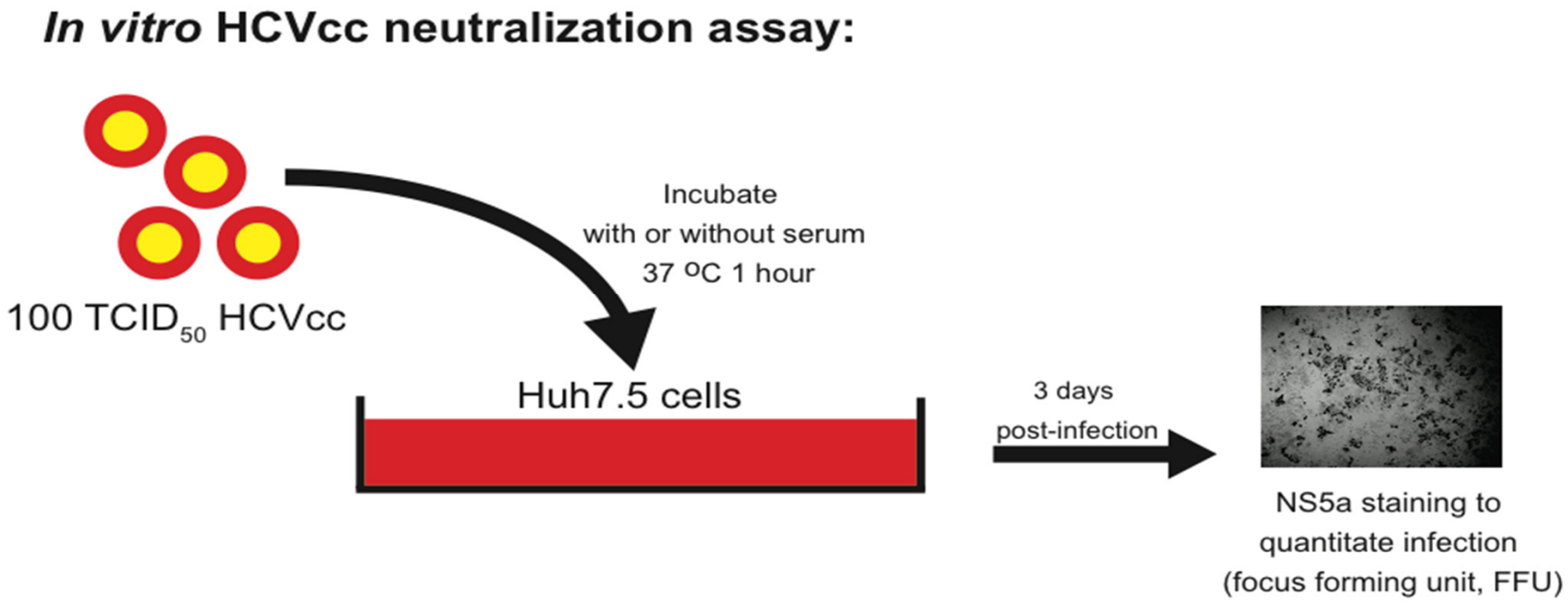
(S. Frey et al Vaccine 2010 ; R.Ray et al JID 2010)

- The investigational E1E2/MF59 vaccine
  - Exhibits satisfactory safety and tolerability
  - Elicits anti-E1E2 (EIA) titers which are in the same range as in vaccinated chimps
    - *But protection in chimps did not always correlate with elicited anti-E1E2 titers*
  - Induces very strong lymphoproliferative responses to E1E2

- 20ug E1E2 antigen dose administered on months 0,1 & 6 elicits optimal immunogenicity

