Progress towards a vaccine against hepatitis C Virus Where are we at in 2025?

Lausanne Jan 2025

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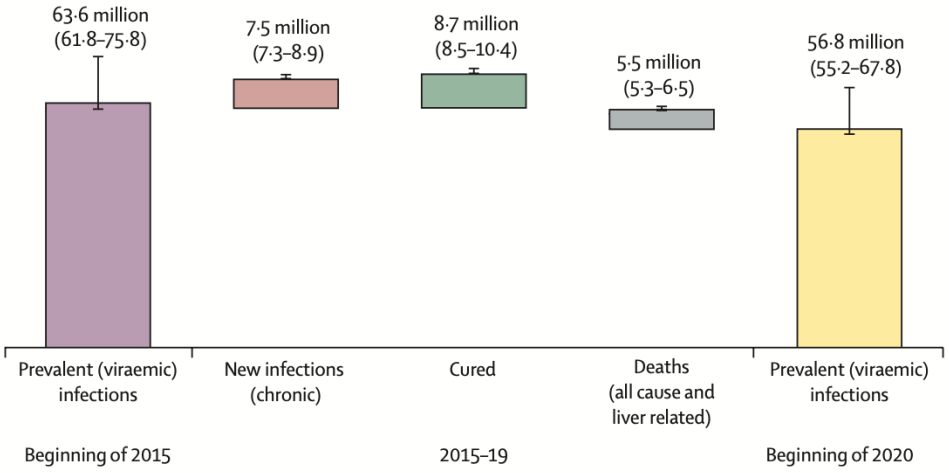
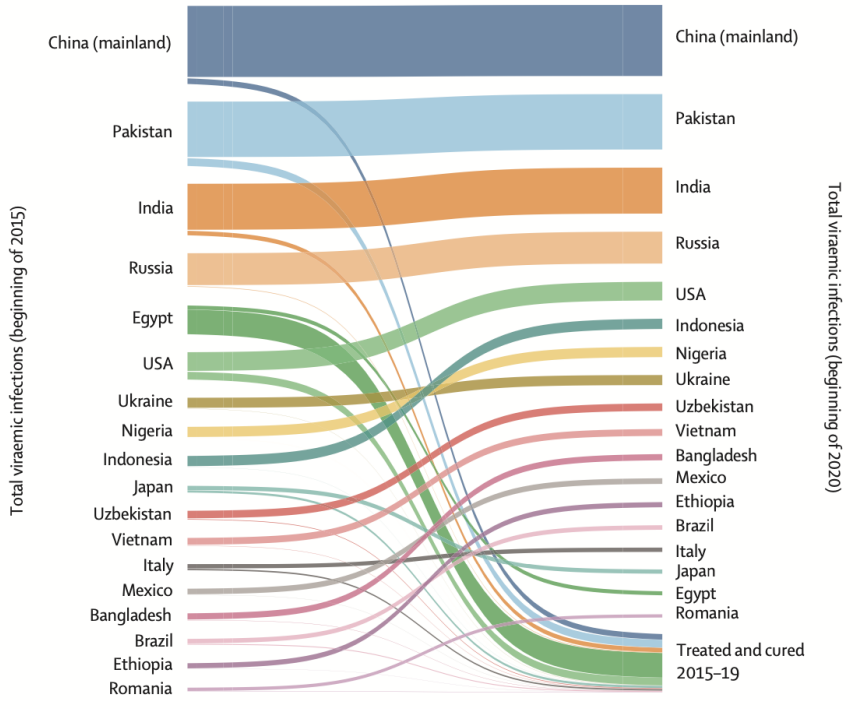
Do we still need a vaccine for HCV?

- >50 million still RNA + (WHO data)
- Viral hepatitis kills more people than malaria and HIV combined/year.
- 1.7 million new infections/year
- Epidemic continues (increasing incidence in USA and elsewhere)

- The Polaris Observatory HCV collaborators :
  - 2015-2020: Decrease 6.8 million –from 63.6 M to 56.8M





Stanway et al Lancet 2016
Polaris collaborators: Lancet Gastro Hep Feb 2022

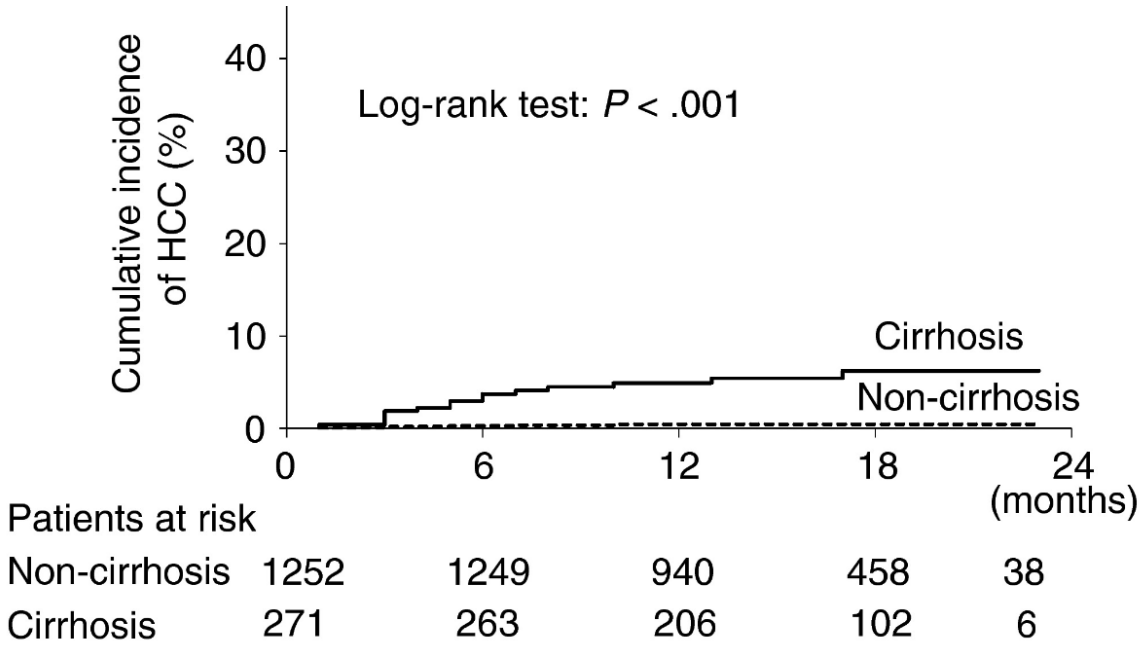
Vaccines or treat ?

- Fantastic new drugs for HCV-almost no side effects.
  -Expensive
  -Prolonged (8-12 weeks)
  -small % failure associated with drug resistance
  -People transmit before they have been treated
  -Do not protect against re-infection:
    - After treatment of active IVDU's in Scotland, 18-month reinfection rate was 17.1/100 person-years (EASL 2018)

  -Most people unaware they are infected presenting with cirrhosis-or worse HCC

- A vaccine is better medicine!

On going risk of liver cancer after HCV cure

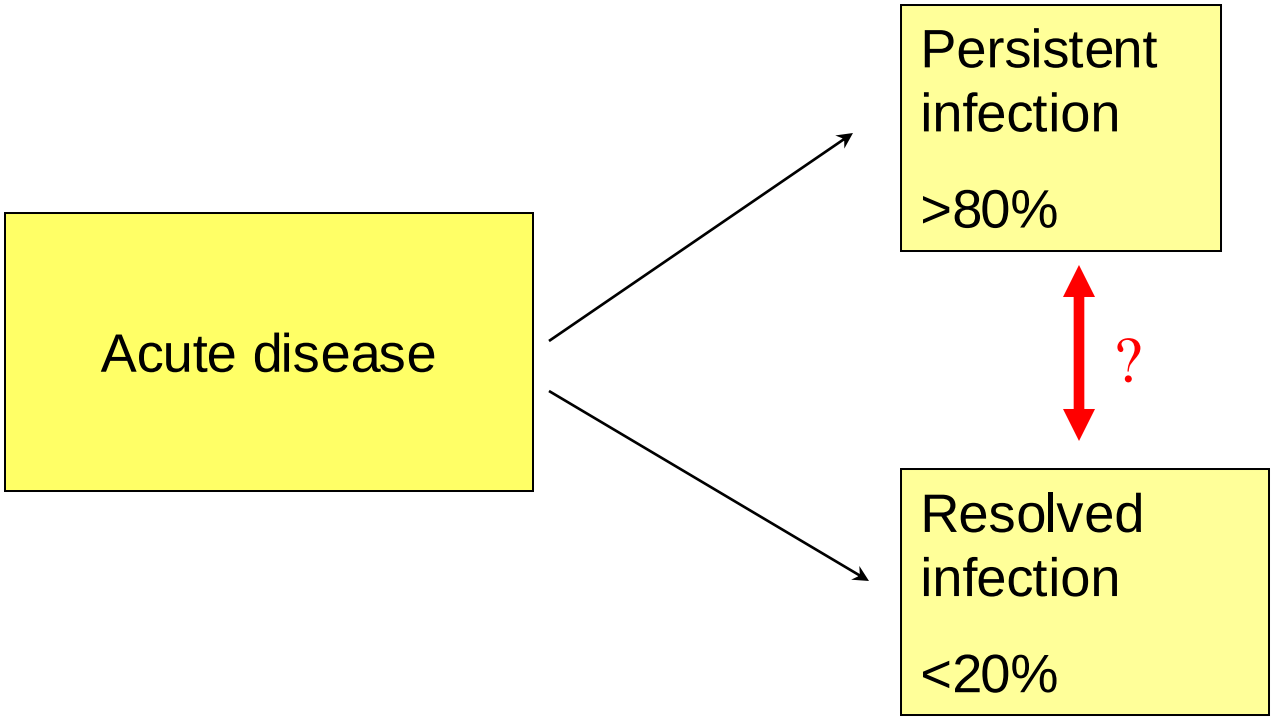


1675 consecutive patients followed up post SVR
Median follow up 17 months
Annual incidence of new HCC 4.9% in cirrhosis

