Prospects for Vaccines against Hepatitis C Viruses

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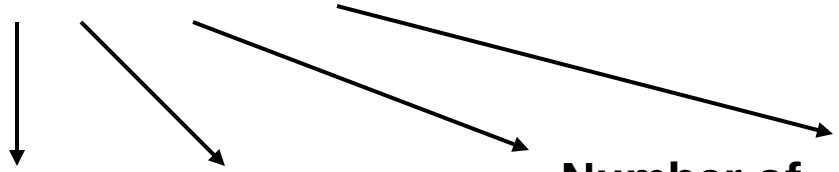
HCV Vaccine

- Prevention strategies
- Protective immunity
- Barriers and solutions
- Vaccine candidates
- Clinical trial design
- Cost-effectiveness analysis

Spread of HCV

$R_o = \beta D c \quad (p)$

Secondary spread



Efficiency of transmission

Duration of infection

Number of exposed individuals

Number of infected individuals

Mary & Anderson, Nature 1987

Protective Immunity

Viral Infection

Sterilizing protection: ***humoral immunity; Vaccines for HBV, HAV and other acute viral illness***

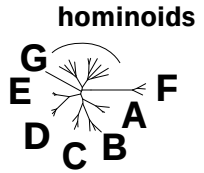
Prevention of chronicity and disease: ***cell-mediated immunity; Vaccines for HIV, HCV, Herpes***

Liang, Nature Medicine 2013

HCV Vaccine: Barriers & Solutions

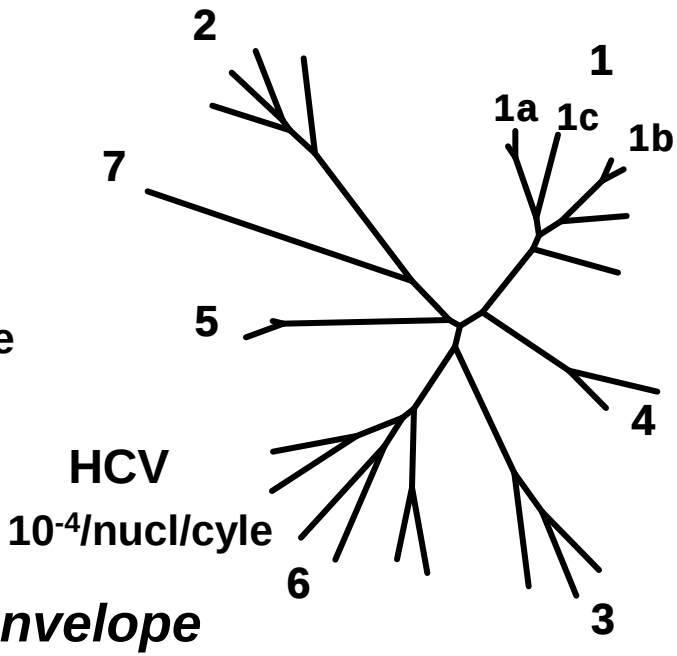
- **High genetic diversity with a high mutation rate**

Genetic Diversity



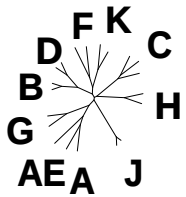
HBV

10^{-5}/nucl/cyle



HCV

10^{-4}/nucl/cyle



HIV

10^{-5}/nucl/cyle

- ***Highly variable envelope proteins and other regions of viral genome***
- ***Humoral and cellular immune escape mutants***

- ***Target conserved regions (T > B cells)***
- ***Raise genetic barrier for escape mutations by inducing a strong & broad immunity***

Barriers ***Solutions***

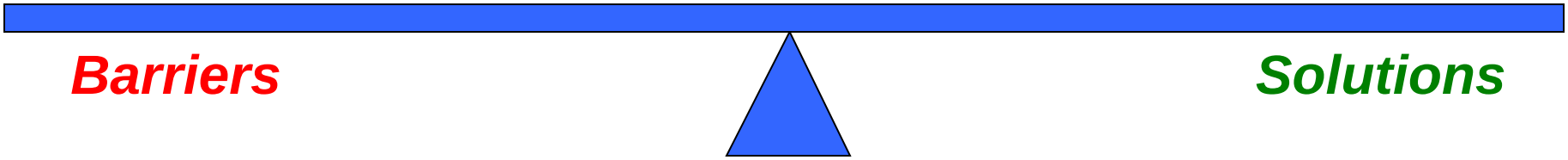
HCV Vaccine: Barriers & Solutions

- High genetic diversity with a high mutation rate
- **Humoral response in viral clearance?**

Humoral Immune Response

- ***Slow and weak anti-envelope response during primary infection***
- ***Hypervariable regions and hyperglycosylation of envelope proteins***
- ***Non-neutralizing and interfering antibodies***
- ***Evasion from neutralizing antibodies by complexing with lipoproteins***

