What does the future hold for a hepatitis C vaccine?

Naglaa H. Shoukry, Ph.D.

Professor of Medicine, Université de Montréal
Centre de Recherche du CHUM, Montréal, QC, Canada
Director, Canadian Network on Hepatitis C (CanHepC)
Naglaa.shoukry@umontreal.ca

Disclosures

I’m a basic scientist, I wish I had something to disclose!!

CRCHUM
CENTRE DE RECHERCHE

Outline

1. Why do we need vaccines in the era of DAAs?
2. What evidence do we have that there is protective immunity against HCV?
3. What are the current vaccine development strategies?
4. Results from the latest trial, what do they mean?
5. Next generation HCV vaccines

Outline

1. Why do we need vaccines in the era of DAAs?
2. What evidence do we have that there is protective immunity against HCV?
3. What are the current vaccine development strategies?
4. Results from the latest trial, what do they mean?
5. Next generation HCV vaccines

CRCHUM
CENTRE DE RECHERCHE

The Case for HCV Vaccines

1. $$$$$
2. If you cannot find them, you cannot treat them
3. Treatment access in marginalized populations, rural and economically constrained settings.
4. Successful treatment will not protect against reinfection
5. A vaccine is the most effective way to prevent a viral infection

"Herd Immunity"

Modeling effect of HCV vaccines on elimination

- A partially effective vaccine could reduce the HCV transmission risk among individuals who share contaminated needles and syringes.

  Major M et al, Science Transl Med 2018:Vol. 10, Issue 449, eaao4496

- Modeling data from 55 countries:
  - Without a vaccine, the WHO 2030 incidence reduction target was only achievable for 25% of countries. With a vaccine, the incidence reduction target was achievable for ~75% of countries
  - Total cost of achieving elimination reduced by >US$0.5B for many countries.

  Scott N, Drummer H, O7.03, HCV2018

- The combination of vaccination and DAAs is the lowest cost-expensive intervention to reach the WHO 2030 targets.

  Echevarria D et al, Vaccine. 2019 May 1;37(19):2608-2616.