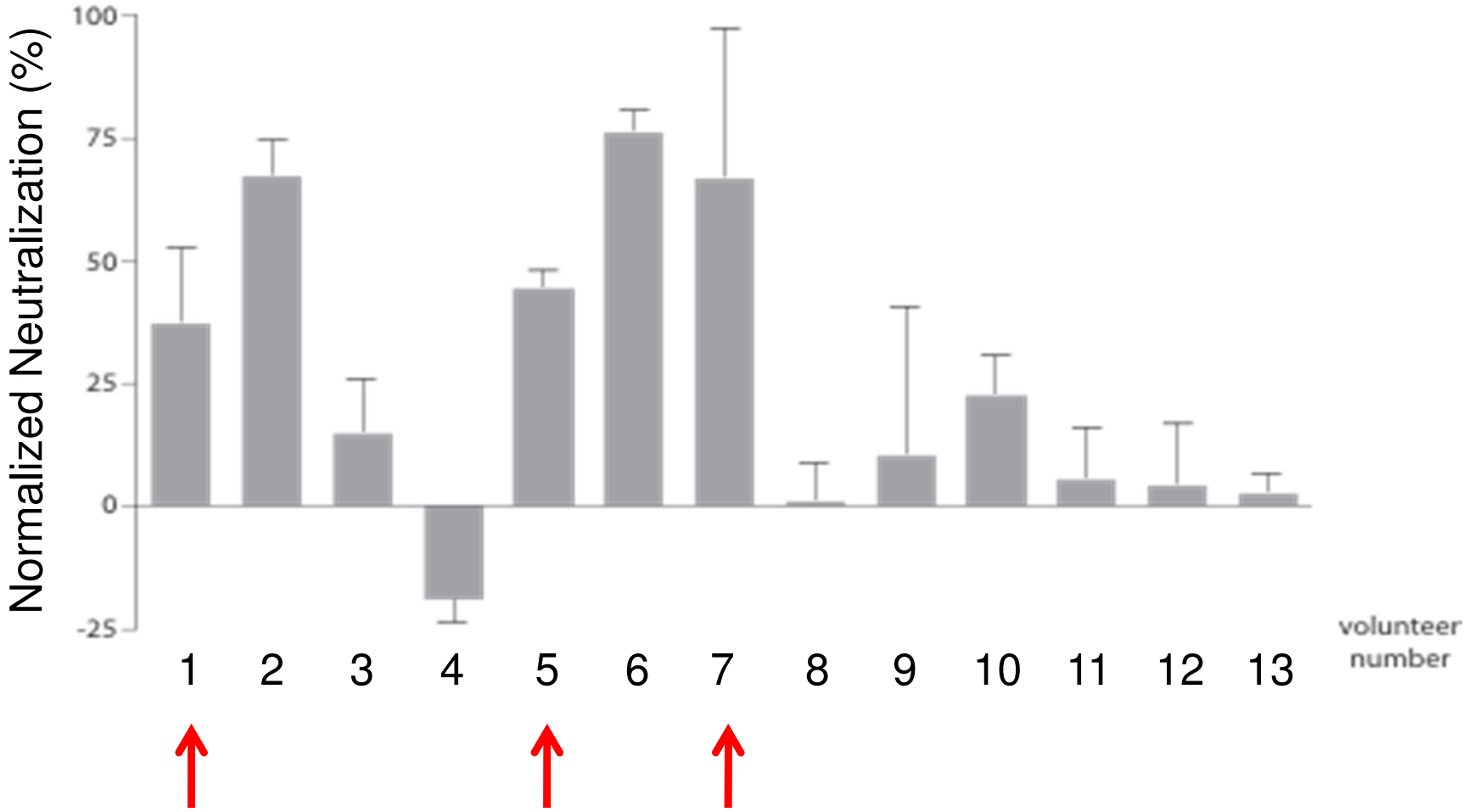
Can antibodies elicited by a rec. gpE1/gpE2 vaccine neutralise viral infectivity ?
If so, is neutralisation strain-specific or broadly cross-neutralising ?

Infection of human hepatoma Huh7.5 cell-line by HCV strain JFH-1
(T.Wakita et al 2005)



