HCV Vaccine Development

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Disclosure speaker interests

Disclosure of speaker interest

No potential conflicts to report
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
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?

- Treatment remains expensive and carries side effects
- Finding the people who need treatment remains challenging
Identification of HCV Infected people is challenging

• Infection usually silent until ESLD present
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Antiviral Therapy Might Be Used to Reduce HCV Prevalence Among Injecting Drug Users

- Annually treating 10 HCV infections per 1000 IDU and achieve SVR of 62.5%

Martin et al. Journal of Hepatology 2011
Antiviral Therapy Might Be Used to Reduce HCV Prevalence Among Injecting Drug Users

- Annually treating 10 HCV infections per 1000 IDU and achieve SVR of 62.5%
- Projected to result in a relative decrease in HCV prevalence over 10 years of 31%, 13%, or 7% for prevalences of 20%, 40%, or 60%, respectively

Martin et al. Journal of Hepatology 2011
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- Knowledge of infection status limited
- Highest risk groups are marginalized
  - PWID
  - Living in endemic regions of the world
Prevalence of Hepatitis C

Data for 2010, presented at the 64th annual meeting of American Association for the Study of Liver Diseases (AASLD), in the U.S. in November 2013.

NUMBER OF INFECTED PEOPLE — IN MILLIONS

- China: 29.8
- India: 18.2
- Egypt: 11.8
- Indonesia: 9.4
- Pakistan: 9.4
- Russia: 5.8
- U.S.: 5.4
- DR Congo: 4.0
- Nigeria: 3.3
- Japan: 3.1
- Cameroon: 2.8
- Brazil: 2.6
- Uganda: 2.2
- Philippines: 1.9
- Italy: 1.9
- Ukraine: 1.9
- Uzbekistan: 1.8
- Turkey: 1.5
- Ethiopia: 1.5
- Thailand: 1.5

INCOME CLASSIFICATION From The World Bank
- High income
- Upper-middle income
- Lower-middle income
- Lower-middle income
- Low income


Staff, 9/04/2014
HCV- Do we need a vaccine?

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Drugs do not provide protection against reinfection
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PWID

MSM
HCV - Do we need a vaccine?

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- Drugs do not provide protection against reinfection
- Potential for DAA resistance unknown
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  Increase likely with treatment of less compliant patients
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Increase likely with treatment of less compliant patients

RAV testing and long treatment courses won’t happen in resource limited settings
HCV- Do we need a vaccine?

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- Potential for DAA resistance unknown
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)
Reinfection with DAA resistant HCV

Documented re-infection with telaprevir resistant HCV (V36M)
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
Potential for DAA resistance unknown
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.

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

- 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

includes persistently reinfected subjects

Osburn et. al. Gastroenterology 2010;138:315–324
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. Gastroenterolgy 2014, 147;870-881
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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  – Current focus is to use vectors to deliver viral antigens in a system that induces robust innate and adaptive immune responses
HCV- Can we make an effective vaccine?

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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

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

Rodents

Proteins, VLP, DNA, Viral vectors

Macaques Chimps

Protein, viral vectors

Low-risk Humans

Viral vectors

High-risk Humans

Prophylactic vaccines to generate T cell immunity based on viral vectors

- Low seroprevalence chimpanzee and a human derived Adenoviruses – 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
Prophylactic vaccines to generate T cell immunity based on viral vectors

• Vectored HCV antigen: “NSmut”

**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
AdCh3NSmut prime with MVANNSmut boost is a highly potent inducer of T cell responses.

Swadling L et al., *Science Translational Medicine*; 5 November 2014; 6:(261)
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All individuals responded to vaccine.

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HCV Vaccine Healthy Volunteer Trial Summary

- AdCh3NSmut prime with MVANSmut boost is a highly potent inducer of T cell responses.
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- The majority of subjects developed responses against multiple HCV proteins.

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Figure 2c

- IFN-γ SFCs/10^6 PBMCs

- NS3p, NS3h, NS4, NS5A, NS5B I, NS5B II

- ○ ChAd3 prime

- ▼ MVA boost

* Significance markers
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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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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
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- **Population**: 18-45 yo active injection drug users at high risk for but not infected with HCV RNA at screening
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- **Size**: Total N=540
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: Vaccine is Prevention
• 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: \( \text{AdCh3NS}_{\text{mut1}} \) & \( \text{MVA-NS}_{\text{mut}} \)
• Immune responses assessed
• HCV RNA tested monthly
Conclusions

• A prophylactic HCV vaccine is needed.
Conclusions

• A prophylactic HCV vaccine is needed.
  – Comprehensive strategy
Conclusions

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

- A prophylactic HCV vaccine is needed.
- Protective immunity likely exists \textit{in vivo}.
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.
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 2017
Acknowledgements

William Osburn
Michael Melia
Shaneca Bowden
Donald Brown
David Hudson

Kimberly Page
Katherine Wagner

Our Study Subjects

Paula Lum
Alice Asher
Ellen Stein

Stefania Capone
Antonella Folgori
Alfredo Nicosia
Elisa Scarselli

Eleanor Barnes
Paul Kleenerman
Leo Swadling
Thank you!!!

- Questions?