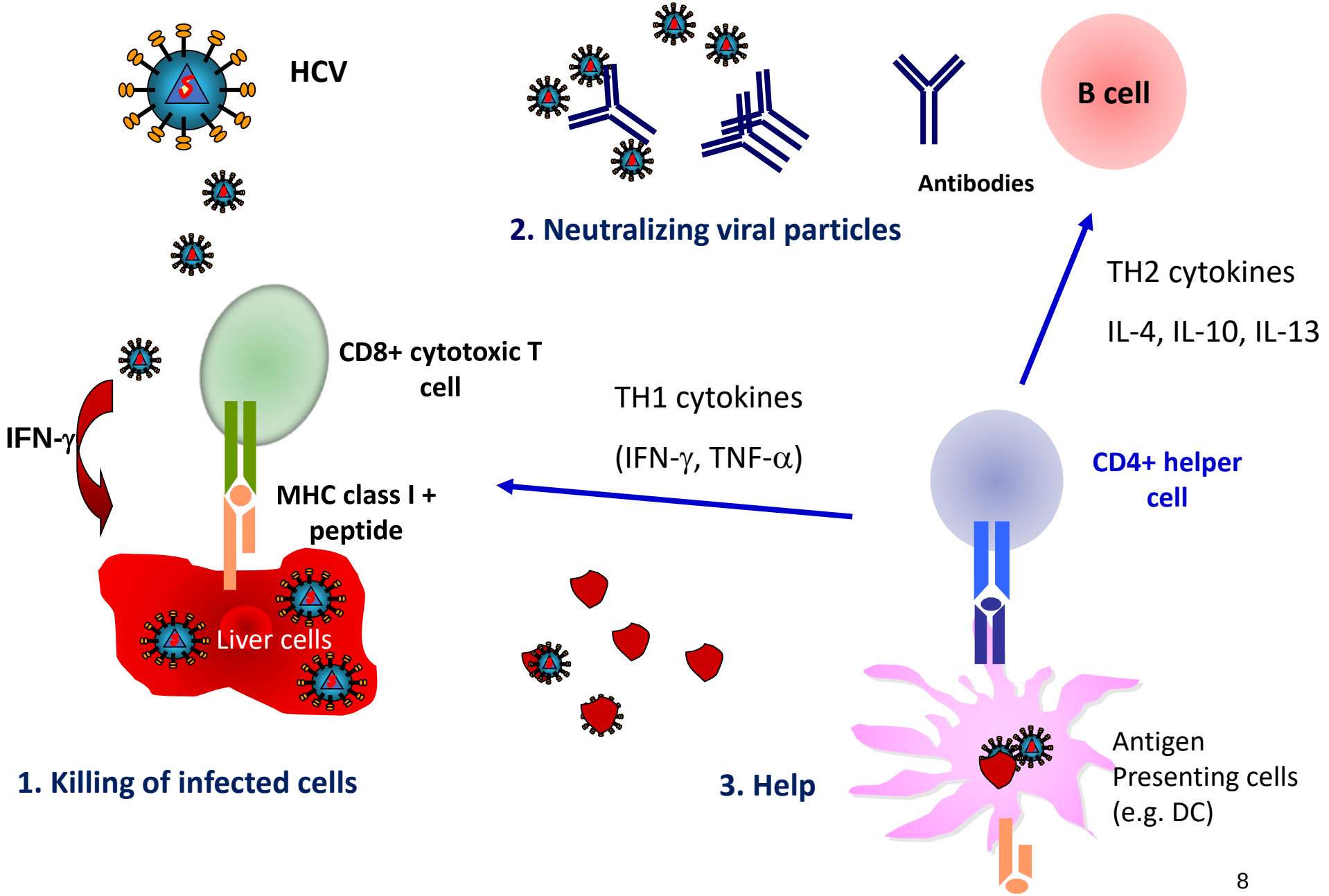
CRCHUM
CENTRE DE RECHERCHE

Outline

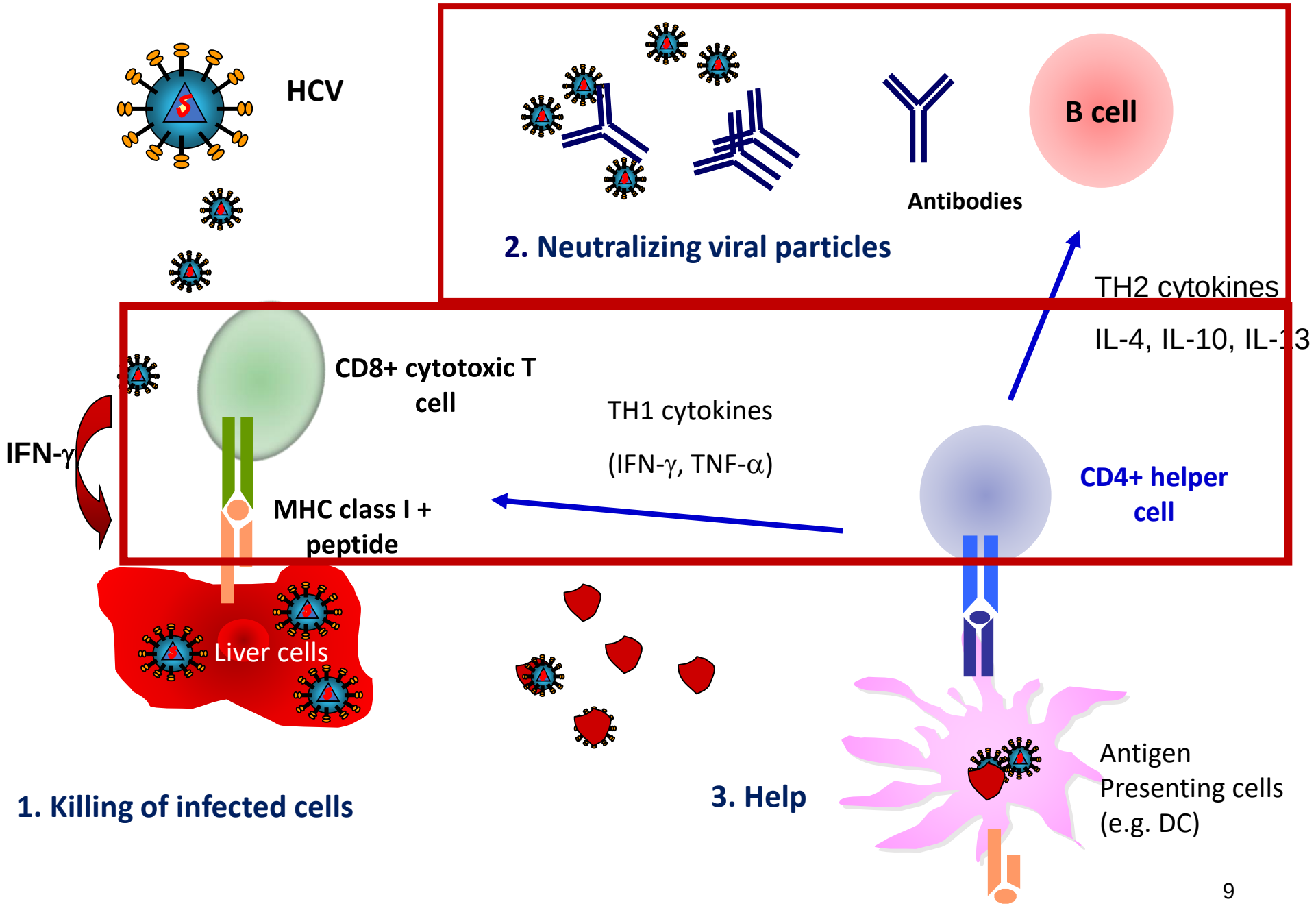
1. Why do we need vaccines in the era of DAAs?
2. What evidence do we have that there is protective immunity against HCV?
3. What are the current vaccine development strategies?
4. Results from the latest trial, what do they mean?
5. Next generation HCV vaccines

CRCHUM
CENTRE DE RECHERCHE

Key players in Immunity against HCV



Key players in Immunity against HCV

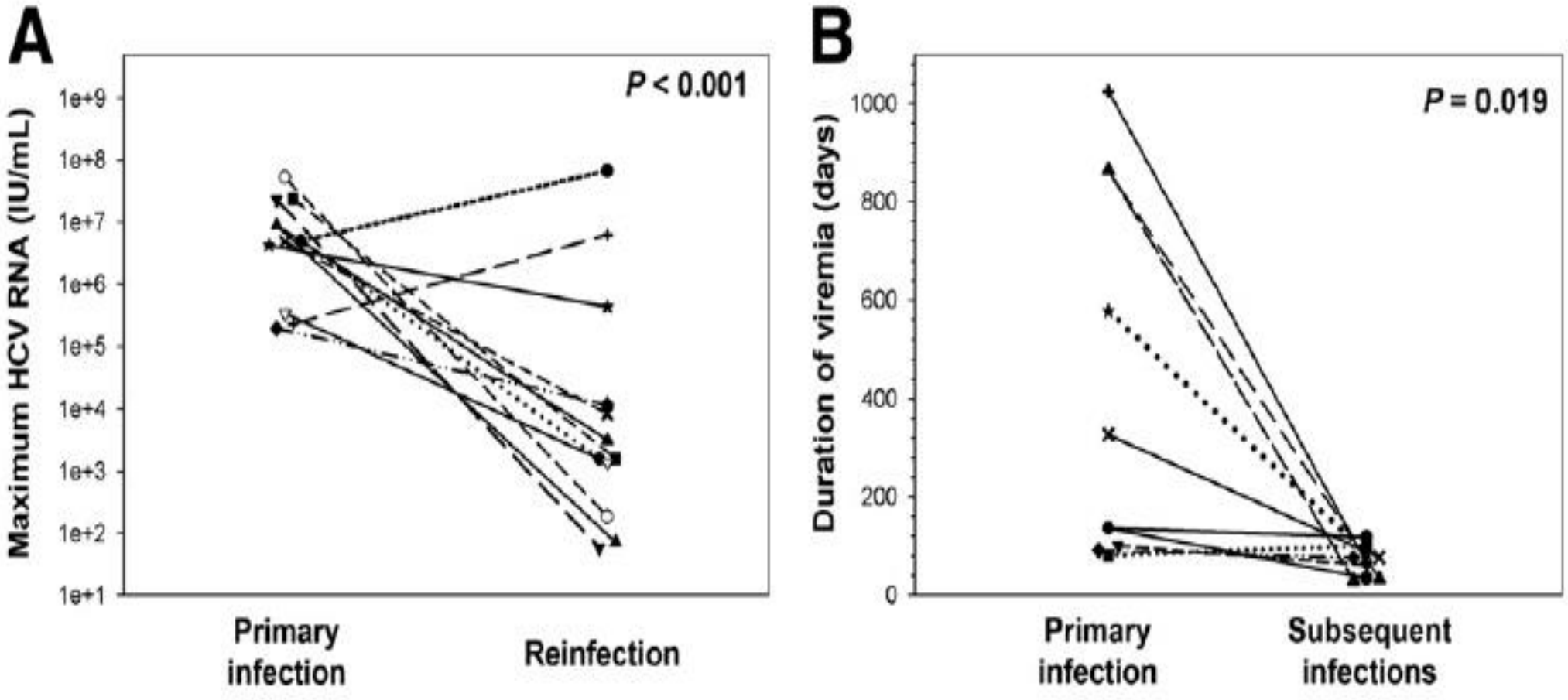


Is there immunological memory after HCV?

- IDUs with known previous exposure to HCV are less likely to be re-infected
  - *Mehta et al., Lancet. 2002 Apr 27;359(9316):1478-83*
  - *Grebely J. et al., Hepatology. 2006 Nov;44(5):1139-45*

- Higher rates of spontaneous clearance in secondary vs primary infection (80% vs 25%)
  - *Osburn WO et al., Gastroenterology. 2010 Jan;138(1):315-24.*

Clearance of a primary infection attenuates the infection kinetics of subsequent infections



