Are we closer to a hepatitis C vaccine?

Andrea L. Cox, MD, PhD

Viral Hepatitis Center
Disclosures

None
Achieving control

• To reduce the prevalence of HCV, the reduction in HCV infected people must exceed new cases.

Cure (+ death) > New infection
Achieving control- a challenge

• Epidemiological data extracted for 210 countries for 2016
Achieving control- a challenge

- Epidemiological data extracted for 210 countries for 2016
- 91 countries with data on SVR, HCV-related deaths, and new infections available for analysis
Achieving control: a challenge

- Epidemiological data extracted for 210 countries for 2016
- 91 countries with data on SVR, HCV-related deaths, and new infections available for analysis
- 47 of 91 countries: more new HCV infections than SVR in 2016.
Achieving control- a challenge

• Very few countries are on target to achieve elimination of HCV as a public health problem by 2030.
Globally, SVR isn’t much greater than incidence

- Net HCV in 91 countries dropped from 57.3 to 56.9 million people- 0.7% reduction.
Globally, SVR isn’t much greater than incidence

- Net HCV in 91 countries dropped from 57.3 to 56.9 million people- 0.7% reduction.
- Projected global net change was from 69.6 to 69.3 million- 0.4% reduction.
We are way off target for eradication…

• Reduce HCV infection in 70 million by 400,000/year…
We are way off target for eradication…

- Reduce HCV infection in 70 million by 400,000/year…175 years
A lot of focus on cure

Cure

New infection prevention
Challenges to cure

- Treatment remains expensive
- We have already treated those easiest to treat
- Finding the people who need treatment remains challenging
- Drugs do not provide protection against reinfection
- Treatment in the later stages doesn’t reverse all disease
Incidence of HCC after SVR is high in cirrhotics.

Consider some additional focus on prevention…
An increasingly common story...

- 21 y.o. Caucasian woman
An increasingly common story...

• 21 y.o. Caucasian woman
• College student
An increasingly common story...

- 21 y.o. Caucasian woman
- College student
- Began recreational oxycodone use at age 18
An increasingly common story...

• 21 y.o. Caucasian woman
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• Transitioned to i.v. heroin at 20
An increasingly common story...

- 21 y.o. Caucasian woman
- College student
- Began recreational oxycodone use at age 18
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- Referred to the Baltimore City needle exchange program
An increasingly common story...

- 21 y.o. Caucasian woman
- College student
- Began recreational oxycodone use at age 18
- Transitioned to i.v. heroin at 20
- Needle exchange started
An increasingly common story...

- 21 y.o. Caucasian woman
- College student
- Began recreational oxycodone use at age 18
- Transitioned to i.v. heroin at 20
- Needle exchange started
- Convinced her boyfriend to begin heroin
An epidemic of opiate use and overdose
An epidemic of opiate use and overdose

- Since 2015 - the leading cause of accidental death in the US
Evolving heroin epidemic in US

- Rising use of oxycodone for recreation and for pain management- “vital sign”
Evolving heroin epidemic in US

- Rising use of oxycodone for recreation and for pain management
- Oxycontin tamper resistant formula developed
Evolving heroin epidemic in US

- Rising use of oxycodone for recreation and for pain management
- Oxycontin tamper resistant formula developed
- Heroin cost fell
Increasing incidence of acute HCV infection, US 2000-2013

https://wwwn.cdc.gov/nndss/
Rising Number of New Acute HCV Cases in PWID in US

Changes in Rates of New HCV Cases Reported by State, 2010-2014

Slide courtesy of John Ward, Data from CDC
2015 HCV incidence: 1.75 million and highly variable

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<th>WHO region</th>
<th>Estimated incidence</th>
<th>Uncertainty (X1000)</th>
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<td>African</td>
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<td>Global</td>
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WHO Global Hepatitis Report 2017
WHO New Infection Goal 2016