- ***Presence of neutralizing antibodies & highly immunogenic formulation for antibody induction***
- ***Immunogens that can induce broadly neutralizing antibodies***
- ***Neutralizing antibodies at post-cell binding step***



Barriers ***Solutions***

HCV Vaccine: Barriers & Solutions

- High genetic diversity with a high mutation rate
- Humoral response in viral clearance?
- **High propensity for chronic persistent infection**

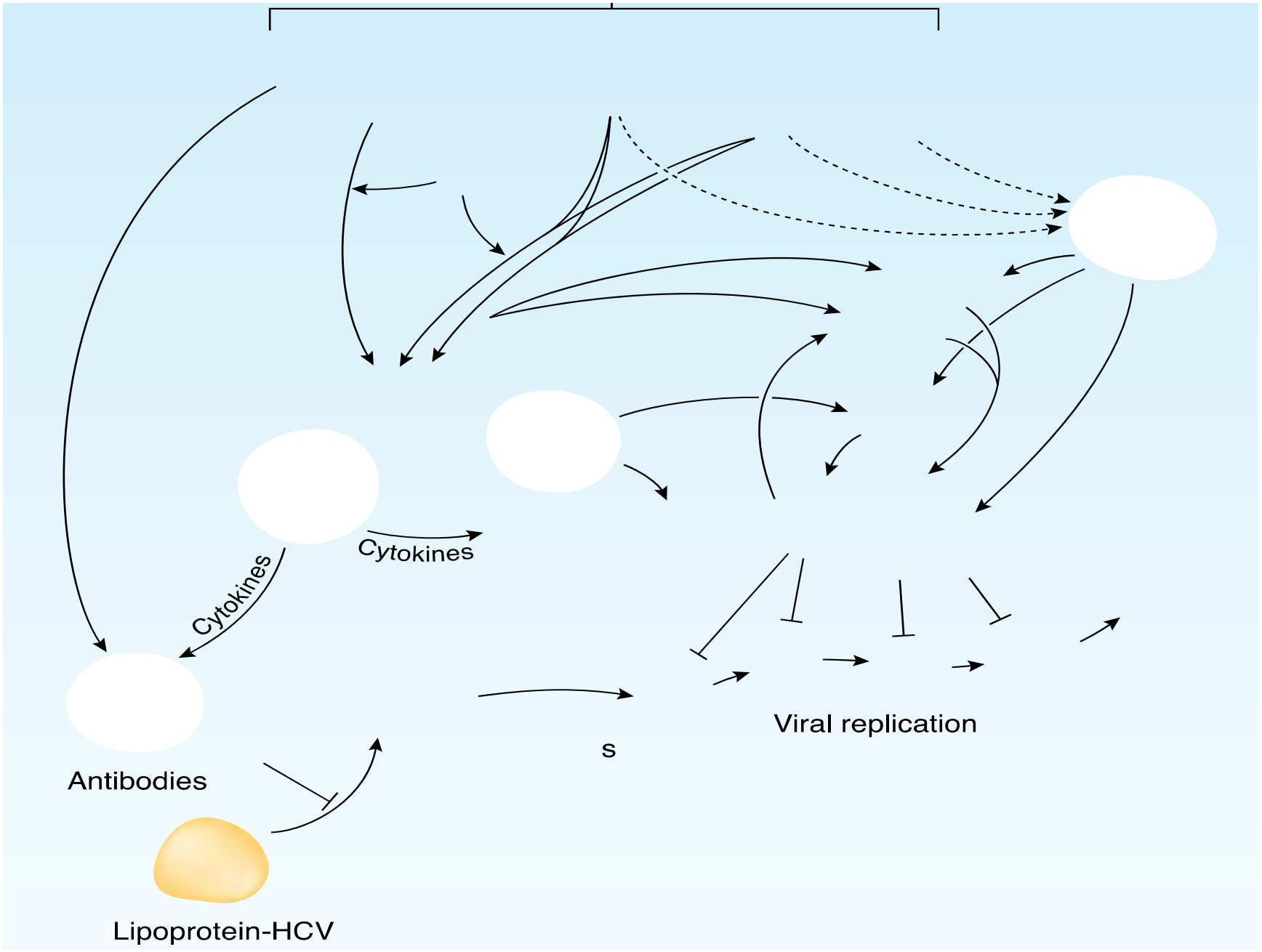
HCV Vaccine: Barriers & Solutions

- High genetic diversity with a high mutation rate
- Humoral response in viral clearance?
- High propensity for chronic persistent infection
- **Protective immunity**
  - **Existence of protective immunity after recovery from natural infection?**
  - **Correlates of protection and mechanisms of viral clearance:**
    - **T-cell immunity: CD4 and CD8**
    - **Innate immunity: IFN-λ and NK cells**

HCV Vaccine: Testing Barriers

- **In vitro model systems: testing of neutralizing antibodies and generation of attenuated virus**
  - **NOB assay, HCV-LP, HCVpp, HCVcc**
- **Lack of convenient small animal models for challenging studies**
  - **Chimpanzees: severe restrictions**
  - **Chimeric human uPA/SCID mice**
  - **Genetically engineered mice**