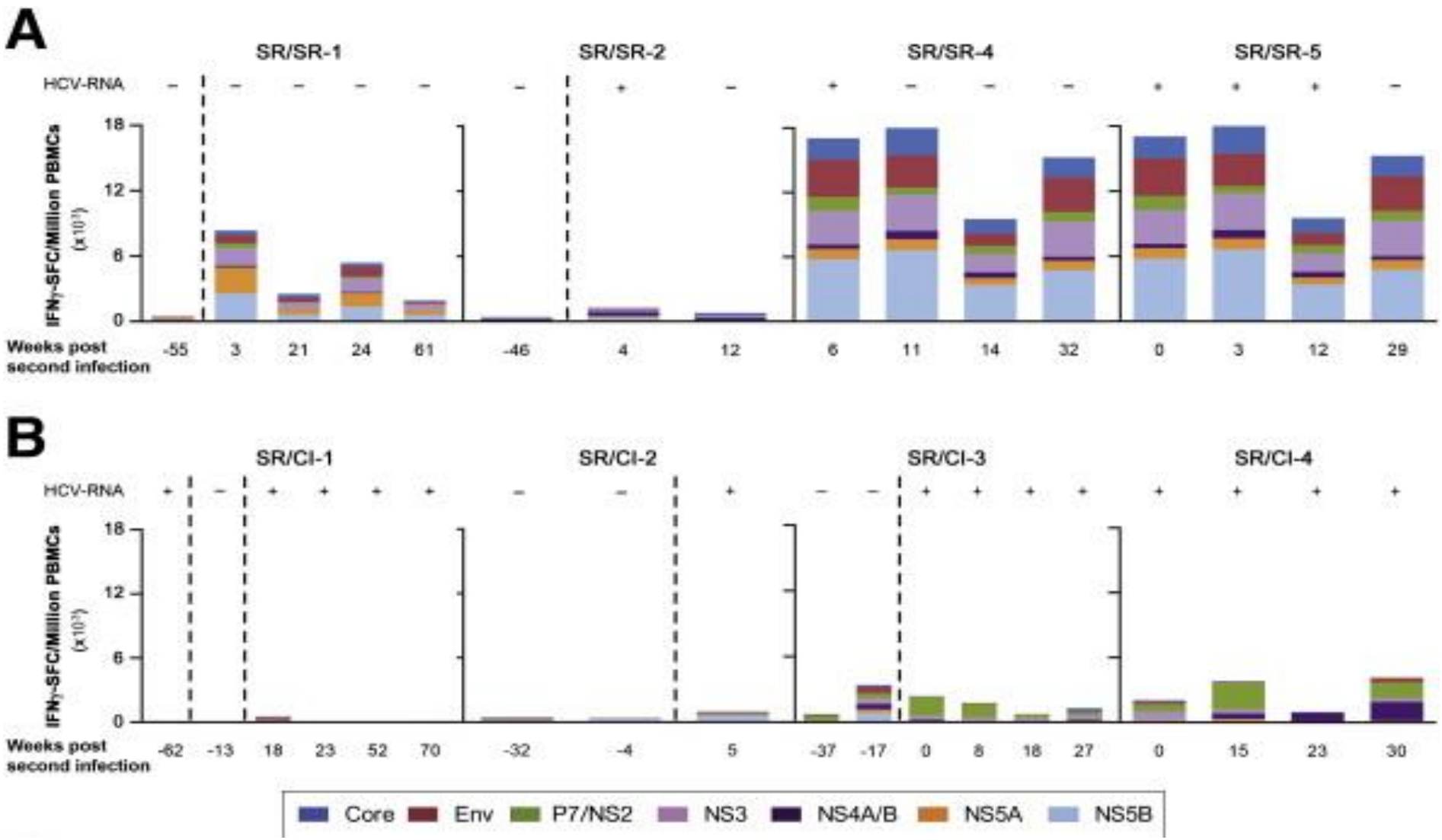
Osburn WO et al., Gastroenterology. 2010 Jan;138(1):315-24.

Does spontaneous resolution afford long-term memory and protection upon reexposure in high risk humans?

Osburn WO et al., Gastroenterology. 2010 Jan;138(1):315-24

Abdel-Hakeem MS et al., Gastroenterology. 2014 Oct;147(4):870-881.e8.

Protection against Reinfection is associated with increased breadth and magnitude of HCV specific responses



Protected

Unprotected

Variant viruses

Abdel-Hakeem MS et al., Gastroenterology. 2014 Oct;147(4):870-881.e8.

What cell subset is important for protection from chronic HCV? Antibody-mediated depletion studies in chimpanzees

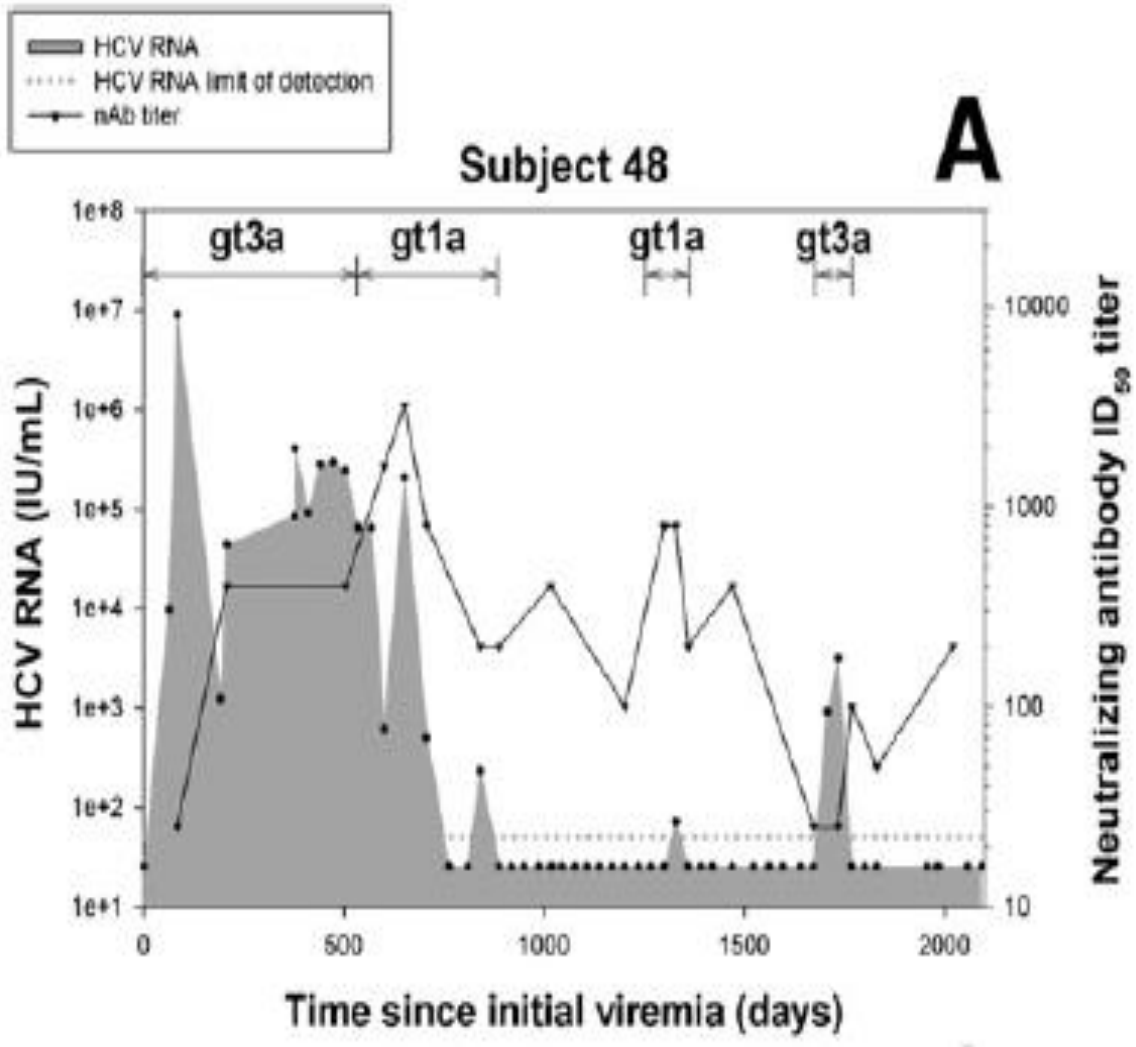
- Removing CD8's, functional CD4's
  (Shoukry NH et al., J Exp Med. 2003;197:1645-55)