Ogawa et al AP&T 2017

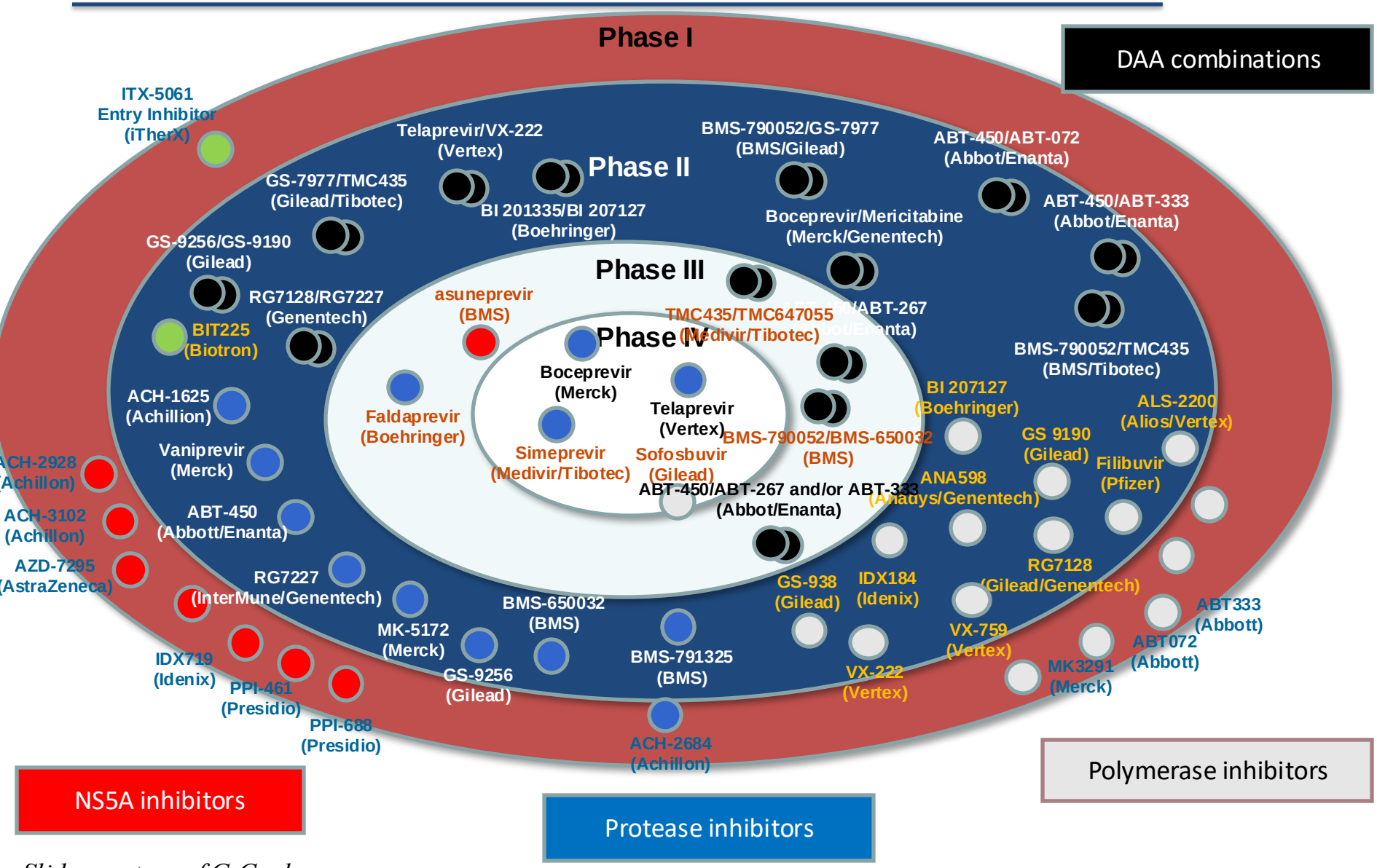
Large UK program in HCC early detection
https://deliver.cancer.ox.ac.uk/

It should be possible to make a vaccine for HCV ?



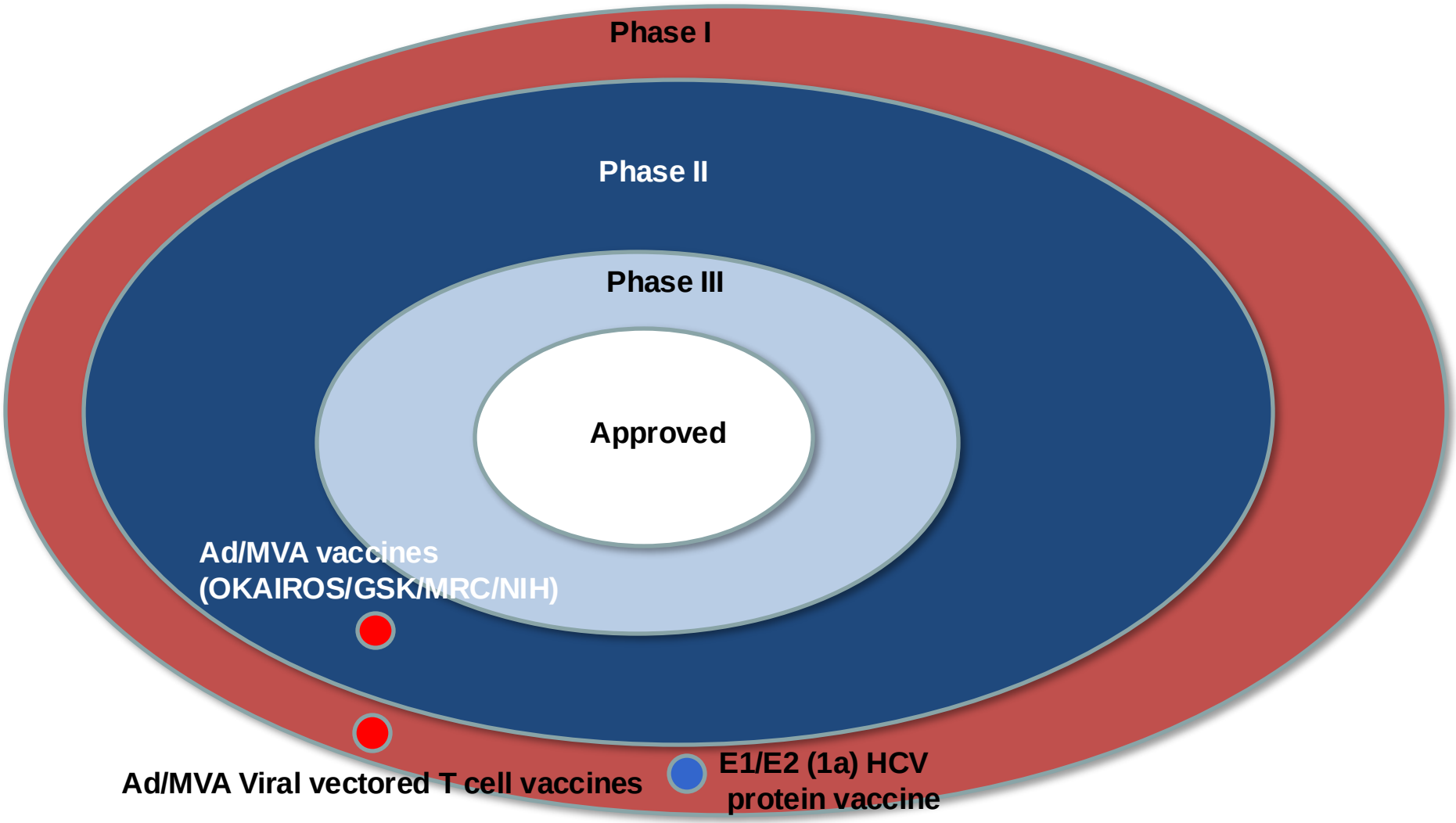
T cell immunity
B cell immunity
GWAS: IFN genes-IFNL4

Hepatitis C therapy pipeline (2013/14)



Slide courtesy of G Cooke

HCV vaccine pipeline – human studies 2023



T cell vaccines

B cell vaccines

A T cell vaccine for HCV-the rationale

- HLA association studies (A3, B57, B27 with clearance)

(Neumann C, et al. Hepatology 2006)

- Chimpanzee CD4+ and CD8+ T cell blocking experiments

(Nagla Shoukry N J Ex Med 2003)

- Association of breadth and magnitude of T cell response with viral clearance

(Lauer et al Gastro 2004)

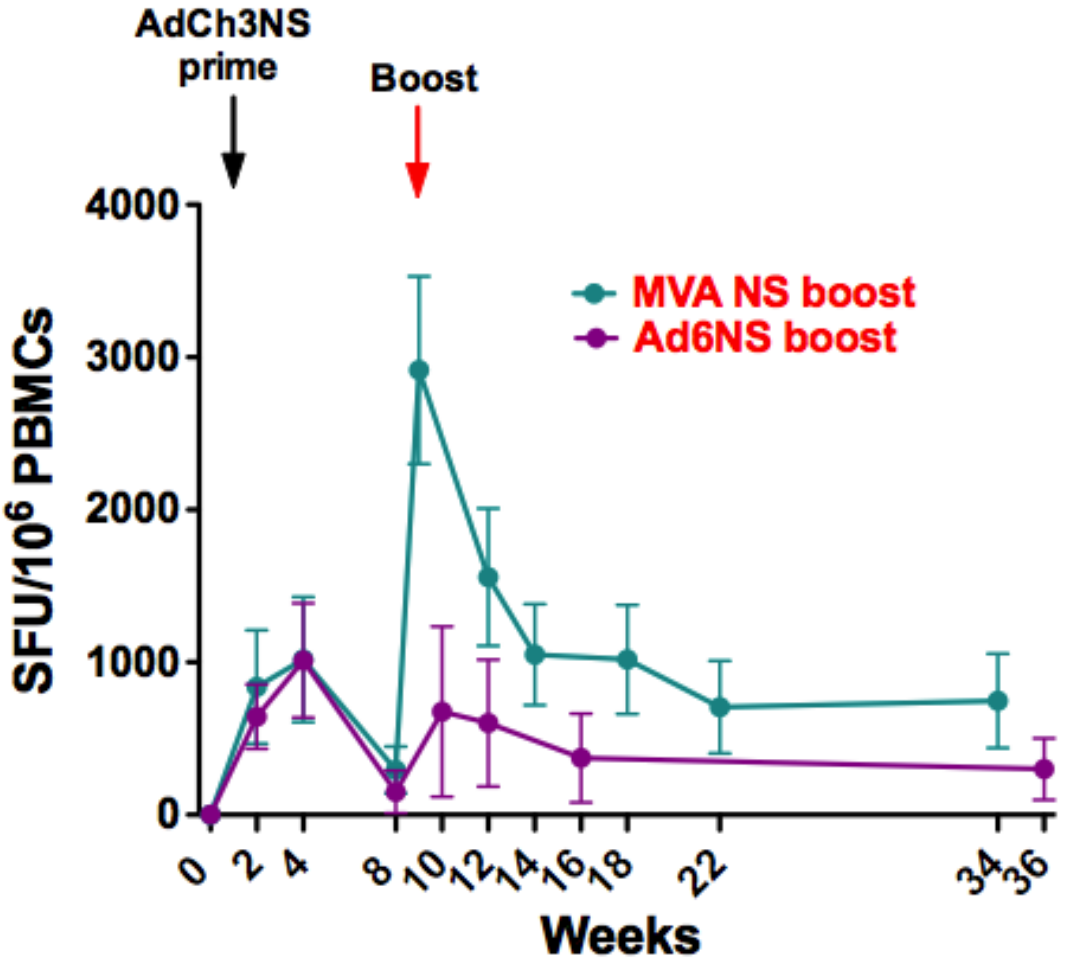
- IFN-g specific $CD8^+$ T cell responses are temporally correlated with reduced viremia after infection