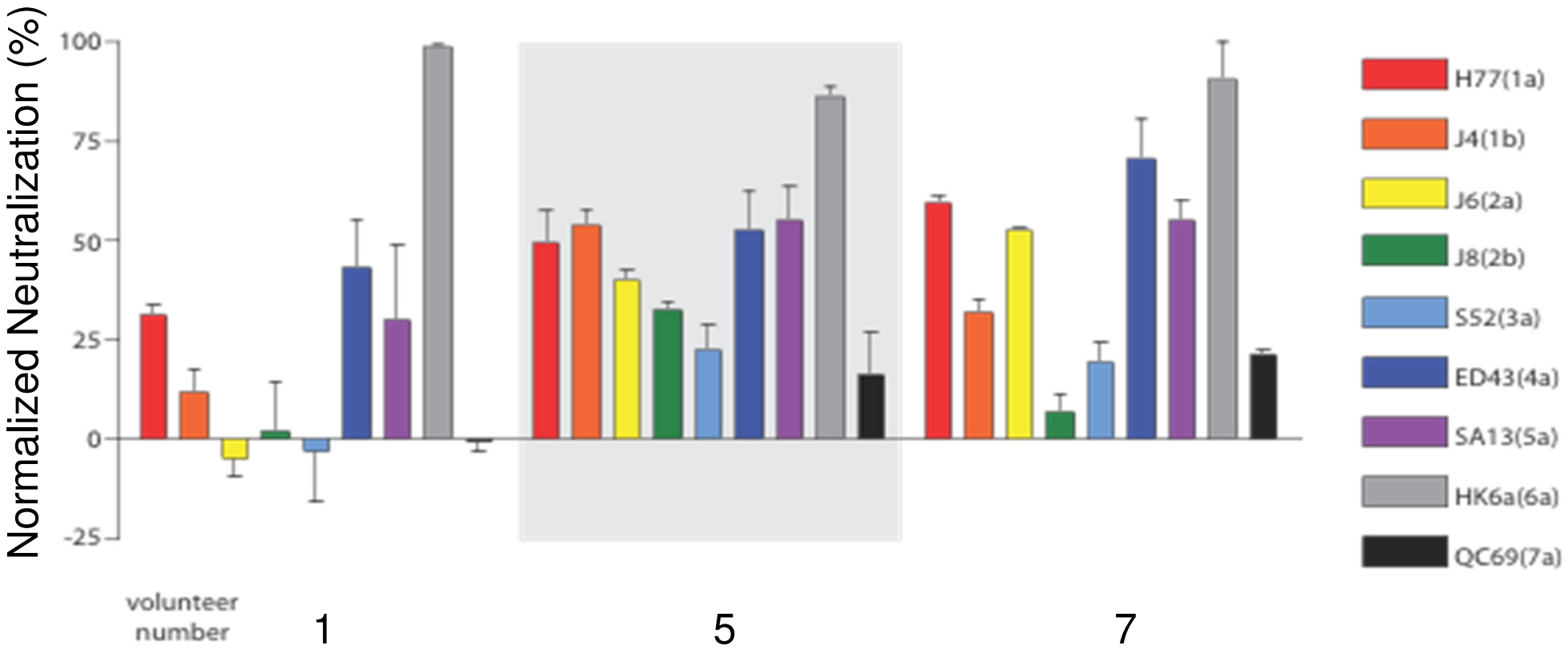
Neutralization activity against chimeric H77/JFH (1a) HCVcc

(J.Law et al Plos One 2013)