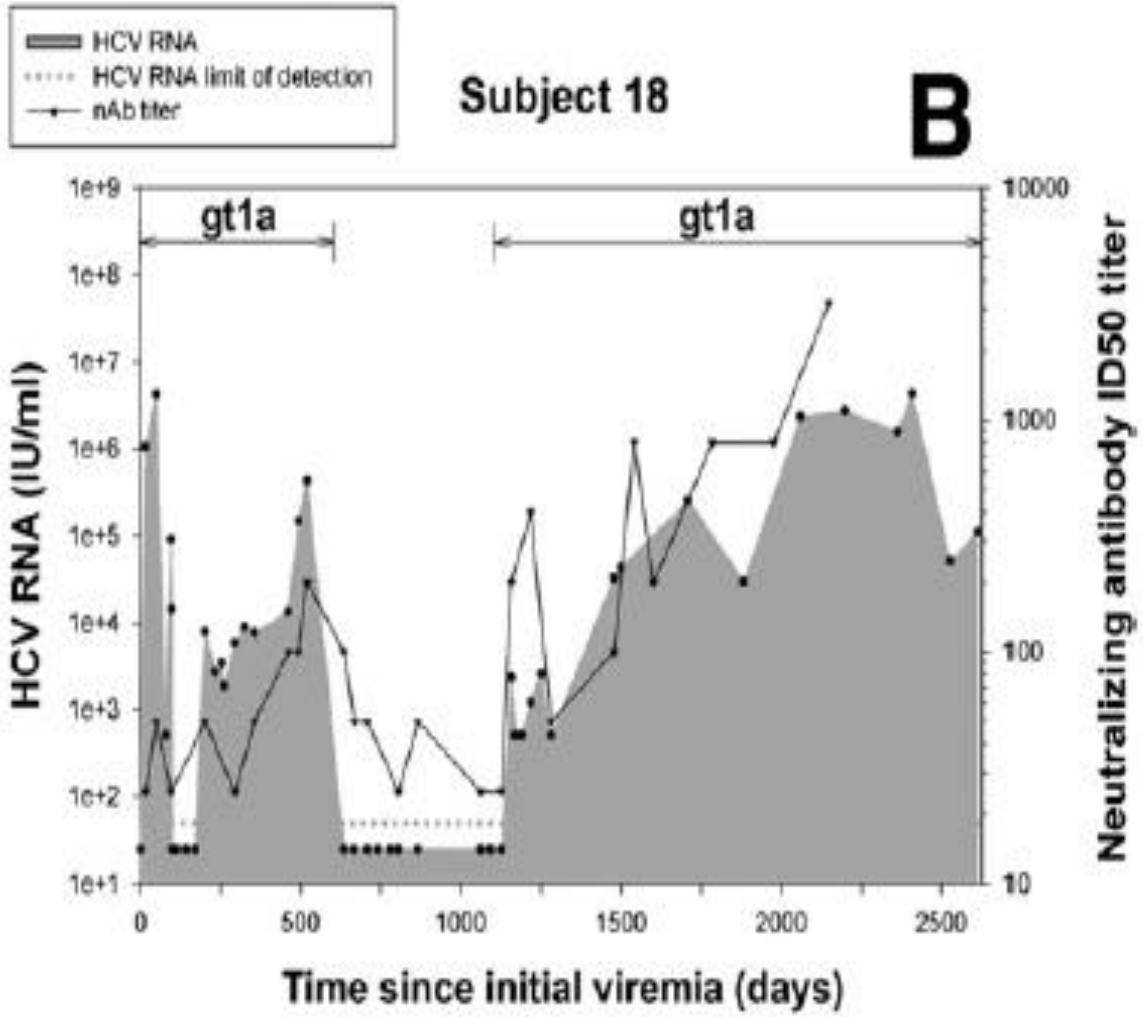
  - Prolonged viremia and clearance coincides with recovery of the CD8's in the liver.
  - CD4+ T cells are unable to clear the virus on their own

- Removing CD4's, functional CD8's
  (Grakoui A et al., Science 2003;302:659-62)

  - Prolonged very low level viremia > 1yr
  - Loss of diversity and decreased frequency of HCV-specific CD8's by Elispot
  - Escape mutations in targeted CD8 cytotoxic epitopes

Reinfection is associated with generation of cross-reactive neutralizing antibody (nAb)





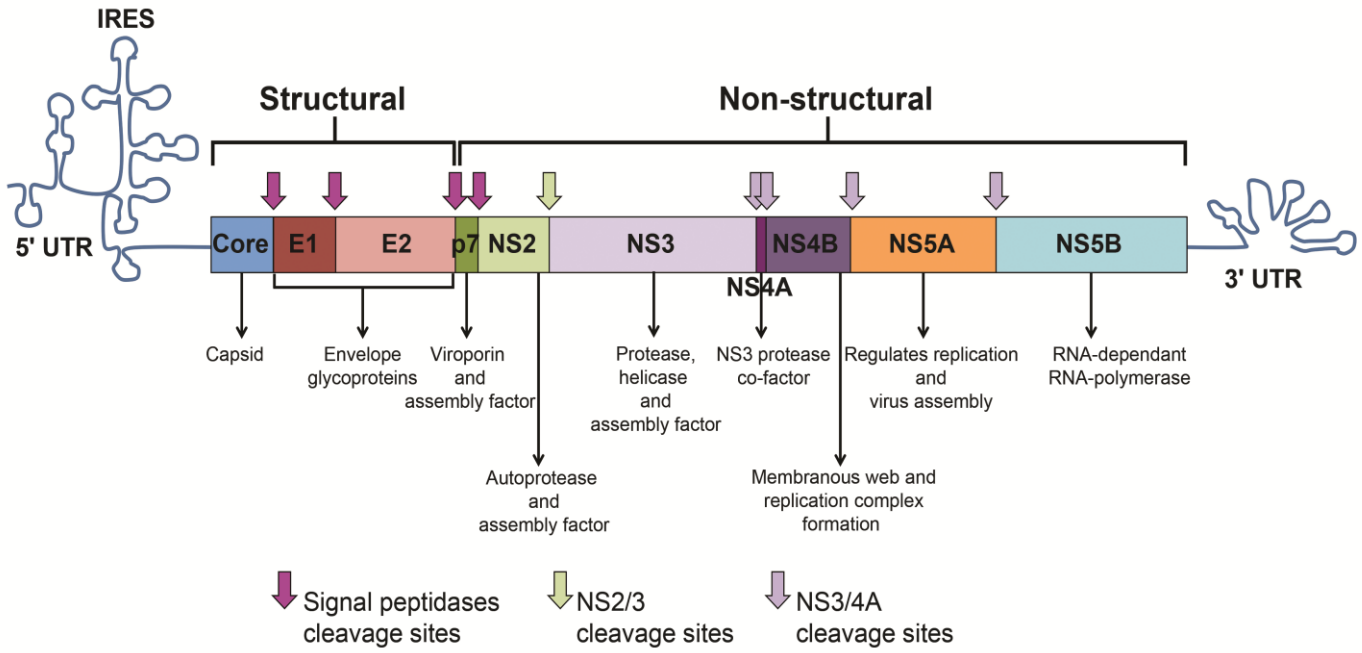
Osburn WO et al., Gastroenterology. 2010 Jan;138(1):315-24.