• Called for 90% reduction in new HCV infections by 2030
Is protective immunity possible?
A challenge for vaccine development: viral diversity

(Ray, Thomas, Mandell 8th ed., 2015)
Broadly neutralizing Ab (BnAbs)

- BnAbs protect against HCV challenge in humanized mice (Law 2008; de Jong 2014; Keck 2016)
Broadly neutralizing Ab (BnAbs)

- BnAbs protect against HCV challenge in humanized mice (Law 2008; de Jong 2014; Keck 2016)

- BnAbs eliminate previously established HCV infection in humanized mice (de Jong 2014)
Baltimore Before and After Acute Study of Hepatitis (BBAASH)

18-35yo People Actively Injecting Enrolled HCV EIA & RNA neg

Anti-HCV Ab = black bar  HCV RNA = red bar

Persistent Infection (73%)

Spontaneous Clearance (27%)
Spontaneous clearance of HCV is associated with early development of broadly neutralizing serum

Osburn, Hepatology, 2014
Similar nAb profiles - but not outcome

<table>
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<tr>
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<th>Subtype 1a</th>
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<th>Subtype 1b</th>
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DPI = days post infection

From Justin Bailey, unpublished
Both clearer and persister develop mutations in E2
Both clearer and persister develop mutations in E2
**Clearer’s mutations in conserved E2 away from ancestral sequence**

<table>
<thead>
<tr>
<th>E2 polyprotein position</th>
<th>434</th>
<th>444</th>
<th>465</th>
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<td>D</td>
<td>Y</td>
<td>Y</td>
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<td>H</td>
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</table>

- **Mutation towards ancestral**
- **Mutation away from ancestral**

Munshaw, Hepatology, 2012
Clearer’s mutations in conserved E2 away from and persister’s mutations towards ancestral sequence

<table>
<thead>
<tr>
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<td>D Y Y V H</td>
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**Mutation key**:
- Green: mutation towards ancestral
- Red: mutation away from ancestral

*From Justin Bailey, unpublished*
Mutations in the clearer and persister have different effects on E1E2 fitness

HCVpp infectivity

Log(Infectivity)

0.1 1 10 100 1000

g(y)

Clearer E1E2 variants

Tif#3 D194 clone 1 D194 clone 2 D285 clone 1 D285 clone 2 D388 clone
Mutations in the clearer and persister have different effects on E1E2 fitness

From Justin Bailey, unpublished
Clearer’s E1E2 variants also had decreased replicative fitness in the HCVcc system.

<table>
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<th>T/F#3</th>
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From Justin Bailey, unpublished
Site directed mutagenesis confirms fitness cost of mutations

Clearer E1E2 SDMs

From Justin Bailey, unpublished
mAb HEPC3 was isolated from the clearer

![Graph showing HCV RNA levels over days after infection](image)

**Graph Details:**
- **Y-axis:** HCV RNA (IU/mL)
- **X-axis:** Days after infection
- **Data Points:**
  - (-) HCV EIA -
  - (+) HCV EIA+

*Bailey, JCI Insight, 2017*
mAb HEPC3 breadth matches clearance subject plasma

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Plasma

- 194 DPI
- 388 DPI

mAb HEPC3

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巴利, JCI Insight, 2017

- <50% neutralization
- >50% neutralization
Mutations in longitudinal E1E2 clones confer progressive HEPC3 resistance

E1E2 ELISA

HEPC3 Concentration (ug/ml)

Optical Density (OD) of E1E2 binding

<table>
<thead>
<tr>
<th>HEPC3 Concentration (ug/ml)</th>
<th>0.001</th>
<th>0.01</th>
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</table>

mutation away from ancestral
BnAb responses

May be crucial in some subjects
Have the potential to prevent infection
T cell Responses Crucial in Control of HCV
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- HLA association studies
T cell Responses Crucial in Control of HCV