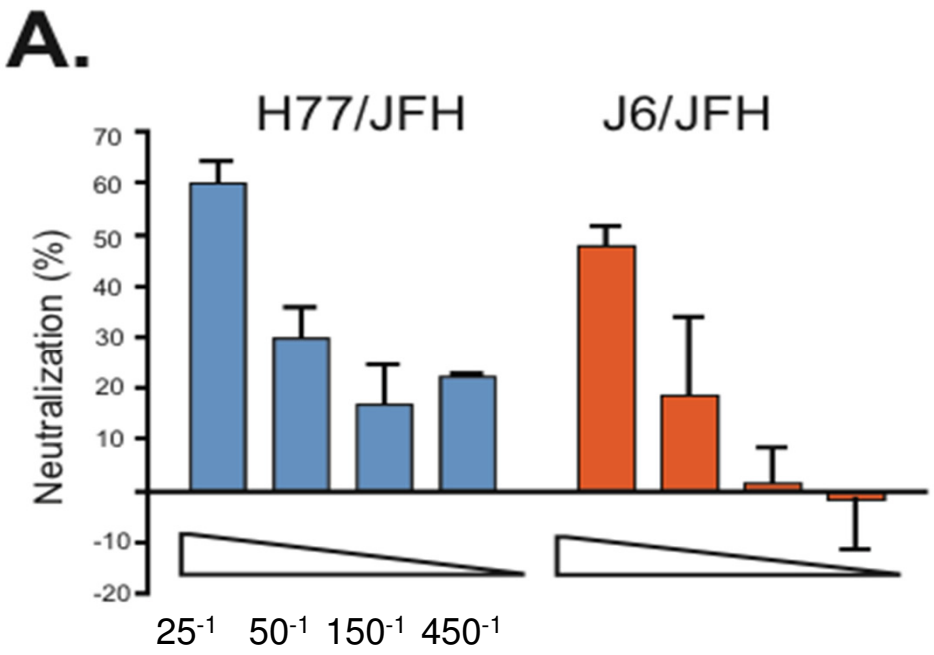


Vaccinees elicit broad cross-neutralizing antibodies

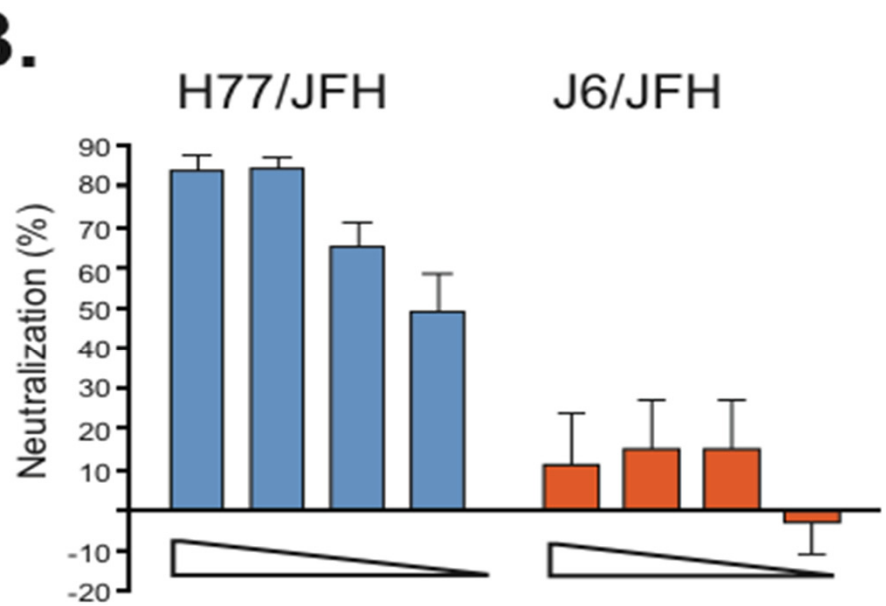
(J.Law et al Plos One 2013)