Outline

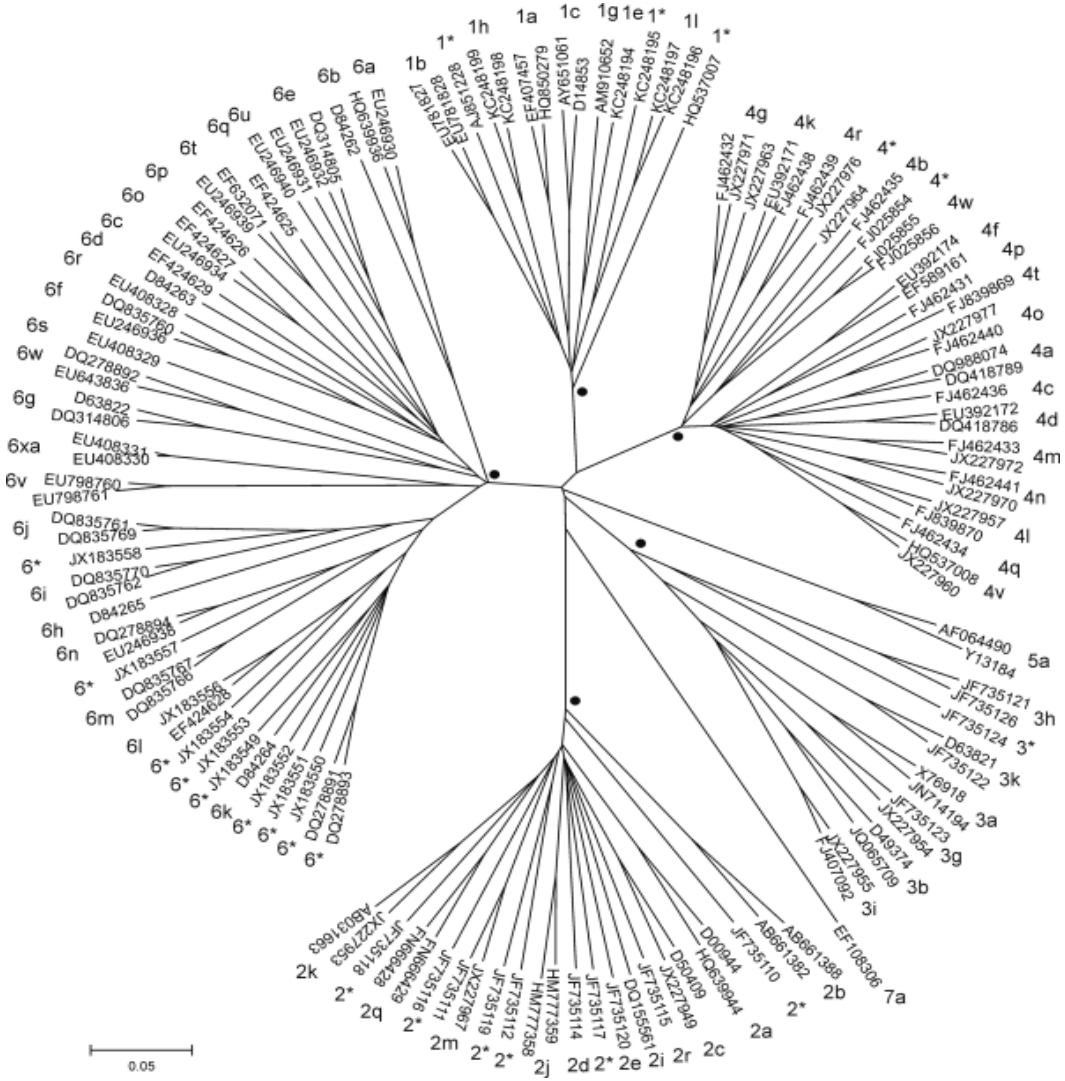
1. Why do we need vaccines in the era of DAAs?
2. What evidence do we have that there is protective immunity against HCV?
3. What are the current vaccine development strategies?
4. Results from the latest trial, what do they mean?
5. Next generation HCV vaccines

CRCHUM
CENTRE DE RECHERCHE

HCV diversity, a major challenge to vaccine development



(+ve RNA ~ 10 Kb, 7 genotypes)

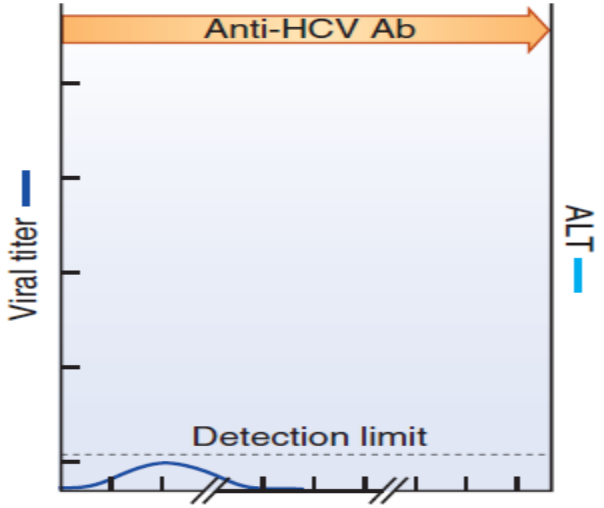


CRCHUM CENTRE DE RECHERCHE

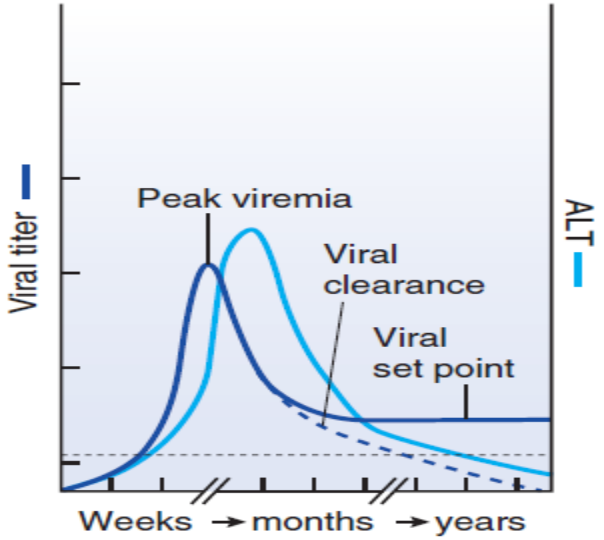
Hepatology
Volume 59, Issue 1, pages 318-327, 20 DEC 2013 DOI: 10.1002/hep.26744
http://onlinelibrary.wiley.com/doi/10.1002/hep.26744/full#hep26744-fig-0001

What should be the goal of a successful vaccine?