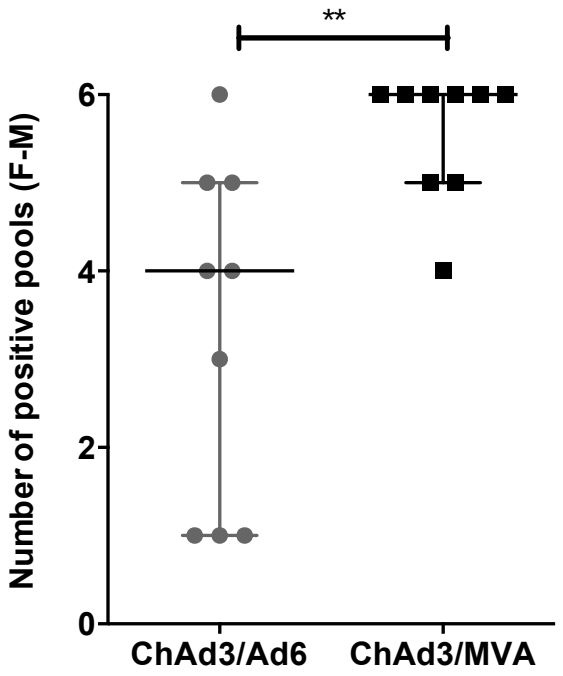
(Lechner F J Ex Med 2000)

- Prophylactic vaccine data (Adeno/DNA) in a chimp challenge model

(Folgori et al Nat med 2008)

One HCV vaccine progressed to efficacy testing





Swadling et al Science Translational Medicine; Nov 2014

Esposita et al Science Translational Medicine; Nov 2020 (genetically enhanced)

One HCV vaccine progressed to efficacy testing

- Testing in BBASH cohort (CI Andrea Cox)
  - Baltimore USA
  - 540 IVDU at risk of HCV
  - placebo controlled trial
  - Results 2020

  - Millions $ and >6 years

Page K. et. al., *N Engl J Med* 2021; 384:541-549

Vaccine failed to protect against chronic infection

The NEW ENGLAND JOURNAL of MEDICINE

Table 2. Vaccine Efficacy against Chronic HCV Infection at 6 Months.*

Analysis and Population†	Vaccine (N=275)		Placebo (N=273)		Vaccine Efficacy (95% CI)‡	Hazard Ratio (95% CI)§	P Value¶
	Censored Data	Chronic Infection	Censored Data	Chronic Infection			
	number of participants				*percent*		
Primary efficacy analysis, per-protocol population‖	261	14	259	14	−53 (−255 to 34)	1.53 (0.66–3.55)	0.31
Secondary efficacy analysis, modified intention-to-treat population	256	19	257	17	−66 (−250 to 21)	1.66 (0.79–3.50)	0.18

Page K. et. al., *N Engl J Med* 2021; 384:541-549

Why did this potent viral vectored vaccine fail to protect against chronic infection?

- T cells alone unable to control HCV viraemia?
- HCV genetic variation?
- Vaccine not immunogenic in PWID?
- Pre-existing ChAd3 Abs?

Maybe clearance is not all about T cells. But……

- HLA association studies (A3, B57, B27 with clearance)

(Neumann C, et al. Hepatology 2006)

- Chimpanzee CD4+ and CD8+ T cell blocking experiments

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(Folgori et al Nat med 2008)