- HLA association studies
- Chimpanzee CD8+ and CD4+ T cell depletion

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

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

Baltimore Before and After Acute Study of Hepatitis (BBAASH)

18-35yo People Actively Injecting Enrolled HCV EIA & RNA neg

Anti-HCV Ab = black bar
HCV RNA = red bar

Persistent Infection (73%)
Spontaneous Clearance (27%)
BBAASH Cohort

**Baltimore Before and After Acute Study of Hepatitis (BBAASH)**

18-35yo People Actively Injecting Enrolled HCV EIA & RNA neg

- Anti-HCV Ab = black bar
- HCV RNA = red bar

- Persistent Infection (73%)
- Spontaneous Clearance (27%)

Assess HCV hemigenomic sequence, T cell responses at initial viremia ($t_0$) and at 6 and 12 months ($t_6, t_{12}$) PI
Substitutions More Frequent in T Cell Epitopes in Persistence

- In 69% of T cell epitopes

Cox et. al, JEM, 2005; 201(11), 741-52
Substitutions More Frequent in T Cell Epitopes in Persistence

- In 69% of T cell epitopes
- In every subject with persistence

Cox et. al, JEM, 2005; 201(11), 741-52
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- 13-fold more often inside than outside T cell epitopes (p < 0.001, range 5-38)

Cox et. al, JEM, 2005; 201(11), 741-52
Substitutions More Frequent in T Cell Epitopes in Persistence

- In 69% of T cell epitopes
- In every subject with persistence
- 13-fold more often inside than outside T cell epitopes (p < 0.001, range 5-38)
- Not seen in clearance

Cox et. al, JEM, 2005; 201(11), 741-52
Effect of HCV Mutations

- Do not affect epitope density
- New TCR repertoire potentially available
- Exploitation of “hole” in repertoire

Wolfl et. al. *J. Immunology* 2008

PD-1 is upregulated on HCV-specific T cells

- Inhibits T cell function

PD-1 is upregulated on HCV-specific T cells

- Inhibits T cell function
- Levels shown to be high on HCV-specific T cells

PD-1 is upregulated on HCV-specific T cells

- Inhibits T cell function
- Levels shown to be high on HCV-specific T cells
- Mechanism of inhibiting T cell function when the virus doesn't escape

TGF-β1 increases *Pdcd-1* transcript levels

Human CD3+ T cells

Park BV et. al. Cancer Discovery 2016
TGF-β Signaling Pathway
TGF-β1 induces higher T cell PD-1 expression via Smad3

Park BV et. al.  
Cancer Discovery 2016
PD-1 blockade - reactivation of HCV Specific T cells?

- Randomized DB, placebo controlled trial in chronic HCV

Gardiner D et. al, PLOS One 2013
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- 3/10 achieved a >4 log HCV RNA reduction

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PD-1 blockade - reactivation of HCV Specific T cells?

- Randomized DB, placebo controlled trial in chronic HCV
- Lower doses tested, but 10 patients received 10 mg/kg of anti-PD-1
- 3/10 achieved a >4 log HCV RNA reduction
- 2/3 with >4 log drop achieved an undetectable HCV RNA - one cured.

Gardiner D et. al, PLOS One 2013
HCV- Can we make an effective vaccine?
Efforts to develop a prophylactic HCV vaccine

Proteins in adjuvants, peptides, DNA, VLP, replicating & non replicating viral vectors

Proteins, VLP, DNA, Viral vectors

Macaques
Chimps

Protein, viral vectors
Low-risk Humans

Viral vectors
High-risk Humans

New Envelope based-HCV vaccine to be tested

Designed to stimulate *both* neutralizing antibodies to stop the virus entering the liver *and* T cell responses to inhibit virus replication and to kill infected cells
- using recombinant surface & other viral proteins

Based on a prototype vaccine proven to reduce the carrier rate in non-human primates
- remains the only vaccine candidate with proven animal efficacy data in preventing HCV infection
Prototype gpE1/gpE2 vaccine protects chimpanzees against the major N.American HCV genotypes