Sterilizing Immunity



Prevention of Chronicity



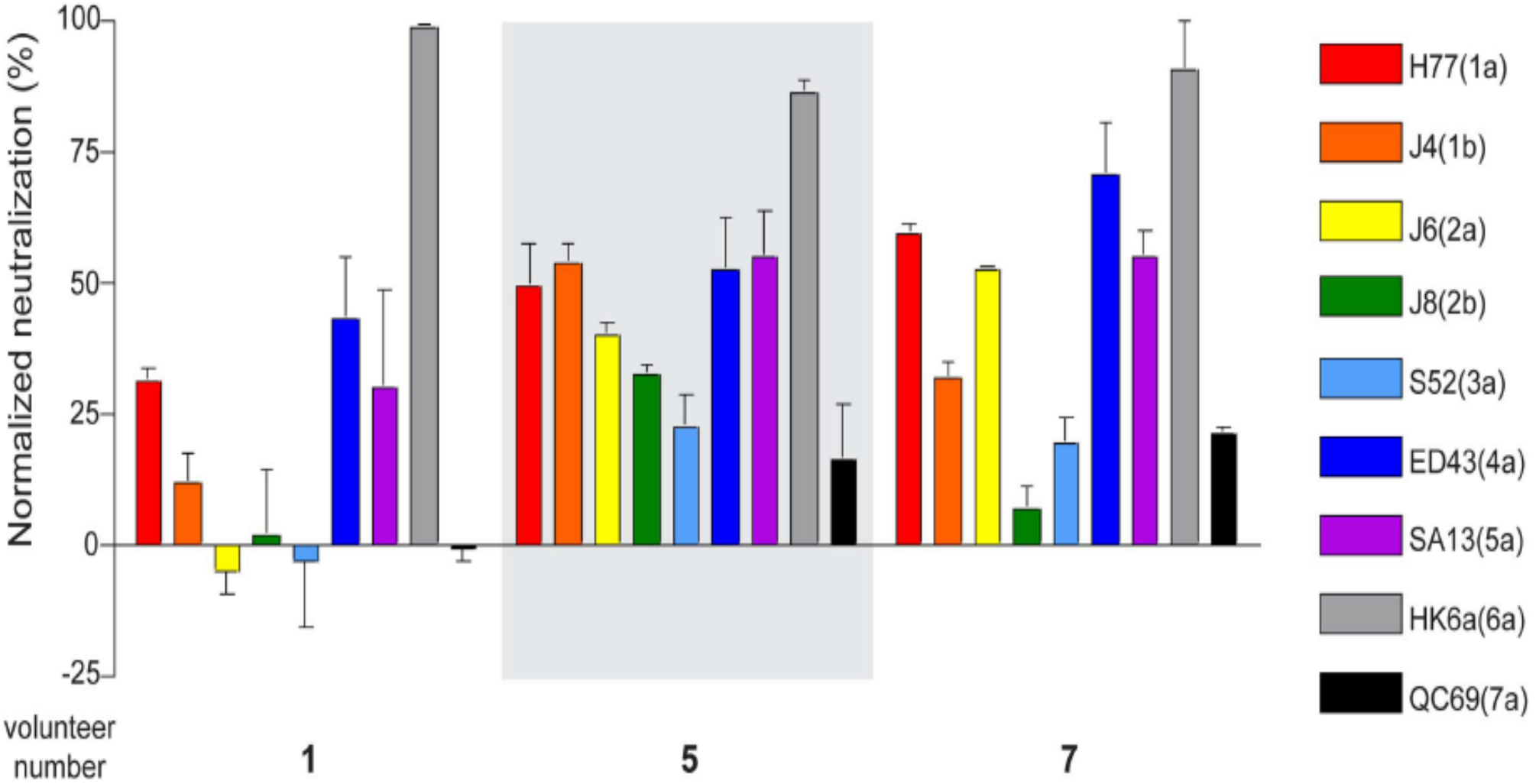
Liang TJ, Nature Med 2013.19:869

Current vaccine development strategies

- Targeting several proteins/protective epitopes
- Inducing antibodies
- Inducing T cells
- Pangenotypic??

- Recombinant Proteins
  (Antibodies and CD4 T cells)
- Vector based vaccines
- Viral like particles (VLPs)

Recombinant E1/E2 Vaccine (Genotype 1a) (M. Houghton, U. Alberta)



Law J et al, PLoS One. 2013;8(3):e59776

Okarios/GSK vaccine
Chimpanzee Adenovirus (ChAd3) prime - MVA boost (NS3-NS5B, genotype 1b)

HEPATITIS C

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]†

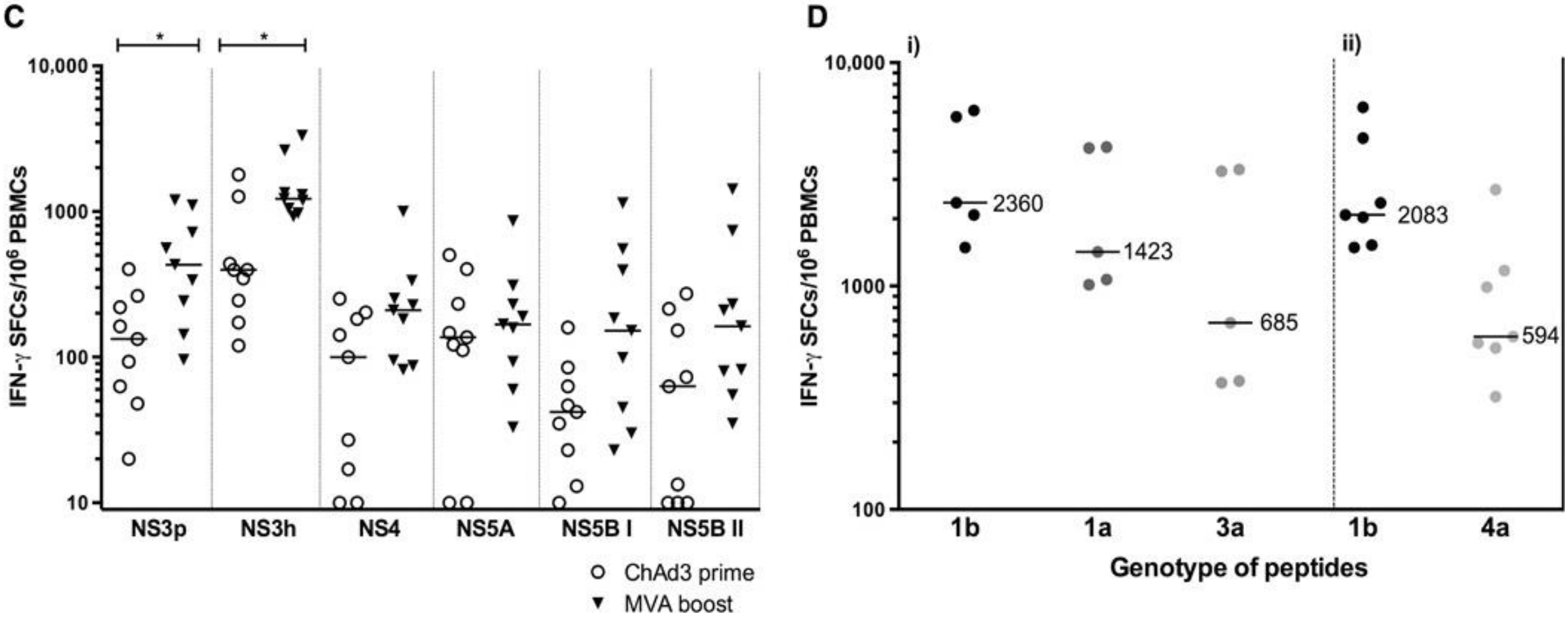
HEPATITIS C VIRUS

A human vaccine strategy based on chimpanzee adenoviral and MVA vectors that primes, boosts, and sustains functional HCV-specific T cell memory

Leo Swadling,[1]* Stefania Capone,[2]* Richard D. Antrobus,[1,3]* Anthony Brown,[1] Rachel Richardson,[1] Evan W. Newell,[4,5] John Halliday,[1,6] Christabel Kelly,[1,6] Dan Bowen,[1] Joannah Fergusson,[1] Ayako Kurioka,[1] Virginia Ammendola,[2] Mariarosaria Del Sorbo,[2] Fabiana Grazioli,[2] Maria Luisa Esposito,[2] Loredana Siani,[2] Cinzia Traboni,[2] Adrian Hill,[1,3] Stefano Colloca,[2] Mark Davis,[4] Alfredo Nicosia,[2,7,8] Riccardo Cortese,[9]† Antonella Folgori,[2] Paul Klenerman,[1,6] Eleanor Barnes[1,3,6]‡

Barnes E et al, Sci Transl Med. 2012 Jan 4;4(115):115ra1, Swalding L et al, Sci Transl Med. 2014 Nov 5;6(261):261ra153