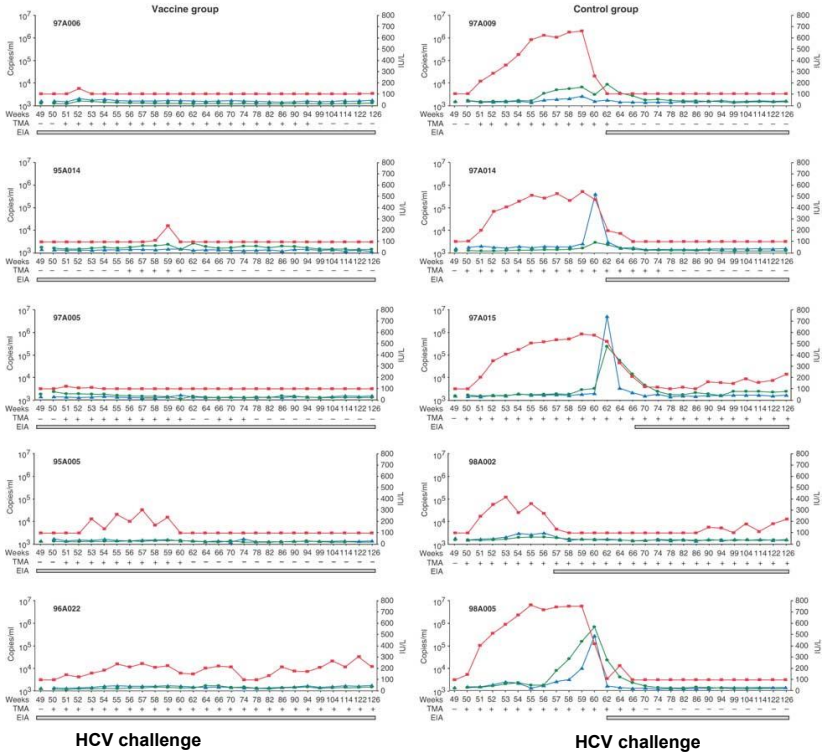
Proof of principle-in vivo studies

Folgori et al Nat Med 2008

Osburn et al (Cox lab)
Gastroenterology 2010

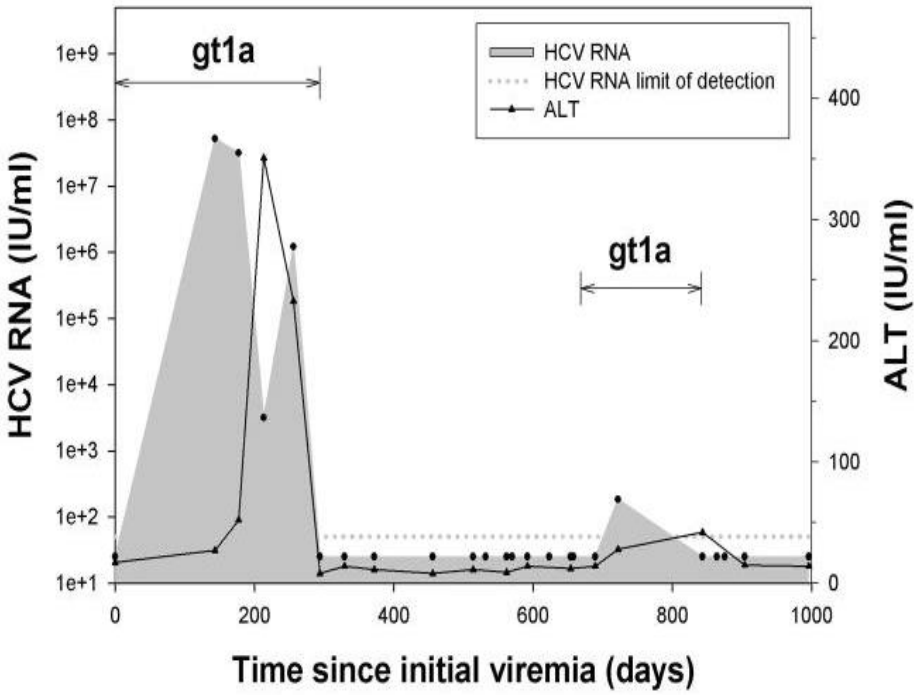
Vaccinated animals **Control animals**

HCV genomes/ml

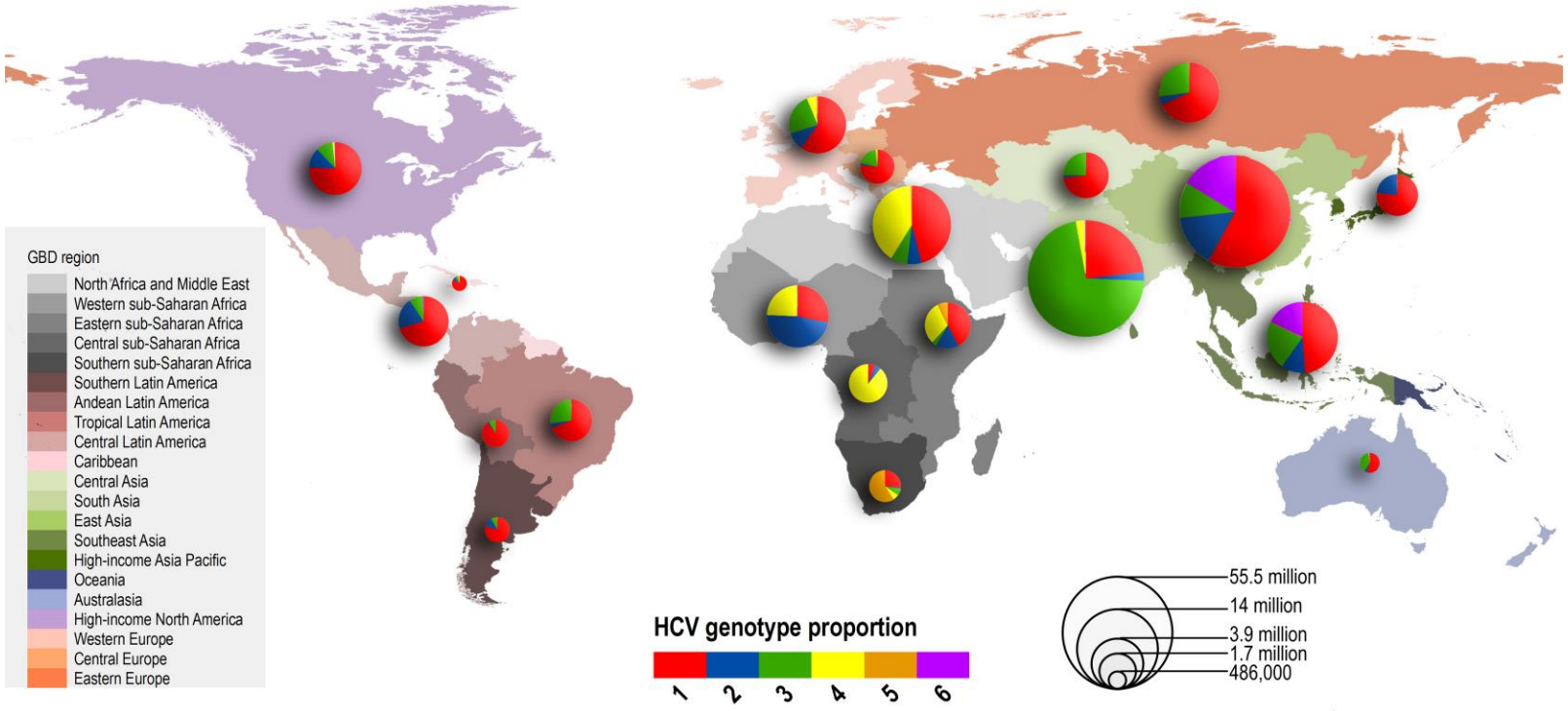


ALT or GGT

Subject 133



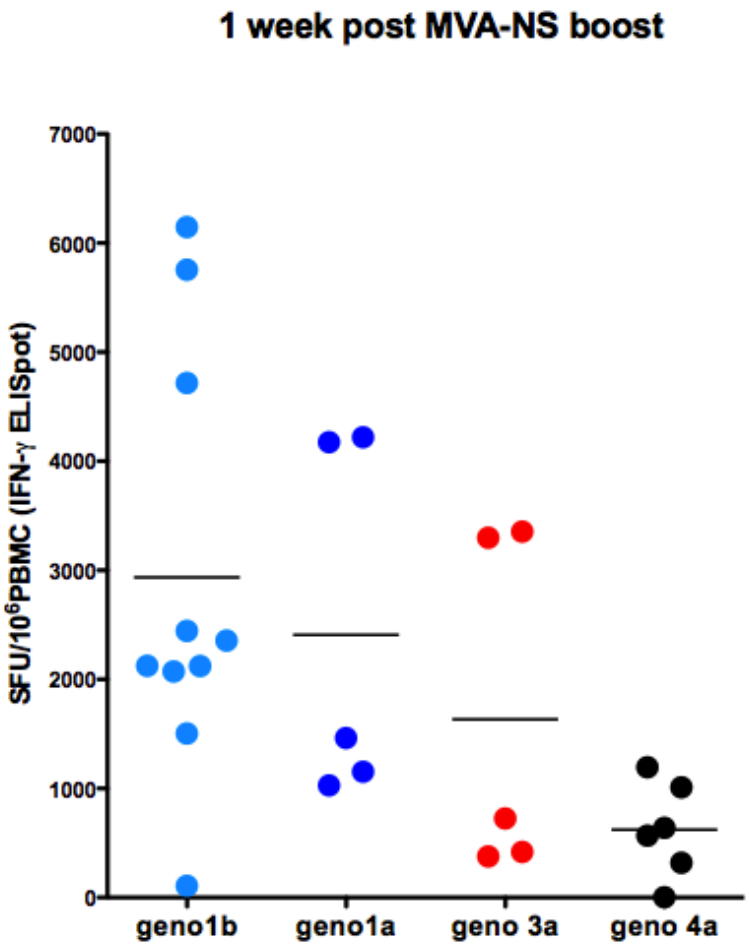
HCV genetic diversity remains a challenge -for both T cell and B cell vaccines



-Messina et al Hepatology 2015 (Data from 1200 papers since hep C was discovered)

HCV genetic variation?

Ad/MVA vaccine in phase 1 study of healthy volunteers

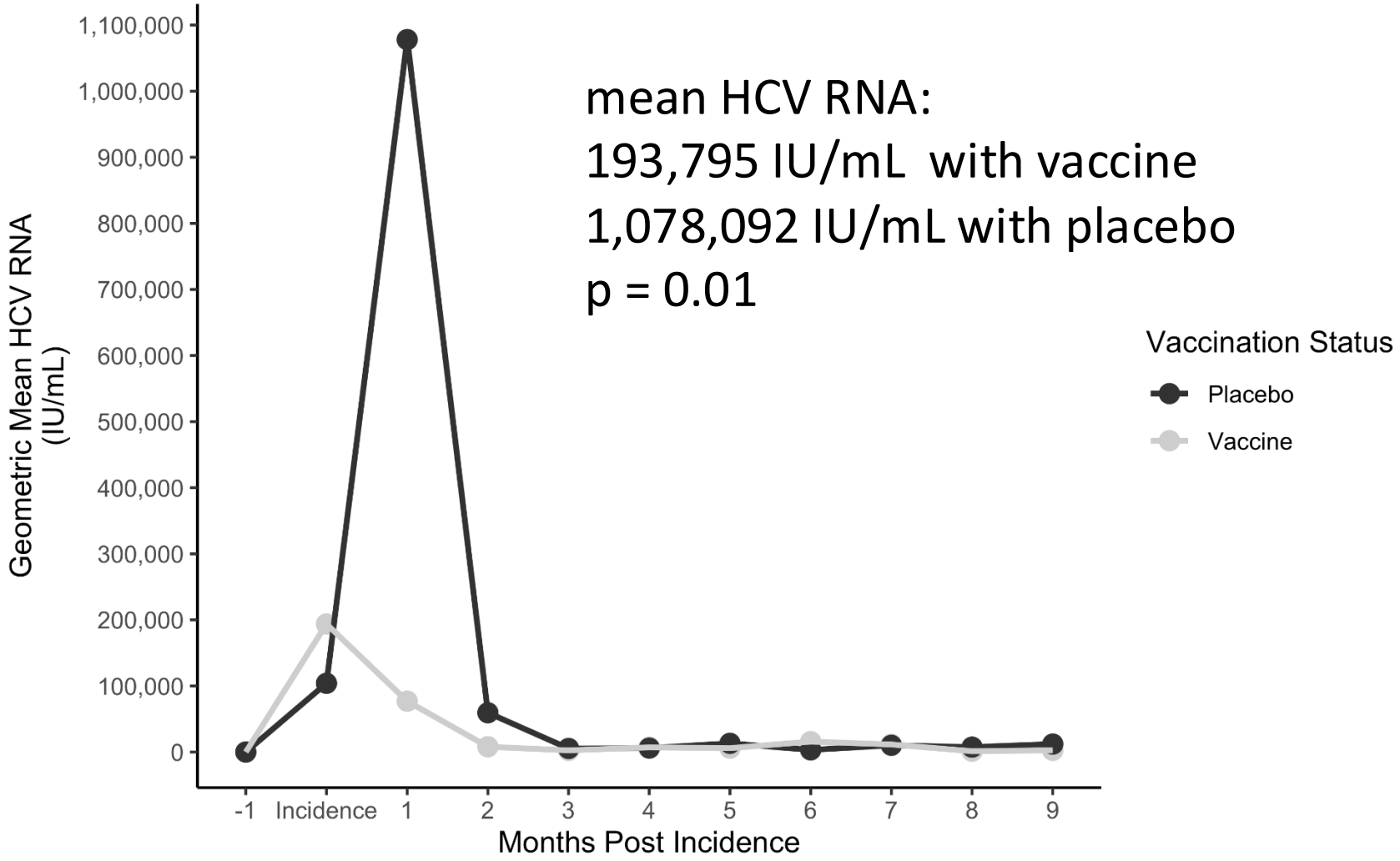


And …..lower magnitude T cells in PWID

- Immunogenic - but less so than in healthy volunteers
- 78% PWID vs. 100% HV responded to vaccine
- Lower (2-3x) magnitude T cell responses by ELISpot

Healthy volunteer not at risk for HCV: Swadling L. et. al., S*cience Translational Medicine;* 5 November 2014; 6:(261)
VIP: Page K. et. al., *N Engl J Med* 2021; 384:541-549

…..but HCV viraemia significantly blunted



Data and slide courtesy of Andrea Cox

PWID did not have significantly higher baseline ChAd3 Abs

Why did this potent viral vectored vaccine fail to protect against chronic infection?

- HCV genetic variation? ✅
- Less immunogenic in PWID? ✅
- Pre-existing ChAd3 Abs? ❌
- T cells alone unable to control HCV viraemia

Solutions?