Dose response of neutralizing antibodies

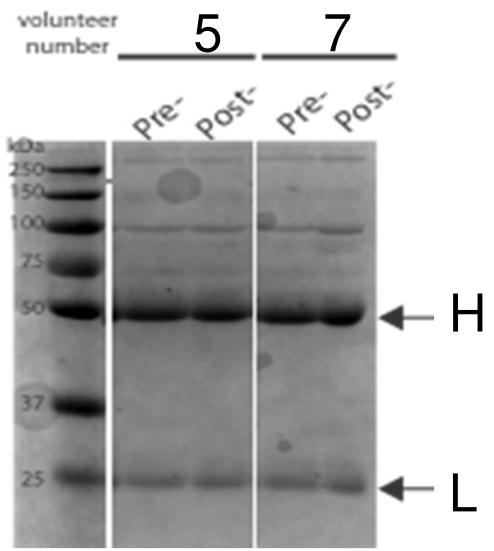


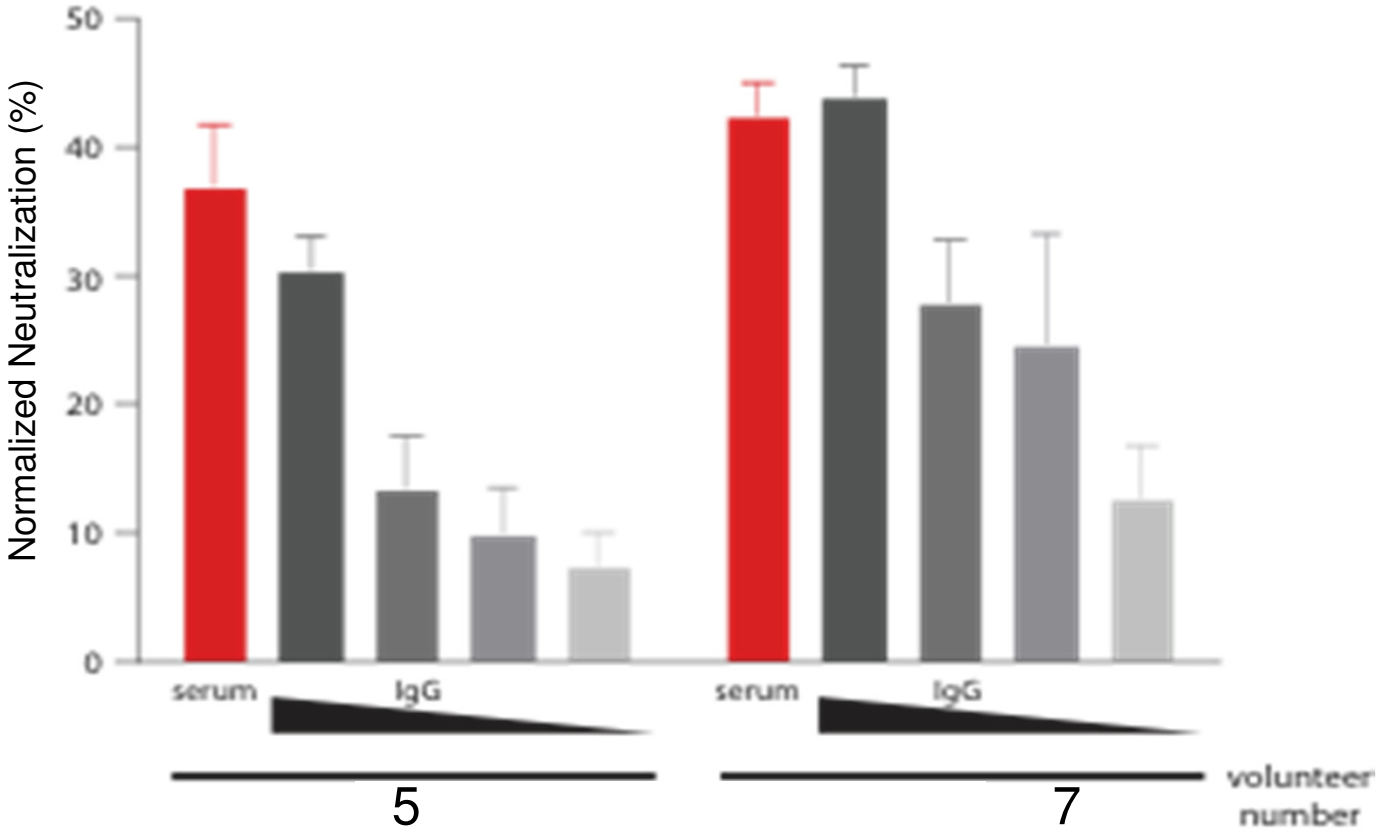
Volunteer 5 serum



Patient serum
(infected with HCV 1a)

Neutralizing activity is Immunoglobulin-dependent





HCV Vaccine : Conclusions

- A *partially*-effective HCV vaccine appears to be feasible
  - ~ 70-80% efficacy likely
- An optimal global vaccine is likely to be produced via generating cross-reactive T cell responses and cross-neutralising antibodies

HCV Vaccine Status

- Phase 2 efficacy of Okairos T cell vaccine to be determined in 2015/16
- We are developing a 2nd-generation HCV vaccine that elicits broad cross-neutralising antibodies ***and*** broad cross-reactive T cell responses
  - *funded by CERC , Alberta Innovates Health Solutions & Li Ka Shing Institute of Virology, University of Alberta*

gpE1/gpE2 vaccine contributors

- John Law, Jason Wong, Chao Chen, Darren Hockman (University of Alberta)
- Qui-Lim Choo, George Kuo, Robert Ralston, Steve Coates, Amy Weiner, Sergio Abrignani (ex-Novartis)
- Charlie Rice, Jens Bukh, Takashi Wakita (HCVcc)
- Sharon Frey, Robert Belshe (St Louis VTEC)
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