Hepatitis C Vaccines: Are we making progress?

Second International Hepatitis Cure and Eradication Meeting.

Vancouver
November, 2015
Objectives:

• Review the need for a preventive vaccine in 2015.

• Identify potential uses for an HCV vaccine.

• Provide update on approaches to vaccination.
Is an HCV vaccine needed in 2015?

• HCV infection is now curable without type I IFN and ribavirin.

• Almost all chronic infections are cured within 12 weeks by direct acting antivirals, including those considered difficult to treat.

Harvoni (Gilead)
NEJM May 15, 2014.

Viekera Pak (Abbvie)
NEJM May 22, 2015.
Patients Cured of HCV Infection

as percentage of treated patients

as fraction of all infected patients

United States

Worldwide

Courtesy of Dr. B. Rehermann
“The double benefit of curative treatment lies in its ability to serve as both individual cure and future prevention, supplementing behavioral control efforts for an even more powerful effect.”
A vaccine may be an important adjunct to therapy for prevention of infection:

- Symptoms are mild/inapparent. Identification of new and existing infections for treatment is therefore difficult.

- Infrastructure to identify infected individuals is inadequate, especially in populations where transmission continues.
Increasing HCV infection rates, 2006-2012

Anil Suryaprasad et. al. Clinical Infect. Disease, August 2014.
Potential uses for an HCV vaccine.

• Reduce the risk of persistence upon first exposure to HCV.

• Prevent a second persistent infection in those who are cured with DAA but remain at risk for exposure to HCV.
The outcome of HCV infection

Persistence (≈70%)

Resolution (≈30%)

neutralizing antibodies

Viremia
CD8+ T cells
CD4+ T cells

Infection
Years

Persistence (≈70%)

Resolution (≈30%)

neutralizing antibodies

Viremia
CD8+ T cells
CD4+ T cells

Infection
Years
Spontaneous resolution of primary HCV infection does protect against persistence.
Protection in chimpanzees is observed even after challenge with multiple HCV genotypes.

Most secondary human infections also resolve, with shorter duration and lower peak viremia.

W.O. Osburn and colleagues
Gastroenterology, 2010.
The *objective of vaccination* is not to prevent infection.

A vaccine that prevents persistence would be considered successful given the absence of acute phase liver disease or latency of HCV genomes.
Approaches to vaccination against HCV.

- Recombinant proteins, viruses and DNA.
- Killed HCV particles
- Virus like particles
- Synthetic peptides

- Rodents
- Chimpanzees
- Humans
Two preventive vaccine concepts have advanced to human trials.

“antibody” vaccine
Chiron/Novartis

“T cell” vaccine
Okairos/GSK
The Antibody Vaccine

- Recombinant genotype 1a (HCV-1) E1 and E2 proteins.
- Produced in CHO cells.
- Microfluidized (MF59) oil in water emulsion adjuvant.
Recombinant adjuvanted gpE1/gpE2 vaccine provided some sterilizing immunity, but also appeared to promote resolution of infection.

<table>
<thead>
<tr>
<th>Challenge</th>
<th>Vaccine</th>
<th>Total</th>
<th>Acute</th>
<th>Chronic (%)</th>
<th>P</th>
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</thead>
<tbody>
<tr>
<td>HCV-1</td>
<td>gpE1/gpE2</td>
<td>12</td>
<td>7</td>
<td>2 (17)</td>
<td>P=0.03</td>
</tr>
<tr>
<td></td>
<td>mock</td>
<td>10</td>
<td>10</td>
<td>7 (70)</td>
<td></td>
</tr>
<tr>
<td>H77</td>
<td>gpE1/gpE2</td>
<td>19</td>
<td>19</td>
<td>3 (16)</td>
<td>P=0.02</td>
</tr>
<tr>
<td></td>
<td>mock</td>
<td>14</td>
<td>14</td>
<td>8 (57)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>gpE1/gpE2</td>
<td>31</td>
<td>26</td>
<td>5 (16)</td>
<td>P=&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>mock</td>
<td>24</td>
<td>24</td>
<td>15 (63)</td>
<td></td>
</tr>
</tbody>
</table>

M. Houghton.  
A phase I trial of vaccine immunogenicity has been completed. (see NCT00500747 at ClinicalTrials.gov)

E1/E2/MF59 elicited broadly neutralizing antibodies in humans.

• E1/E2/MF59 is not necessarily just an “antibody vaccine”.

• It also elicits a potent response by CD4+ T cells, the very subset that fails during acute HCV infection.


The current status of this vaccine is unknown.
Rationale for a vaccine that induces T cells and not E1/E2 antibodies.

T cell vaccine
Okairos/GSK
CD4+ or CD8+ T cell depletion from immune chimpanzees results in prolonged or persistent infection.

A. Grakoui et al. 2003. Science
Chimpanzees were primed with a recombinant adenovirus vector expressing HCV genotype 1b non-structural proteins NS3 though NS5B.

Boosted with vector and plasmid DNA vaccine over 39 weeks.

Challenged 10 weeks after the last boost with a mismatched virus (H77, g1a).
Peak viremia reduced 100-fold in vaccinees vs. controls.

Duration of infection shorter in vaccinees (1-7 weeks) versus controls (16-20 weeks)

A. Folgori et. al.  
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 Joanna 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 Barnes1,3,6‡
A heterologous prime-boost strategy induces strong, durable T cell immunity against non-structural HCV proteins.
T cell responses are multi-specific and recognize an array of HCV genotypes.
A variant of this vaccine (AdCh3 prime/MVA boost) is now being assessed in a phase I/II clinical trials.