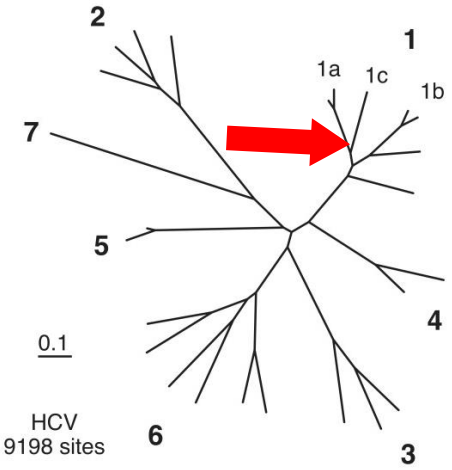
Broad consensus that the next generation of vaccines should contain antigens that generate bnAbs and genotype cross-reactive T cells

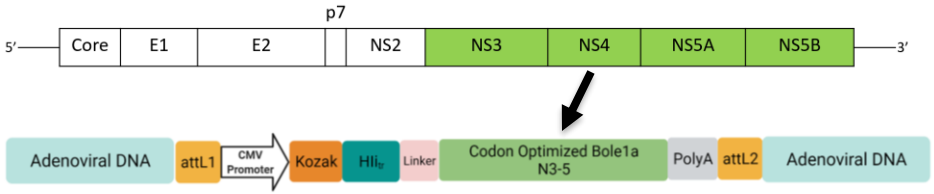
HCV pre-clinical vaccine pipeline 2025

Please contact Ellie Barnes re this data slide

Strategies for bi-valent HCV T and B cell vaccine ……..Optimising T cell antigens

Ancestral sequence

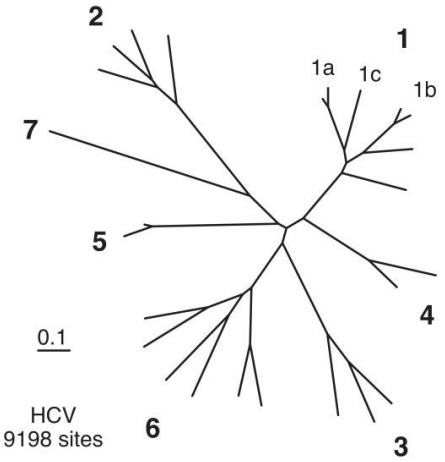


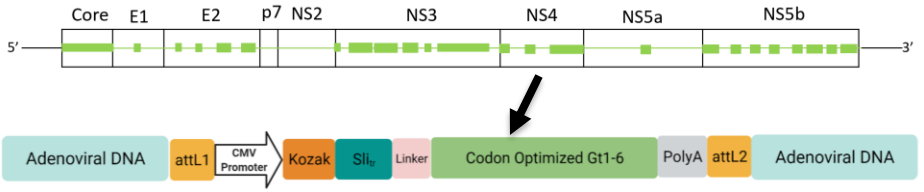


ChAd-Bole1a-NS

Munshaw, S. et al. (2012) Journal of virology

Conserved sequence

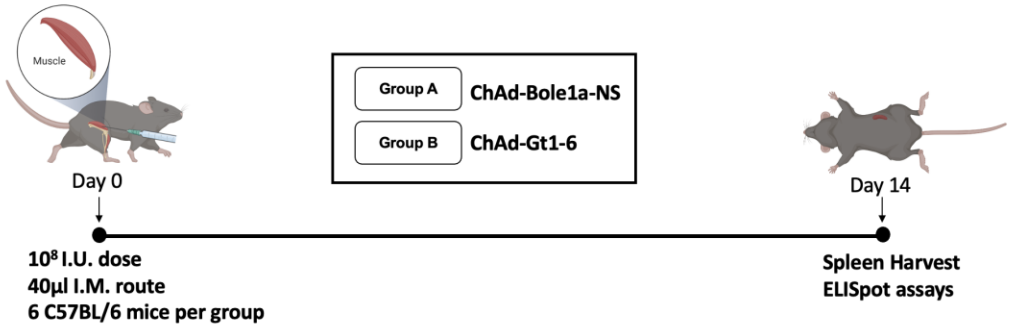




ChAd-Gt1-6

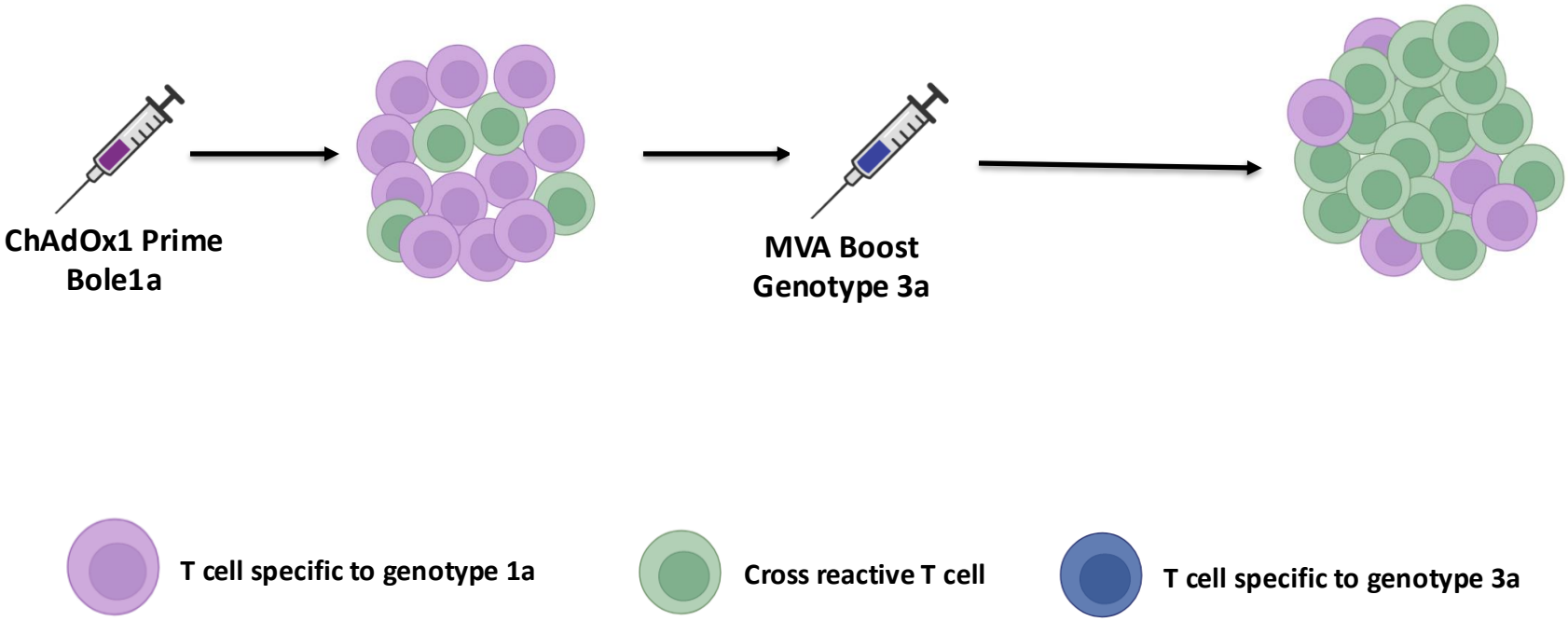
von Delft, A. *et al.* (2018) *Vaccine*
Donnison et al (2020) Vaccine
Esposito I et al (2020) Science Translational Medicine

