An HCV Vaccine: Can we get there?

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No Conflicts of Interest
Outline

• Reasons to develop an HCV vaccine
• What constitutes protective immunity to HCV
• What challenges exist in HCV vaccine development
• Overcoming the challenges
• A prophylactic HCV vaccine is being tested in at-risk subjects for the first time
HCV- Do we need a vaccine?

• Therapies dramatically better but…
HCV- Do we need a vaccine?

- Treatment remains expensive and carries some side effects
HCV- Do we need a vaccine?

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- Drugs do not provide protection against reinfection
HCV- Do we need a vaccine?

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- Drugs do not provide protection against reinfection
- Finding the people who need treatment remains challenging
Identification of HCV Infected people is challenging

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• Knowledge of infection status limited
  – 5% of those infected world-wide
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  - Australia, Canada, France, Denmark, and Scotland as models
    - Aggressive screening

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    - Australia, Canada, France, Denmark, and Scotland as models
      - Aggressive screening
      - 60-80% aware

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  - Living in endemic regions of the world
    - limited access to testing
    - poor needle injection and blood product hygiene
    - Limited access to therapies

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- Highest risk groups are marginalized
- Treatment in the later stages doesn’t reverse all disease

Eradication of HCV reduces but doesn’t eliminate liver failure

HCV- Do we need a vaccine?

- US Department of HHS says we do
- US Dept HHS Viral Hepatitis Action Plan 2011:
  - “Development of a vaccine that prevents new HCV infections remains a high priority task.”
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• US Dept HHS Viral Hepatitis Action Plan 2011:
  – “Development of a vaccine that prevents new HCV infections remains a high priority task.”
  – Actions to be initiated in 2011:
    “Facilitate development of candidate hepatitis C vaccines designed to induce protective immune responses.”
What Are Protective Immune Responses?

- It’s in your genes...
rs12979860 C IL-28B allele associated with higher probability of natural clearance of HCV

<table>
<thead>
<tr>
<th>Gene</th>
<th>HIV association</th>
<th>Hepatitis association</th>
</tr>
</thead>
<tbody>
<tr>
<td>HLA-C promoter SNP</td>
<td>Protective (Fellay, <em>Science</em> 2007)</td>
<td>HCV-possible protection (Thio et al. unpublished data)</td>
</tr>
<tr>
<td>IL-18 promoter SNP</td>
<td>Protective (Sobti et. al., <em>BJMG</em>, 2011)</td>
<td>HCV-protective against persistence in AA (Ping et al, <em>JID</em> 2008)</td>
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What Are Protective Immune Responses?

• It’s in your genes…

• And the immune response
T cell Responses Crucial in Control of HCV

- HLA association studies
- Chimpanzee CD8+ and CD4+ T cell depletion
- Association of breadth and magnitude of T cell response with viral clearance
- IFN-γ HCV specific CD8+ T cell responses are temporally correlated with reduction in viremia after infection

The Protective Immune Response…Can it be acquired?

- Reinfection does not always result in clearance- no protective immunity
- Some evidence that says yes…
Baltimore Before and After Acute Study of Hepatitis

18-35yo Active IDU
HCV EIA & RNA neg

Anti-HCV Ab = black bar  HCV = red bar

Persistent Infection
Spontaneous Clearance
Protection from Persistent HCV

113 HCV Seroconverters (anti-HCV antibody+)

31 seroconverters control initial infection (27%)  
82 seroconverters chronically-infected (73%)

22 cleared seroconverters assessed for reinfection

9 cleared seroconverters excluded from analysis of reinfection

11 subjects reinfected with heterologous virus (50%)

11 subjects - no new viremia  
No reinfection (50%)

12 reinfections with sufficient follow-up to assess outcome  
(2 subjects reinfected twice)

1 reinfection with insufficient follow-up to assess outcome

10 reinfections cleared (83%)

2 reinfections with persistent viremia (17%)  

(P = .001)

Osburn et. al. Gastroenterology 2010;138:315–324
Decreased magnitude of viremia during reinfection