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of carriers (%) (homologous &amp; heterologous 1a challenges)</th>
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<tbody>
<tr>
<td>Control unvaccinated</td>
<td>15/24 (63%)</td>
</tr>
<tr>
<td>Vaccinated</td>
<td>5/31 (16%)</td>
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</tbody>
</table>

( highly significant reduction ! )

M.Houghton  Immunol Rev 2011
Produces antibodies in chimpanzees and humans that neutralize the infectivity of HCV of diverse gt

J.Meuniere et al JID 2011; J.Law et al Plos One 2013
Humans receiving prototype HCV gpE1/gpE2 vaccine make neutralizing antibodies diverse gts

Slide courtesy of M. Houghton, J.Law et al Plos One 2013
HCV vaccine currently being manufactured at the University of Alberta under GMP guidelines

Plan to start phase 1 clinical trial in early 2019

Funded by:
- CERC Chair program
- Alberta Innovates
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- Li Ka Shing Institute of Virology
- CFI
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Slide courtesy of M. Houghton on behalf of the Collaborative HCV Vaccine Team
HCV- Can we make an effective vaccine?

• Use vectors to deliver HCV antigens in a system that induces robust innate and adaptive immune responses
HCV- Can we make an effective vaccine?

• Use vectors to deliver HCV antigens in a system that induces robust innate and adaptive immune responses
Prophylactic vaccine to generate T cell immunity based on viral vectors

• Prime: Low seroprevalence chimpanzee derived Adenovirus – ChAd3

• Boost: MVA attenuated strain, non-replicating in mammalian cells
Prophylactic vaccine to generate T cell immunity based on viral vectors: the antigen

- Vectored HCV antigen: “NSmut”
Prophylactic vaccine to generate T cell immunity based on viral vectors: the antigen

- Vectored HCV antigen: “NSmut”
  - NS3-NS5B (NS = 1985 aa)
  - Several known human CD4 and CD8 T cell epitopes
  - Genotype 1, subtype 1b
• AdCh3NSmut prime with MVANSmut boost is a highly potent inducer of T cell responses.

Swadling L et al., Science Translational Medicine; 5 November 2014; 6:(261)
HCV Vaccine Healthy Volunteer Trial Summary

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• Polyfunctional CD4+ and CD8+ T cells are induced.

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T cells responses across genotypes detected.

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T cells responses across genotypes detected.

Vaccines safe and well tolerated.

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VIP: Vaccine is Prevention

- **Design:** Double blind, randomized, placebo controlled at JHU, UCSF, UNM
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- **Goal**: assessment of safety, induction of HCV specific immune responses, and efficacy in preventing *chronic* HCV infection
VIP Design

- Two injections administered at 0 and 8 weeks: $\text{AdCh3NS}_{\text{mut1}}$ & $\text{MVA-NS}_{\text{mut}}$
- Immune responses assessed
• Two injections administered at 0 and 8 weeks: AdCh3NS_{mut1} & MVA-NS_{mut}
• Immune responses assessed
• HCV RNA tested monthly
VIP Results

• Aiming for release in Fall 2018
Conclusions

- A prophylactic HCV vaccine is needed.
Conclusions

• A prophylactic HCV vaccine is needed.
  – Comprehensive strategy
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• A prophylactic HCV vaccine is needed.
  – Comprehensive strategy
    • Prevention, harm reduction
    • Diagnosis
    • Treatment
Conclusions

• A prophylactic HCV vaccine is needed.
• Protective immunity likely exists *in vivo*.
Conclusions

• A prophylactic HCV vaccine is needed.
• Protective immunity likely exists in vivo.
• A new prophylactic vaccine is in trials for the first time in at risk subjects- data due out in fall of 2018
Are we closer to a hepatitis C vaccine?
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