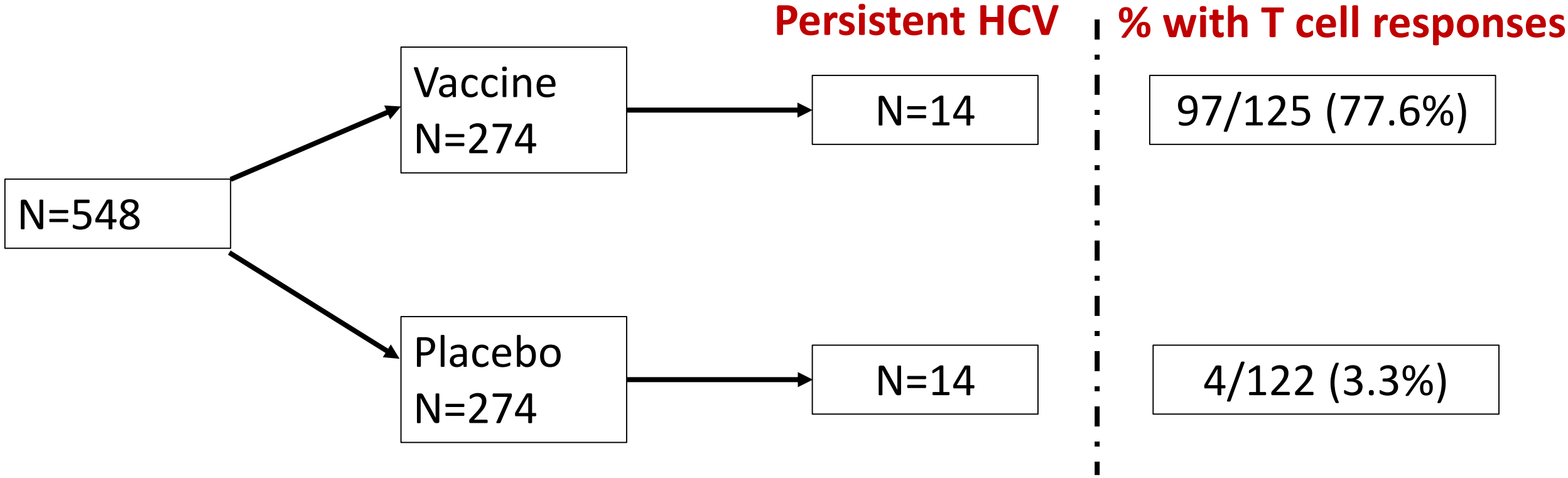
Broad, cross reactive T cell response following vaccination in healthy volunteers



Swalding L et al, Sci Transl Med. 2014 Nov 5;6(261):261ra153

Staged Phase I/II Hepatitis C Prophylactic Vaccine (NCT01436357) (2012 -2016)

- PIs: Andrea Cox, Kim Page
- PWID (Age 18-45) recruited at 3 clinical sites (Johns Hopkins, UCSF, UNM)



Outline

1. Why do we need vaccines in the era of DAAs?
2. What evidence do we have that there is protective immunity against HCV?
3. What are the current vaccine development strategies?
4. Results from the latest trial, what do they mean?
5. Next generation HCV vaccines

CRCHUM
CENTRE DE RECHERCHE

Why the vaccine did not work despite high immunogenicity in healthy donors?

1. Immune responses in PWID are weaker?
2. Genotype differences? Vaccine is 1b, infections are 1a or other?
3. Lack of a neutralizing antibody responses?
4. Other factors???

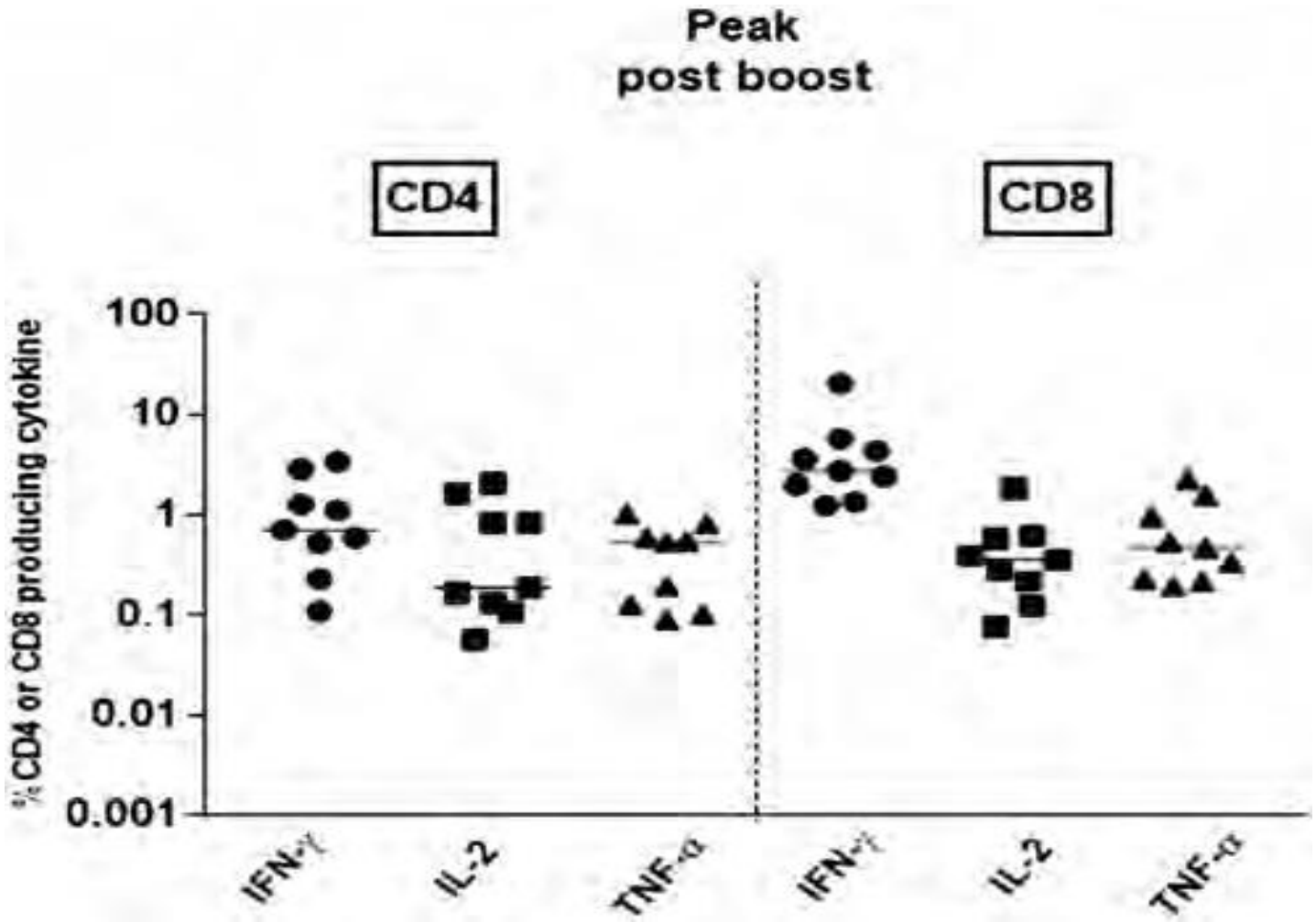
CRCHUM
CENTRE DE RECHERCHE

What else is in the pipeline?

1. Recombinant E1/E2 (Abs + CD4 T cells) and modifications thereof (U of Alberta)
2. A combination of a T cell based and an Ab based vaccine?
3. Viral like particles (Australia)
4. New vectors/Modified vectors/Adjuvants?