Head-to-head comparison of novel T cell vaccine candidates

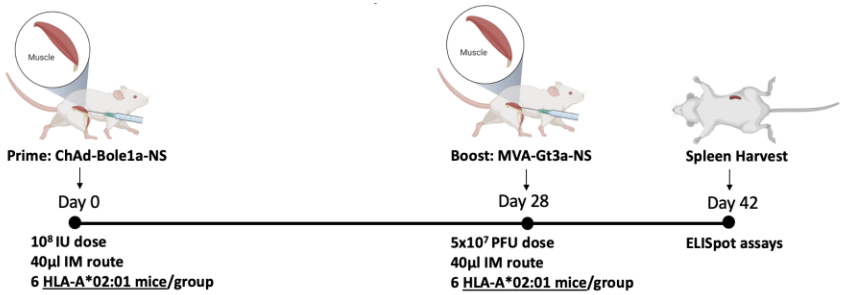


ChAd-Gt1-6 induces pan-genotypic T cell responses

Prime-boost regimens to generate pan-genotypic T cell responses

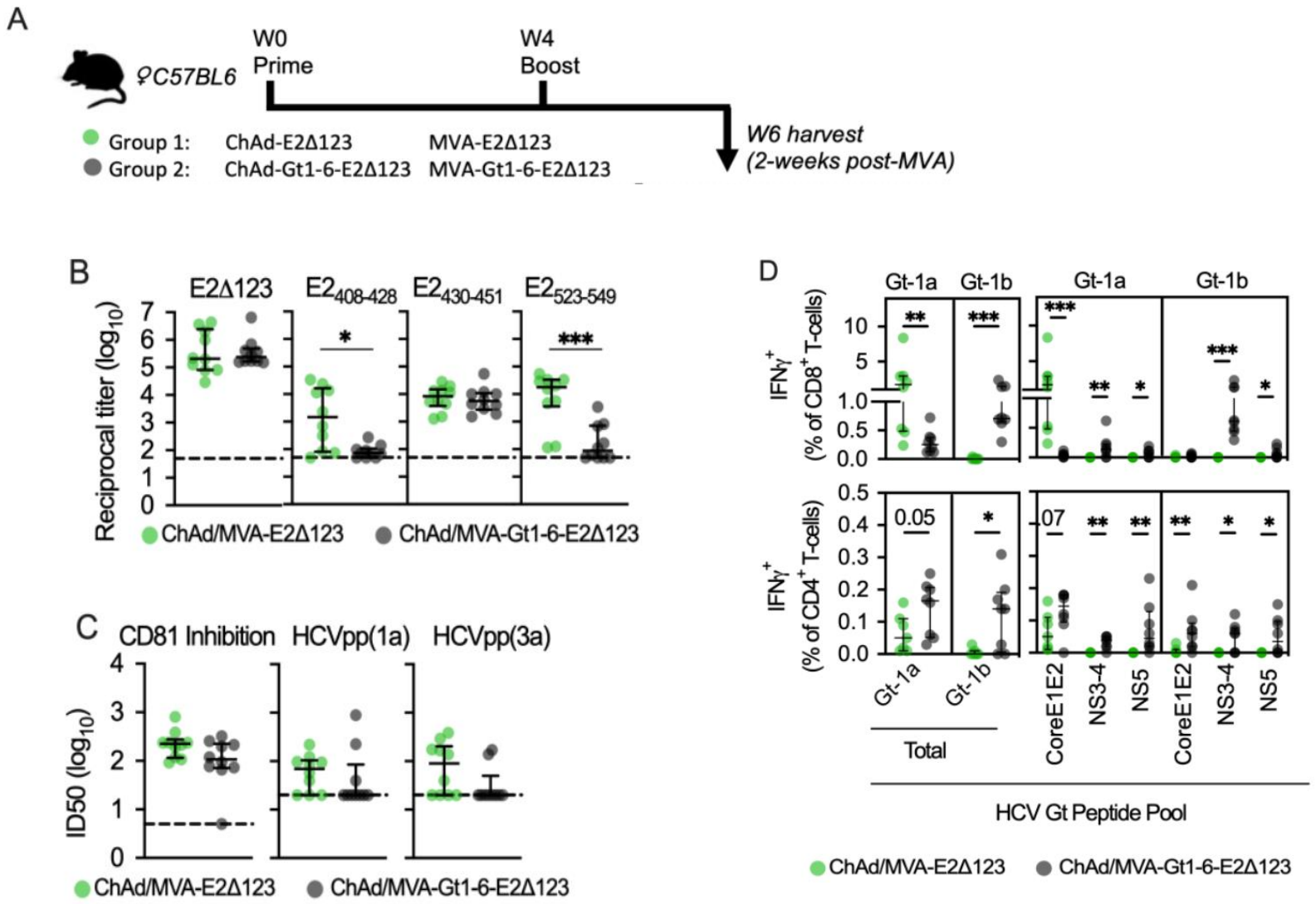


Prime-boost regimens to generate pan-genotypic T cell responses



ChAd-Bole1a-NS boosted with MVA-Gt3a-NS generates high magnitude T cell responses to both genotype 1 and genotype 3a

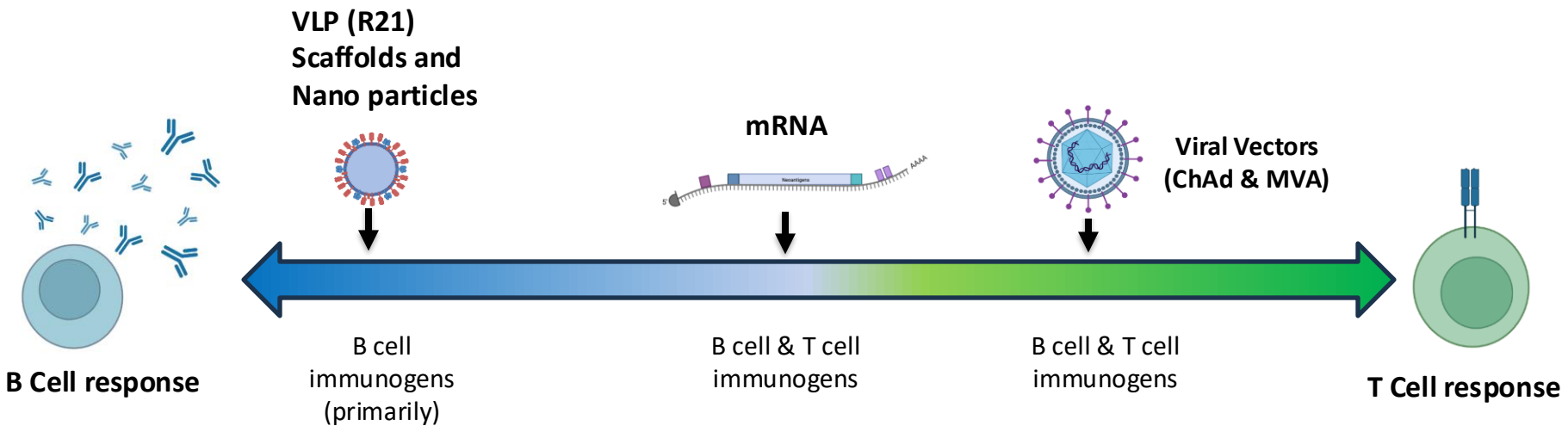
Viral vectors expressing T cell and B cell immunogens



Donnison and McGregor et al – Hepatology March 2022

HCV Vaccine Platforms under evaluation
New insights COVID pandemic

Platforms



New antigens in a range of platforms

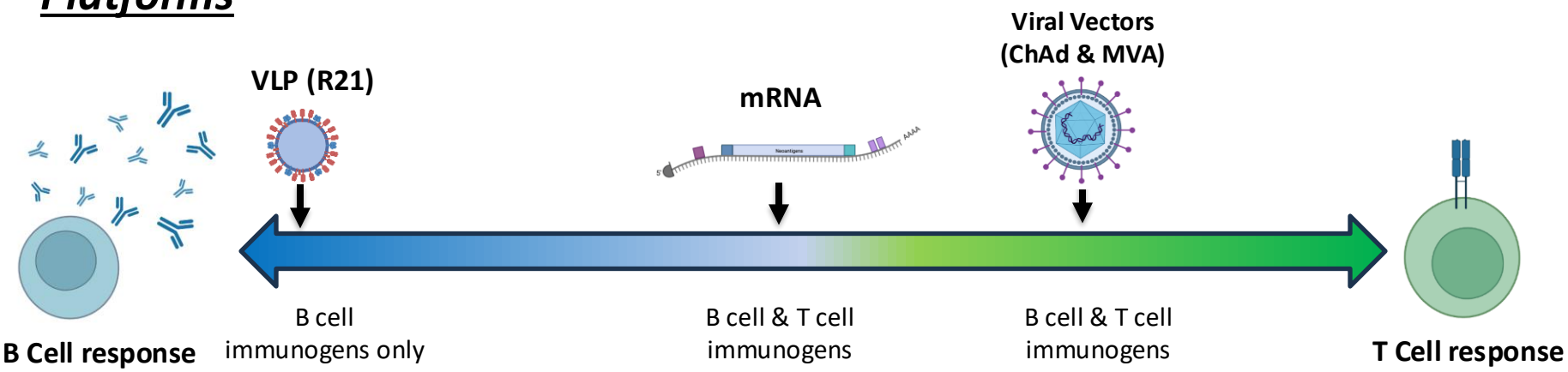
B Cell Immunogens

- HCV Soluble E2
- HCV Membrane bound E1/E2

T Cell Immunogens

- Conserved segment vaccine
- Ancestral sequence used in heterologous prime-boost

Platforms



Qu's: Developing vaccines that generate bNAbs

1. Do you need E1/E2 heterodimer?

   Debated – some potent bNAbs sit at the E1/E2 interface (vs E2 HVR deleted)

2. E1/E2 is retained in the ER (retention sequence)

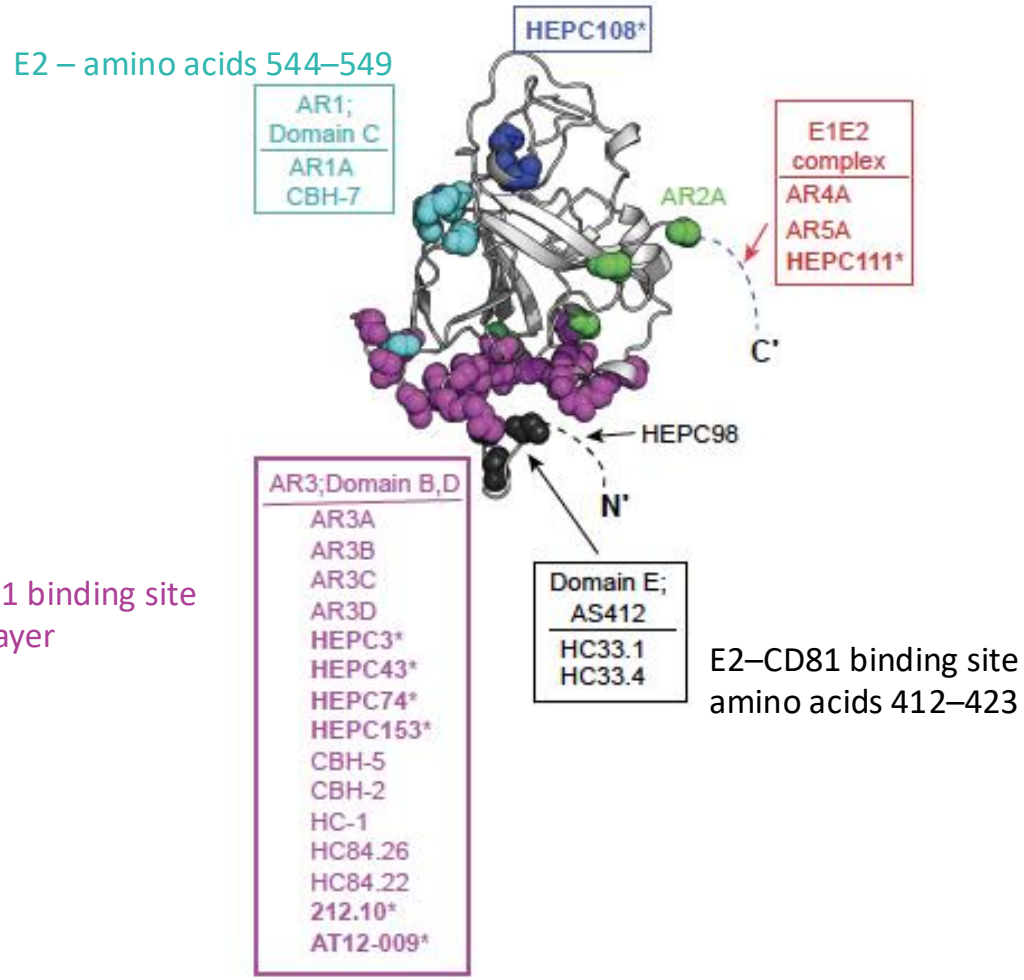
- Issue for manufacturing E1/E2 protein vaccines, but may not affect immunogenicity…..
- Recent soluble E1/E2 reported & soluble (Tr) E2 well established

3. Many bnAbs use V_H1-69 gene
   - Testing in WT mice problematic (mice don't have it)

4. How do you generate an Antigen to make the Abs that you want?

Do you need the E1/E2 heterodimer?