$P < 0.05$

includes persistently reinfected subjects

Osburn et. al. Gastroenterology 2010;138:315–324
Shorter duration of viremia during reinfection

P = 0.019

Osburn et. al. Gastroenterology 2010;138:315–324
Broadening of T cell responses in HCV Reinfection

Updated from Osburn et. al. Gastroenterology 2010;138:315–324
Repeated HCV Controllers-
83% clear

• Recurrent detectable viremia with broadening of the immune response:
  – Lower maximum HCV RNA
  – Shorter duration of viremia

• Subjects who have cleared a fourth, fifth, and sixth infection…
Super HCV Controllers
Is sterilizing immunity required?

• Sterilizing immunity is a high bar
• HCV vaccines in animal models have not provided sterilizing immunity
• When all else fails...
Lower your standards!
Is sterilizing immunity required?

• Almost all significant disease is from chronic infection
• After spontaneous clearance, documented reinfection is common and without sequelae

HCV- Can we make an effective vaccine?

• Challenges parallel to HIV
  – Highly diverse virus
Ray SC and Thomas DL. *PPID 7th ed*, Chapter 154 2009
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  • Preexisting vector immunity limits responses
Preventing pre-existing anti-vector immunity from limiting vaccine efficacy

• Okairos search for novel adenoviral strains in non-human primates worldwide

• **Goals:** Discover adenoviral vectors that
  • Are highly immunogenic
  • Are easily manufactured to high titers
  • BUT do not stimulate cross reactive immunity (humans rarely exposed)
Preventing pre-existing anti-vector immunity from limiting vaccine efficacy

• **Success:**
  
  • Adenoviruses derived from chimpanzees (ChAd) differ from human adenovirus primarily in hexon (surface) proteins, making Ab cross reactivity low
  
  • many are highly immunogenic
Prophylactic vaccines to generate T cell immunity based on viral vectors

- Low seroprevalence chimpanzee and a human derived Adenoviruses – ChAd3, Ad6
- MVA attenuated strain, non-replicating in mammalian cells

- Vectored HCV antigen: “NSmut”
  - NS3-NS5B (NS = 1985 aa)
  - Several CD4 and CD8 T cell epitopes mapped in humans
  - Most conserved HCV region
  - Genotype I, subtype 1b

**Aim:** induce antiviral immunity with functional characteristics analogous to those associated with viral control in natural infection – broadly targeted, durable, functional CD4+CD8+ T cell response
HCV Vaccine Healthy Volunteer Trial Summary

- AdCh3NSmut prime with MVANSmut boost is a highly potent inducer of T cell responses.
- All individuals responded the vaccination.
- The majority of subjects developed responses against multiple HCV proteins.
- Polyfunctional CD4$^+$ and CD8$^+$ T cells are induced.
- T cells responses across genotypes detected.
- Vaccines safe and well tolerated.

Swadling L et al., Science Translational Medicine; 5 November 2014; 6:(261)
Figure 2c

![Graph showing IFN-γ SFCs/10^6 PBMCs for various NS proteins (NS3p, NS3h, NS4, NS5A, NS5B I, NS5B II) with ChAd3 prime (circles) and MVA boost (triangles). Significant differences are indicated by asterisks.](image)
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• Two injections administered at 0 and 8 weeks: $\text{AdCh3NS}_{\text{mut1}}$ & $\text{MVA-NS}_{\text{mut}}$
• Immune responses assessed
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• Immune responses assessed
• HCV RNA tested monthly
• Subject participation:
  • Non-viremic subjects → followed 20 months
  • Viremic subjects → referred for Rx, followed 9 months after virus detected or 20 months
Conclusions

• A prophylactic HCV vaccine is needed.
• Protective immunity likely exists *in vivo*.
• As with HIV, it will not be easy to create a successful vaccine.
• A new prophylactic vaccine is in trials for the first time in at risk subjects- data due out in early 2016
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Our Study Subjects

Stefania Capone
Antonella Folgori
Alfredo Nicosia
Elisa Scarselli
Cinzia Traboni