CRCHUM
CENTRE DE RECHERCHE

GS-05: MHC-II invariant chain adjuvanted chimpanzee adenoviral and MVA hepatitis C vaccines elicit unprecedented levels of anti-viral T-cell immune responses in humans (Esposito I et al, EASL-2019, Late Breaker)



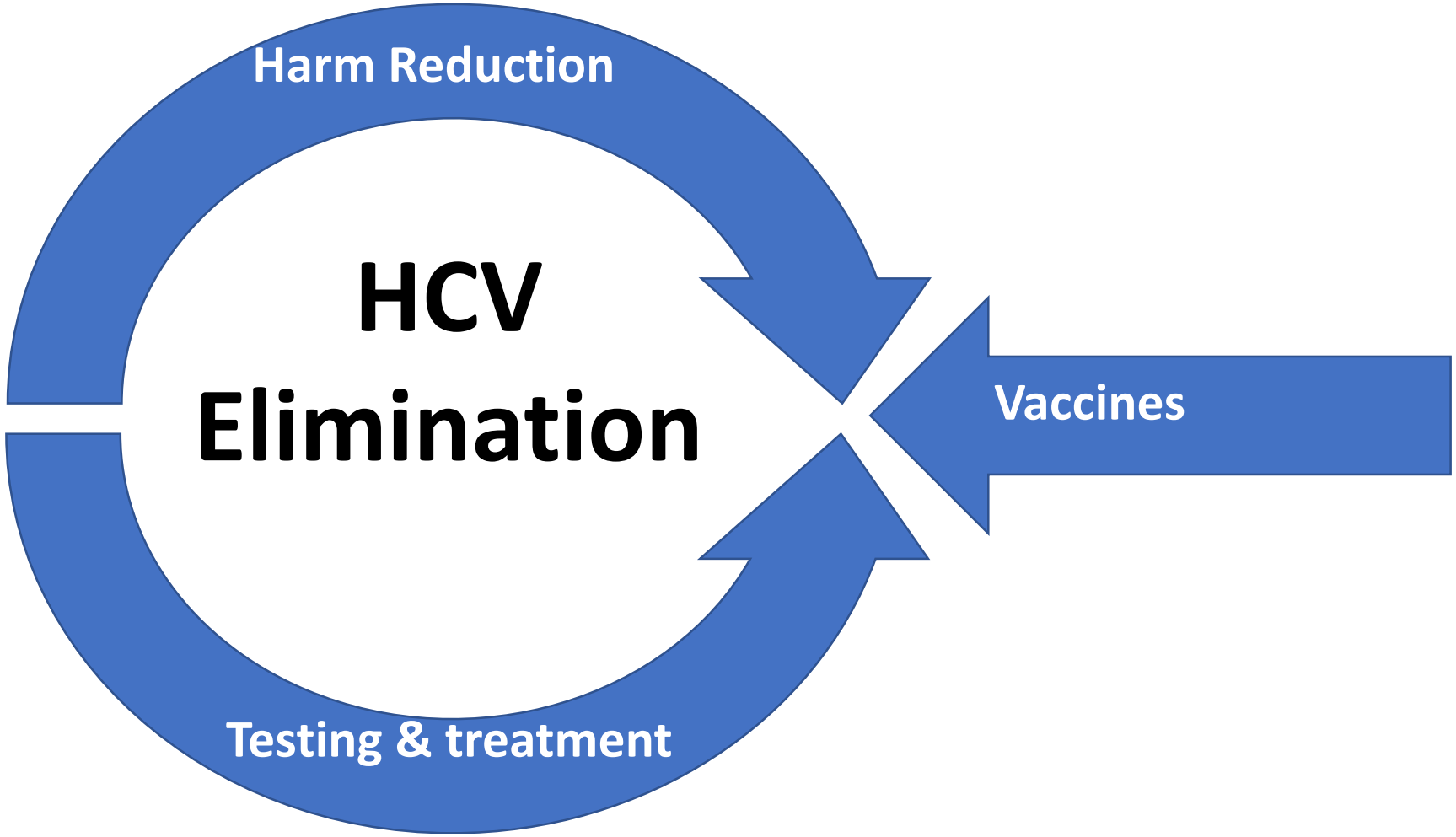
CRCHUM
CENTRE DE RECHERCHE

What are the next steps for research?

1. Understanding protective immunity in PWID
2. Vaccine preparedness
3. Concerted funding efforts (Industry, funding agencies, WHO)
4. Vaccination in DAA cured individuals
5. A live virus challenge???

CRCHUM
CENTRE DE RECHERCHE

Take Home Message



CRCHUM
CENTRE DE RECHERCHE

Acknowledgements

Study Subjects and Blood donors

Lab Members
Nathalie Bédard
Sarah Tran
Maude Boisvert
Manuel Flores Molina
Mohamed Abdelnabi
Sabrina Mazouz

Lab Members (past)
Mohamed Abdel Hakeem

Collaborators
Dr. Julie Bruneau
The St-Luc cohort study/HEPCO

Arash Grakoui, Emory University
Chris Walker, Nationwide Childrens'
Michael Houghton, University of Alberta

CIHR IRSC

CanHepC
Canadian Network on Hepatitis C
Réseau Canadien sur l'Hépatite C

InC3
International Collaboration of Incident HIV and Hepatitis C in Injecting Cohorts

NIH National Institutes of Health

Fonds de la recherche en santé Québec

Réseau SIDA/MI du FRSQ

SAVE THE DATE

HCV2020

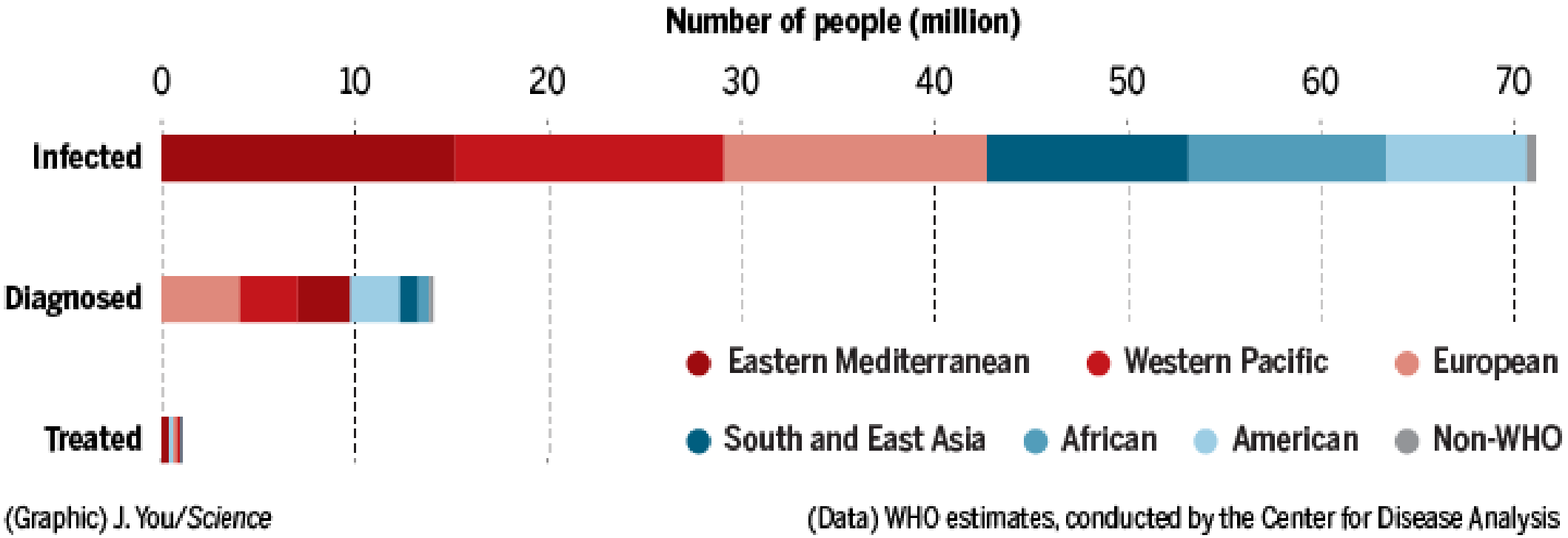
MONTRÉAL | JULY 6–9, 2020

LOCATION: CENTRE MONT-ROYAL, MONTREAL, CANADA

27TH INTERNATIONAL SYMPOSIUM ON
HEPATITIS C VIRUS AND RELATED VIRUSES

WWW.HCV2020.COM

Gap between Infection, diagnosis and treatment



CRCHUM
CENTRE DE RECHERCHE

Cohen J, Science, 2017