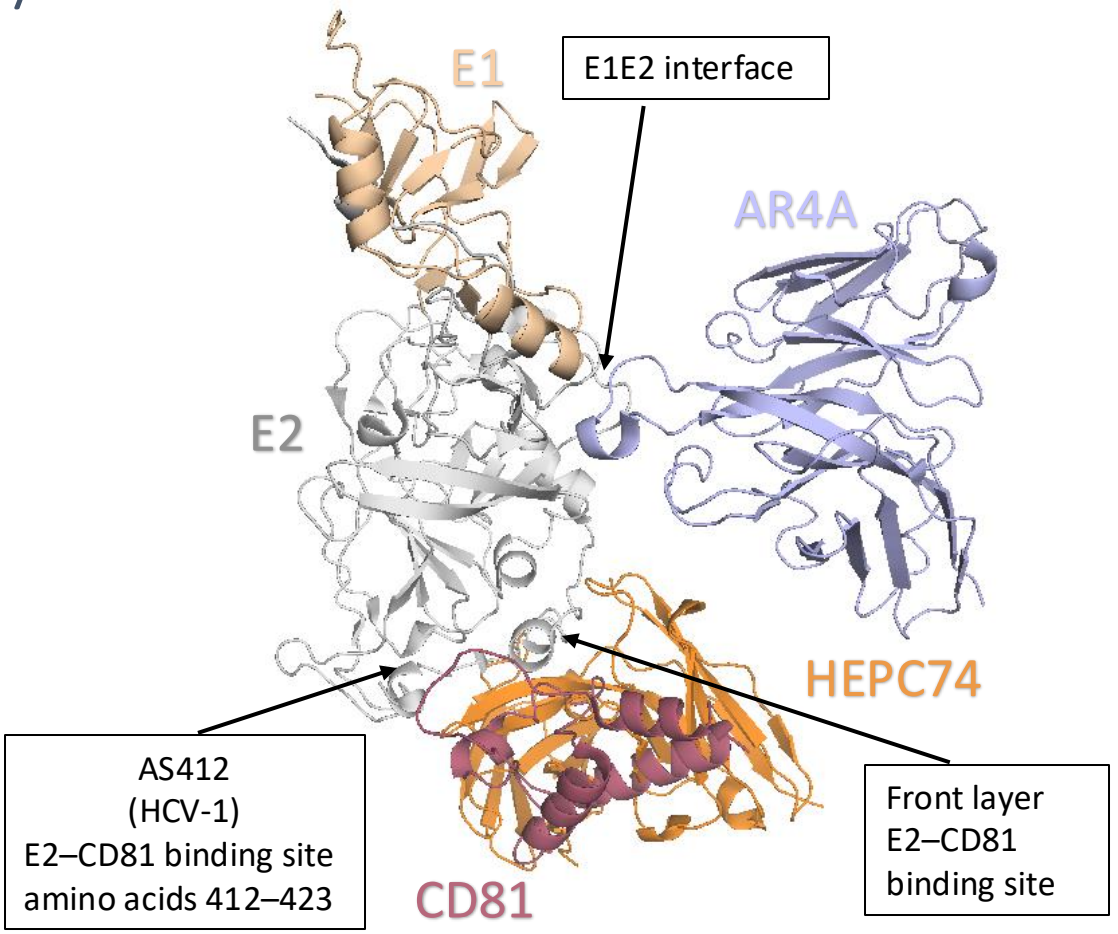
bNAbs develop in both chronic and cleared infections



Hadlock, J Virol, 2000
Law, Nature Med, 2008
Bailey, JCI Insight, 2017
Colbert, J Virol, 2019
Merat, PlosOne, 2016
Giang, PNAS, 2012
Keck, PlosPath, 2012
Keck, J Virol, 2013
Keck, PlosPath, 2019

HCV E2 protein: mAb binding residues previously identified by alanine-scanning mutagenesis (colored sphere)s on the crystallized structure of the HCV E2 protein

bNAbs displayed on the E1E2 cryoelectron microscopy (cryo-EM) structure



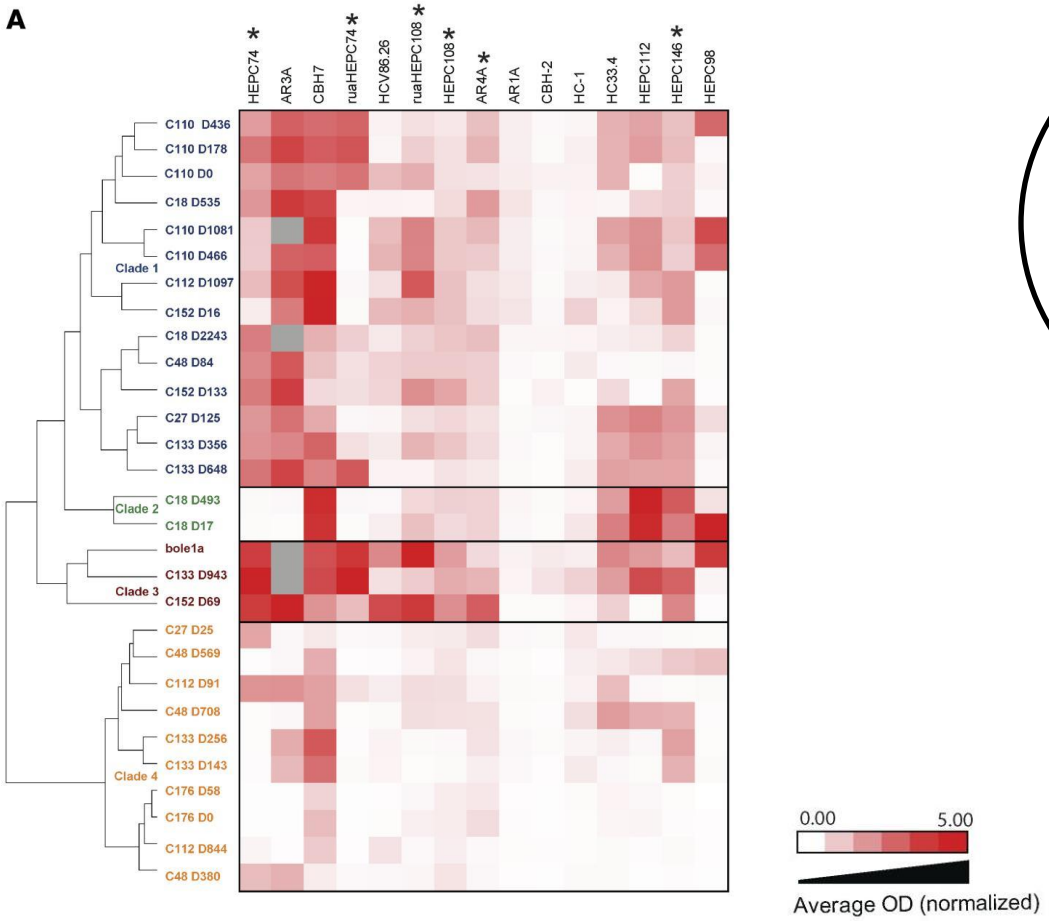
The most potent bNABS target conformational epitopes in the E2 front layer and the E1E2 interface.

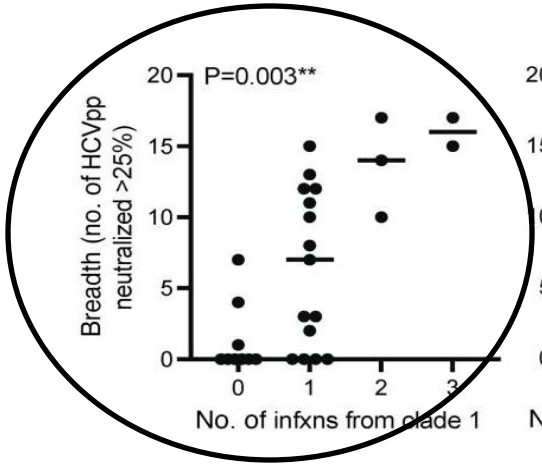
PDB: 7T6X
Torrents de la Pena, A., Science, 2022

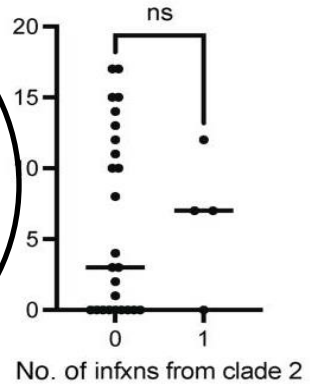
Rational B cell antigen design

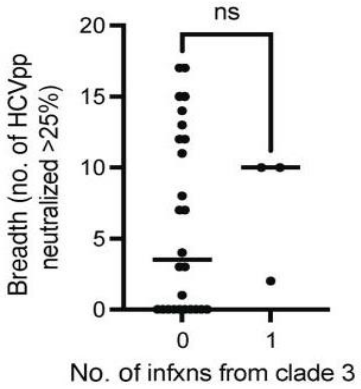
E1/E2 proteins from repeat clearing subjects segregate into 4 antigenic clades based upon binding sensitivity to reference mAbs

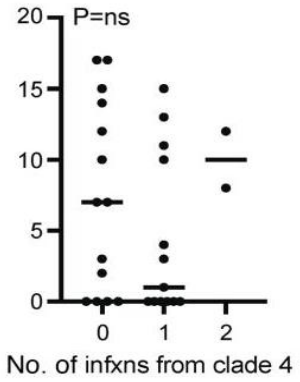
Neutralizing breadth is associated with repeated exposure to antigenic clade 1





