HCV Vaccine Development: Where do we stand?

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No Conflicts of Interest
HCV- Do we need a vaccine?

• Acute infection rates are not decreasing everywhere

Rising Number of New Acute HCV Cases in PWID in US

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

Data and slide courtesy of John Ward and the CDC
HCV- Do we need a vaccine?

• Therapies dramatically better but…

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

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- Finding the people who need treatment remains challenging

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  - 5% of those infected world-wide

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- Highest risk groups are marginalized
  - PWID
  - Living in endemic regions of the world

HCV - Do we need a vaccine?

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Drugs do not provide protection against reinfection

Incidence of hepatitis C reinfection following SVR

Patients
2004–05: Treated PWID abstinent from drug use ≥6 months prior to treatment

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2012-14: 94 PWID and 44 non-PWID with SVR
  Median f/u ~7years

Results
37 of 94 (39%) PWID relapsed to active injection after SVR

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HCV reinfection in 12 patients (12.8%)


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**Patients:** 114 HIV+ MSM with SVR

Martin TC et al. AIDS 2013 Oct 23;27(16):2551-7
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27 reinfections, reinfection rate of 9.6/100py (95% CI 6.6–14.1)
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27 reinfections, reinfection rate of 9.6/100py (95% CI 6.6–14.1)
25% of patients treated for HCV virus infection became reinfected within 2 years of follow-up.

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**HCV- Do we need a vaccine?**

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Drugs do not provide protection against reinfection
Treatment in the later stages doesn’t reverse all disease
Eradication of HCV reduces but doesn’t eliminate liver failure


Incidence of HCC after SVR is high in cirrhotics.

HCV- Do we need a vaccine?

- Treatment remains expensive and carries side effects
- 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
- Potential for DAA resistance unknown

Long-term follow-up of treatment-emergent resistance-associated variants in NS3, NS5A and NS5B

- Resistance in 2510 patients in Phase 2 and 3 trials who received DAAs (PTV/r-, OBV- and DSV-based regimens)

Long-term follow-up of treatment-emergent resistance-associated variants in NS3, NS5A and NS5B

- Resistance in 2510 patients in Phase 2 and 3 trials who received DAAs (PTV/r-, OBV- and DSV-based regimens)
- 67 G1a and 7 G1b failures (2.9% of total population)


Long-term follow-up of treatment-emergent resistance-associated variants in NS3, NS5A and NS5B

- NS5A RAVs persist beyond FU48
- NS3 RAVs decline to low levels by FU48
- NNI RAVs persist but not a lot of crossover across class

Reinfection with DAA resistant HCV

HIV-infected male sexual partners with HCV:
SVR in one
DAA failure in the other with documented telaprevir resistant HCV (V36M)

Franco et al. Gastroenterology 2014

Reinfection with DAA resistant HCV

Documented re-infection with telaprevir resistant HCV (V36M)

Franco et al. Gastroenterology 2014
The global reach of HCV infection.

185 million infected
(3% world)

- 5% are aware
of those

- 95% are NOT treated
and

- 5% are treated
of those

- 5% no response
- 95% reduced
risk of liver failure,
cancer, and death
(disease progression and reinfection can still occur)

Andrea L. Cox Science 2015;349:790-791

Is protective immunity possible?
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• Reinfection does not always result in clearance- no protective immunity

• Some evidence that says yes…
BBAASH Cohort

Baltimore Before and After Acute Study of Hepatitis

18-35yo Active IDU
HCV EIA & RNA neg

Anti-HCV Ab = black bar  HCV = red bar

Protection from Persistent HCV

113 HCV Seroconverters (anti-HCV antibody+)

31 seroconverters control initial infection (27%)

22 cleared seroconverters assessed for reinfection

11 subjects reintected with heterologous virus (50%)

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

10 reinfections cleared (83%)

82 seroconverters chronically infected (73%)

9 cleared seroconverters excluded from analysis of reinfection

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

1 reinfection with insufficient follow-up to assess outcome

2 reinfections with persistent viremia (17%)
Decreased magnitude of viremia during reinfection

Evidence of protective immunity

- Peak HCV RNA level significantly lower during reinfection than primary infection
  - Mehta et. al. Lancet 2002,
  - Grebely et. al. Hepatology 2006
  - Sacks-Davis et. al. JID 2015
Shorter duration of viremia during reinfection

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
**Broadening of T cell responses in HCV Reinfection**

- Confirmed in Montreal Acute Hepatitis C Injection Drug User Cohort:
  - Increased magnitude and breadth
  - Higher T cell proliferative capacity

Abdel-Hakeem, M et. al. Gastroenterology 2014, 147;870-881

**HCV- Can we make an effective vaccine?**

- Challenges parallel to HIV
  - Highly diverse virus
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  – Increasing interest in vaccines that induce robust T cell responses

• Current focus is to use vectors to deliver viral antigens in a system that induces robust innate and adaptive immune responses
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  - Increasing interest in vaccines that induce robust T cell responses
    - Current focus is to use vectors to deliver viral antigens in a system that induces robust innate and adaptive immune responses
  - Preexisting vector immunity limits responses

Efforts to develop a prophylactic HCV vaccine

Vaccines for Hepatitis C, 25 Years After the Discovery of Hepatitis C, Springer, in press
Preventing pre-existing anti-vector immunity from limiting vaccine efficacy

- Adenoviruses derived from chimpanzees (ChAd) differ from human adenovirus primarily in hexon (surface) proteins, making Ab cross reactivity low

Preventing pre-existing anti-vector immunity from limiting vaccine efficacy

- Adenoviruses derived from chimpanzees have low Ab cross reactivity
- many are highly immunogenic
Prophylactic vaccines to generate T cell immunity based on viral vectors

- Low seroprevalence chimpanzee derived Adenovirus – ChAd3
- MVA attenuated strain, non-replicating in mammalian cells

Prophylactic vaccines to generate T cell immunity based on viral vectors

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

- Vectored HCV antigen: “NSmut”
  - NS3-NS5B (NS = 1985 aa)
  - Several known human CD4 and CD8 T cell epitopes
  - 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 to vaccine.

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- 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)
VIP: Vaccine is Prevention

- **Design:** Double blind, randomized, placebo controlled at JHU, UCSF, UNM

- **Population:** 18-45 yo active injection drug users at high risk for but not infected with HCV RNA at screening
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• **Design:** Double blind, randomized, placebo controlled at JHU, UCSF, UNM

• **Population:** 18-45 yo active injection drug users at high risk for but not infected with HCV RNA at screening

• **Size:** Total N=540

• **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:
  AdCh3NS_{mut1} & MVA-NS_{mut}
- Immune responses assessed

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- Immune responses assessed
- HCV RNA tested monthly
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

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• Protective immunity likely exists in vivo.
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• As with HIV, it will not be easy to create a successful vaccine.

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 2017
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Thank you!!!

• Questions?