(see NCT01436357 at Clinical Trials.gov)

Subjects are HCV naïve but at risk (IDU).

Primary study endpoints are safety and immunogenicity.

Key study endpoint is prevention of HCV persistence.

Data are expected in 2016.
Is a vaccine needed to prevent HCV reinfection after DAA cure?
Daclatasvir plus Sofosbuvir for Previously Treated or Untreated Chronic HCV Infection

Mark S. Sulkowski, M.D., David F. Gardiner, M.D., Maribel Rodriguez-Torres, M.D., K. Rajender Reddy, M.D., Tarek Hassanein, M.D., Ira Jacobson, M.D., Eric Lawitz, M.D., Anna S. Lok, M.D., Federico Hinestrosa, M.D., Paul J. Thuluvath, M.D., Howard Schwartz, M.D., David R. Nelson, M.D., Gregory T. Everson, M.D., Timothy Eley, Ph.D., Megan Wind-Rotolo, Ph.D., Shu-Pang Huang, Ph.D., Min Gao, Ph.D., Dennis Hernandez, Ph.D., Fiona McPhee, Ph.D., Diane Sherman, M.S., Robert Hindes, M.D., William Symonds, Pharm.D., Claudio Pasquinelli, M.D., Ph.D., and Dennis M. Grasela, Pharm.D., Ph.D., for the A444040 Study Group

DOI: 10.1056/NEJMoa1306218
• One patient with a history of IDU was treated with DCV/SOF/RBV.

• High levels of HCV RNA were detected after treatment.

• The virus had a unique genomic sequence and no resistance mutations to DCV and SOF.

• Reinfection after cure provides the most likely explanation for HCV persistence.
• What are the defects in adaptive immunity in chronic hepatitis C?
• Are they reversed by successful DAA treatment?
• Do they protect from reinfection?
T cell defects in chronic hepatitis C.

Neutralizing antibodies develop slowly and contemporaneous viruses are not recognized.
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The CD4+ T cell response is not sustained.
Neutralizing antibodies develop slowly and contemporaneous viruses are not recognized.

The CD4+ T cell response is not sustained.

CD8+ T cells persist in the chronically infected liver. They are exhausted and/or target escape mutations.
Treatment and reinfection of a chimpanzee with persistent HCV infection.
Two direct acting drugs were delivered orally for 28 days:

- **NS5B inhibitor** (MK0608, nucleoside analog).

  ![NS5B inhibitor structure]


- **NS5A inhibitor** (BMS 790052).

  ![NS5A inhibitor structure]

Treatment was successful.
Two years after cure, rechallenge with the virus that established the first persistent infection.
CD8+ T cells were present in liver before and after cure of infection.

inoculum

E2\textsubscript{630} (Patr A*0901)

E2\textsubscript{680} (Patr B*0101)

NS5a\textsubscript{1992} (Patr B*0101)

NS5b\textsubscript{2423} (Patr B*0101)

circulating

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-I-------

---------V
Track intrahepatic T cell expansion against 2 epitopes.

**inoculum**
- E2\textsubscript{630} (Patr A*0901)
- RMYVGGVEHRL

**circulating**
- E2\textsubscript{680} (Patr B*0101)
- TTLPALSTGLI
- \textbf{KTWLQSKLL} [I--]
- NS5a\textsubscript{1992} (Patr B*0101)
- NS5b\textsubscript{2423} (Patr B*0101)
- YWTGALI [---]
Is T cell failure explained by mutational escape of epitopes.

sequence epitopes $E_{2680}$ and $NS5a_{1992}$

-14 7 28 183

study day

HCV RNA (log10 IU/ml serum)

-14 0 7 28 56 112 189

re-infection (day 183)

treatment
Inoculum before cure

2nd infection

<table>
<thead>
<tr>
<th>Study Day</th>
<th>Treatment</th>
<th>Re-infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>-14</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>7</td>
<td>28</td>
<td>183</td>
</tr>
</tbody>
</table>

HCV RNA (log10 IU/ml serum)

**E2\textsubscript{680}**

<table>
<thead>
<tr>
<th>680 \textasciitilde TTLPALSTG LI</th>
</tr>
</thead>
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**NS5a\textsubscript{1992}**

<table>
<thead>
<tr>
<th>1992 \textasciitilde KTWLQSKLL</th>
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</thead>
</table>

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-**I**---

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Conclusions from this case report:

HCV epitope escape during the first infection spared CD8+ T cells from exhaustion. These T cell responded to the second infection, but the virus again rapidly escaped.

CD8+ T cells targeting epitopes that do not escape remain exhausted, even after DAA cure. They do not respond upon reinfection with HCV.
T cell function before and after DAA-mediated cure of HCV infection in humans.

- 51 previously untreated subjects with chronic HCV infection.
- Treated with Fladaprevir (PI) and Deleobuvir (NNI) +/- ribavirin.
- T cell immunity measured before and after treatment.

B. Martin et al, J. Hepatol. 2014.
Recovery of T cell proliferation after successful treatment.

**treatment success**  
(svrv12)

**treatment failure**  
(no svr12)

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B. Martin et al, J. Hepatol. 2014.
Questions and Challenges for the Future.

• Does the CD4+ T cell response recover after DAA cure and will it be more resistant to inactivation?

• Does improvement in CD8+ T cell function and phenotype after DAA cure predict protection from a second persistent infection?

• Will vaccines designed to prevent primary infection also elicit protective immunity after cure of chronic infection with DAA?

• In this setting, the line between preventive and therapeutic vaccination may begin to blur.
With thanks to:

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Okairos/GSK