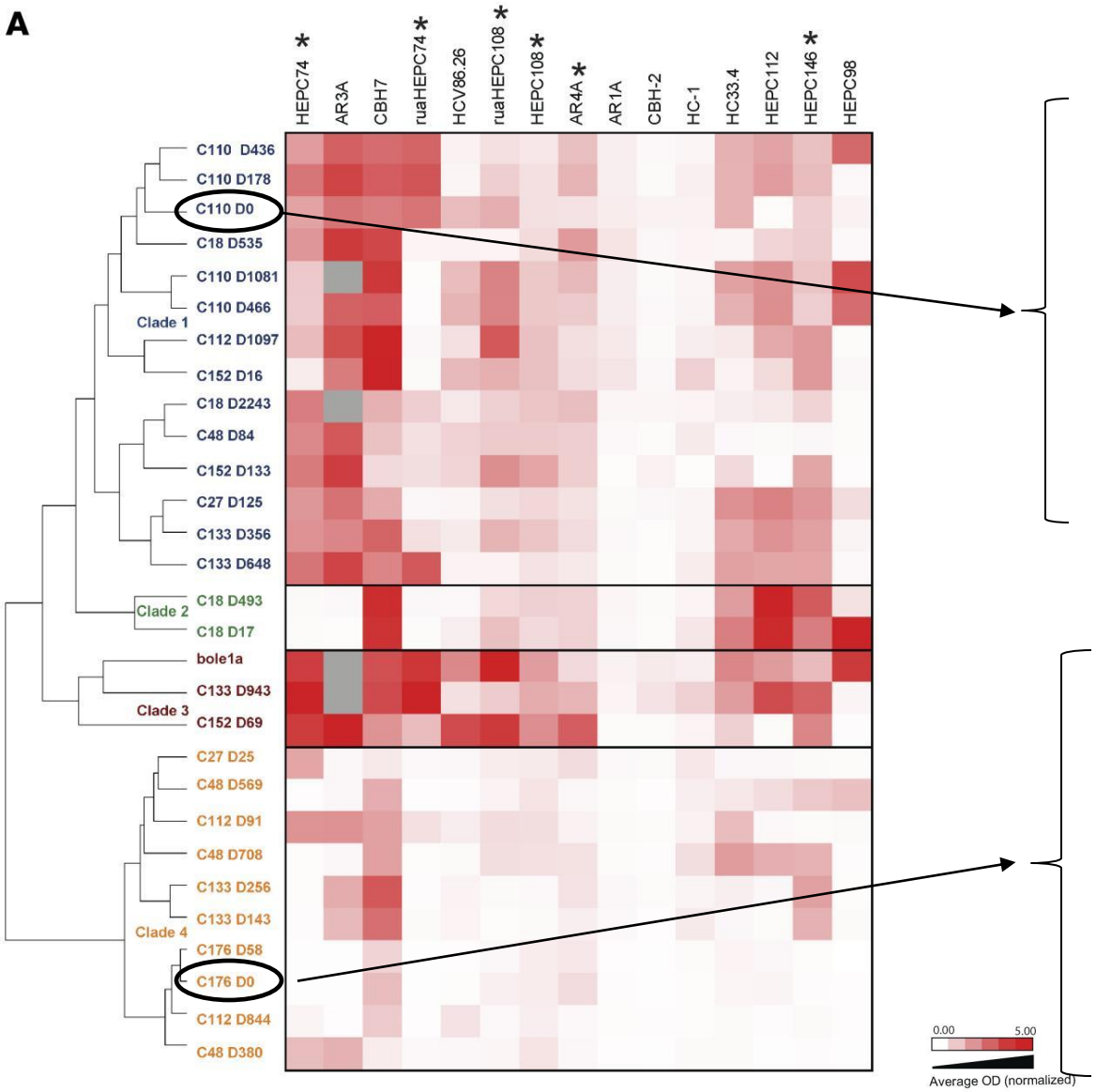






Nicole Frumento *et al* 2022, JCI insight

New vaccine constructs in process



Vaccine List

Broadly neutralising

- ChAdOx1 & mRNA HCV **Clade 1** (C110-D0) E1/E2 membrane bound
- ChAdOx1 HCV **Clade 1 (C111-D0)** E2△Stem-TM

Limited neutralisation

- ChAdOx1 & mRNA HCV **Clade 4 (C176-D0)** E1/E2 membrane bound
- ChAdOx1 HCV Clade 4 (C111-D0) E2△Stem-TM

Nicole Frumento *et al* 2022, JCI insight

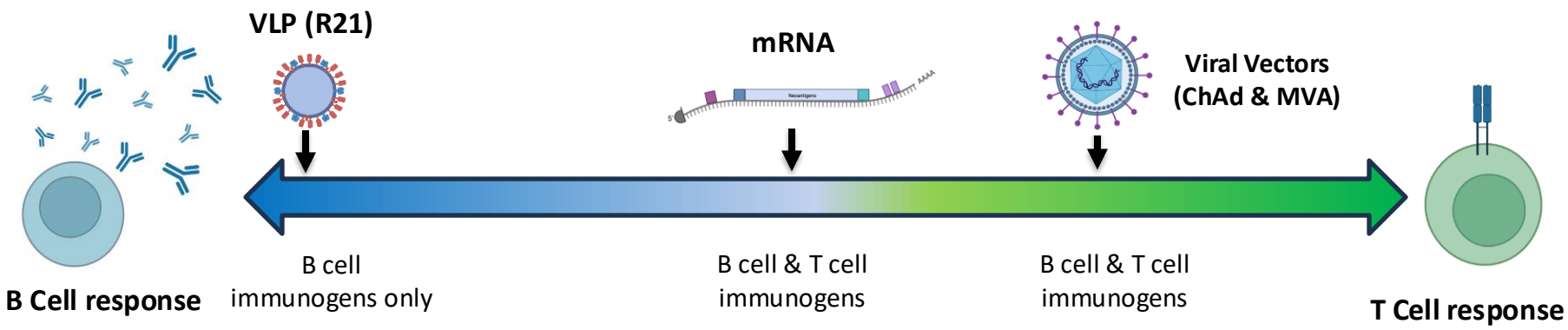
HCV Vaccine Platforms under evaluation

B Cell Immunogens

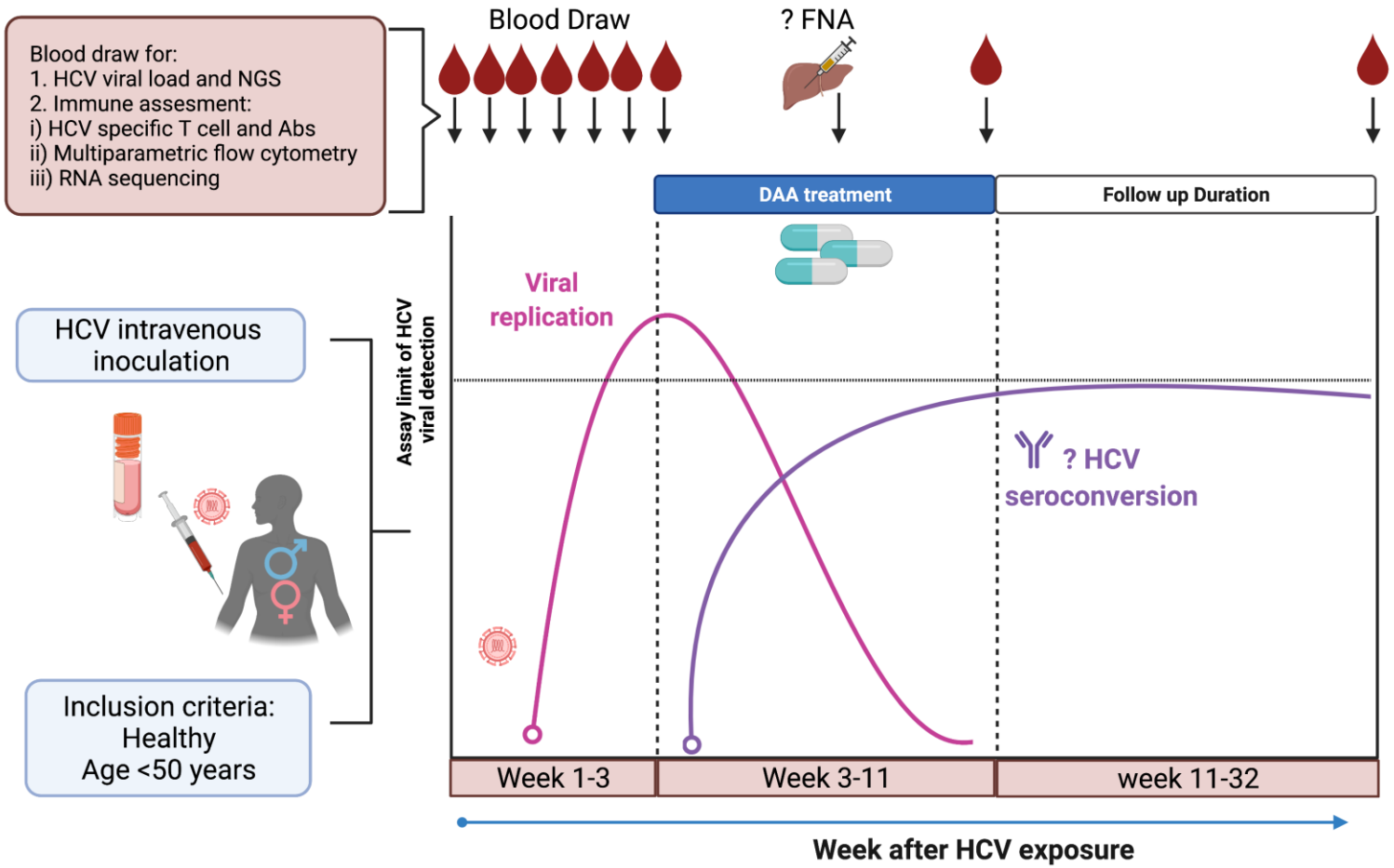
Platform	Construct
mRNA	E1E2mb Clade 1 (C110D0) E1E2mb Clade 4 (C176D0)
ChAdOx1	H77 E2 E1E2mb Clade 1 (C110D0) E2tr Clade 1 (C110D0) E1E2mb Clade 4 (C176D0) E2tr Clade 4 (C176D0)

T Cell Immunogens

Platform	Construct
mRNA	Gt1-6 (conserved segment) Bole1a-NS (ancestral sequence) Gt3a-NS T cell genetic adjuvants
ChAdOx1	Gt1-6 (conserved segment) Bole1a-NS (ancestral sequence)
MVA	Gt1-6 (conserved segment) Gt3a-NS



Open Philanthropy supporting an HCV CHIM study



Barnes et al Hepatology 2022

Acknowledgements

HCV Work (recent)

Barnes Group

- **Rebecca Strain**
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- **Callum Beard**

Klenerman Group

- Claire Hutchings

Viral Vector Core Facility (Jenner Institute)

U19 Consortium

- **Andrea Cox**
- **Justin Bailey**
- **Andrew Flyak**
- **Nicole Frumento (now at Oxford)**
- **Justin Bailey**

Oxford NIHR Biomedical Research Centre

NIH
National Institutes of Health