## New vaccine approaches for infectious diseases

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#### HCV is widespread and genetically diverse

- 185 million people infected with HCV worldwide.
- Many develop liver cirrhosis or liver cancer leading to ~500,000 deaths/yr.
- HCV has 7 genotypes, 6 of which are common.
- Each responds differently to treatments and vaccines.



Messina, Humphreys, Flaxman, Brown, Cooke, Pybus and Barnes. (2014) Global distribution and prevalence of hepatitis C virus genotypes. Hepatology. doi: 10.1002/hep.27259

#### Genotypes and sub-genotypes

- HCV has an error-prone RNAdependent RNA polymerase.
- The mutation rate is very high: 2.5 mutations per genome replication<sup>1.</sup>
- There are 7 genotypes, G1 to G7, which differ by 30-35%<sup>2</sup>.
- Within these genotypes, there are 67+ subtypes that differ by up to 20%<sup>2</sup>.



<sup>1</sup> Ribeiro et al, (2012). Quantifying the diversification of Hepatitis C Virus (HCV) during primary infection: estimates of the in vivo mutation rate. PLoS Pathogens doi: 10.1371/journal.ppat.1002881

<sup>2</sup> Smith, Bukh, Kuiken, Muerhoff, Rice, Stapleton and Simmonds (2014). Expanded classification of hepatitis C virus into 7 genotypes and 67 subtypes: updated criteria and genotype assignment Web resource. Hepatology 59:318-327

## Hepaciviruses and pegiviruses infecting different mammalian species.



**mBio**°

Amit Kapoor et al. mBio 2015; doi:10.1128/mBio.01466-15

# Is it worth worrying about immunity and vaccines?



Couldn't we just treat people as needed?

Needs:

- 1. To identify all those infected
- 2. A therapy that works for all

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## What is being done?



Swadling et al ERV 2013

# Some similar problems for HCV and HIV vaccines

- Complex antibody target structures
- Mutable antigenic targets for humoral response

• Potential for immune escape from T cells

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- Dysfunction of T cell responses in chronic disease
- BUT HCV=clear pathway for robust defence

#### **HCV clinical outcomes**



## Humoral responses and viral control

- Evolution of HCV envelope (E1/E2) under immune selection associated with progression
- Strain-specific antibodies early later becoming more broadly cross-reactive
- Development of Neutralising Ab has been temporally associated with clearance

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#### T Cell Immunity contains HCV - the evidence

- HLA association studies and GWAS (Class I and Class II HLA with clearance) (Neumann C, et al. Hepatology 2006;Duggal et al, Ann Int Med 2013)
- Chimpanzee CD4+ and CD8+ T cell depletion experiments (Shoukry N J Ex Med 2003)
- Association of breadth and magnitude of T cell response with viral clearance (Lauer et al Gastro 2004)
- IFN-γ HCV specific CD8<sup>+</sup> T cell responses are temporally correlated with reduced viremia after infection (Lechner F J Exp Med 2000; Thimme et al J Exp Med 2001)
- Prophylactic vaccine data (Adeno/DNA) in a chimp challenge model. (Folgori et al Nat med 2008)
- BUT...NO ONE CORRELATE OF PROTECTION (BIG, BROAD, SUSTAINED, FUNCTIONAL etc)

#### **Vaccination = acceleration (by 3 months)**



Folgori et al. Nature Medicine, 2006

#### Getting your retaliation in first\*: How to experimentally induce an HCV specific T cell response?



- Adenoviral vectors disabled genetically
- Vector foreign antigens
- Induce strong cellular immunity
- combined with other vectors in heterologous prime boost regimens

Adenoviral vectors highly potent in priming antigen specific T cell responses (malaria, HIV etc)

#### A problem: pre-existing anti-adenoviral immunity

Adenoviruses are shared by Humans and Chimps



- chimps catch colds too!
- have their own adenovirus strains
- little exposure of humans to these

#### **Adenoviral vectors-phylogenetic analysis**



Colloca et al Science translational medicine Jan 2012; Barnes et al Science translational medicine Jan 2012

#### The HCV immunogen

NS3-NS5B (NS = 1985 aa) Genotype 1, subtype 1b Multiple epitopes Genetically inactivated NS5B (NSmut)



#### **Development of T cell vaccine for HCV**



Barnes et al Science Tr Med 2012; Swadling et al Science Tr Med 2014

#### **Development of T cell vaccine for HCV**



Barnes et al Science Tr Med 2012; Swadling et al Science Tr Med 2014

## Next example? RSV

Editor's Summary Abstract Full Text PDF

#### Chimpanzee adenovirus – and MVA-vectored respiratory syncytial virus vaccine is safe and immunogenic in adults

BY CHRISTOPHER A. GREEN, ELISA SCARSELLI, CHARLES J. SANDE, AMBER J. THOMPSON, CATHERINE M. DE LARA, KATHRYN S. TAYLOR, KATHRYN HAWORTH, MARIAROSARIA DEL SORBO, BRIAN ANGUS, LOREDANA SIANI, STEFANIA DI MARCO, CINZIA TRABONI, ANTONELLA FOLGORI, STEFANO COLLOCA, STEFANIA CAPONE, ALESSANDRA VITELLI, RICCARDO CORTESE, PAUL KLENERMAN, ALFREDO NICOSIA, ANDREW J. POLLARD

SCIENCE TRANSLATIONAL MEDICINE | 12 AUG 2015: 300RA126 |

The RSV vaccine candidates PanAd3-RSV and MVA-RSV were safe and immunogenic in healthy adults.

Editor's Summary Abstract Full Text DPDF

#### Efficacy of a virus-vectored vaccine against human and bovine respiratory syncytial virus infections

BY GERALDINE TAYLOR, MICHELLE THOM, STEFANIA CAPONE, ANGIOLO PIERANTONI, EFRAIN GUZMAN, REBECCA HERBERT, ELISA SCARSELLI, FEDERICO NAPOLITANO, ALESSANDRO GIULIANI, ANTONELLA FOLGORI, STEFANO COLLOCA, RICCARDO CORTESE, ALFREDO NICOSIA, ALESSANDRA VITELLI

SCIENCE TRANSLATIONAL MEDICINE | 12 AUG 2015: 300RA127 | €

A vectored human RSV vaccine protects young seronegative calves.

Editor's Summary Abstract Full Text PDF



ONLINE COVER Moving Forward with an RSV Vaccine. Calves are natural hosts for bovine respiratory syncytial virus (RSV) infection. In people, RSV causes a severe lower respiratory tract disease that affects both children and the elderly. A pair of papers by Taylor *et al.* and Green *et al.* translate a prime-boost vaccine strategy for human RSV first into calves and then into humans in a phase 1 clinical trial. [CREDIT: TREASUREPHOTO/THINKSTOCK]

## Conclusions

- T cells can provide protection against HCV and potentially other chronic viruses
- We still need to prove that an <u>immunogenic</u> vaccine is actually <u>protective</u>.
- Harnessing of vectors across species may be a useful strategy
- A combined assault on some infections (e.g. RSV) might be really effective.



#### **Ellie Barnes**

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