HCV Vaccine Candidates



Liang, Nature Medicine 2013

HCV Vaccine Candidates

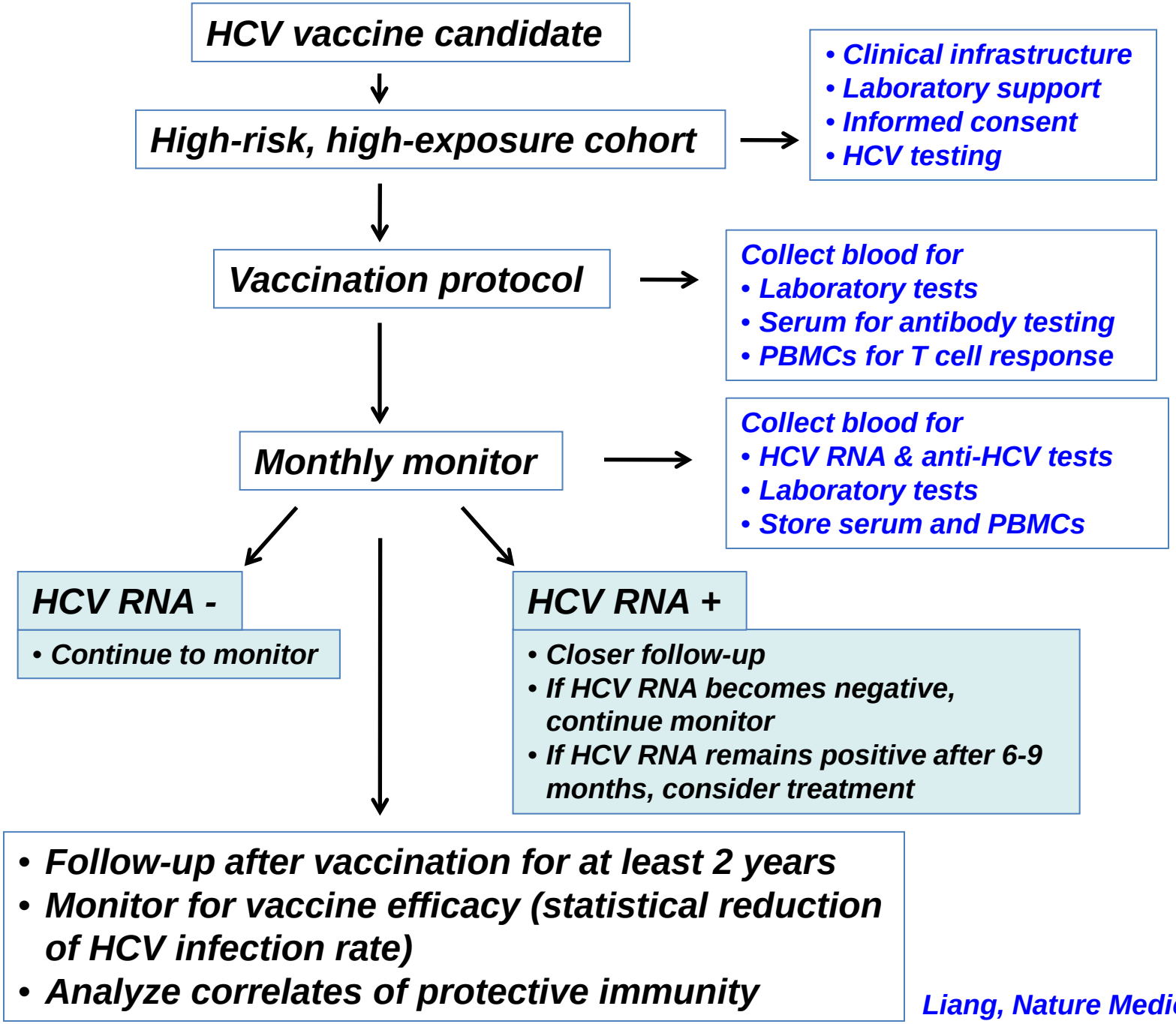
- **Chimpanzee studies**
  - **gpE1-E2 with adjuvant**
  - **core with adjuvant**
  - **HCV-like particles (core-E1-E2) with adjuvant**
  - **DNA prime and viral vectors (adenovirus, MVA, VV)**
- **Human trials**
  - **gpE1-E2 with MF59 adjuvant**
  - **NS3-NS5B (Ad3Ch3 prime and MVA boost)**

Choo et al, PNAS 1994; Frey etal, Vaccine 2010; Drane et al Hum Vaccine 2009; Leroux-Roels et al, Vaccine 2004; Elmowalid et al, PNAS 2007; Folgori et al, Nat Med 2006; Rollier et al, Hepatology 2007; Youn et al, J Virol 2008; Barnes et al, Sci Transl Med 2012; ClinicalTrails.gov)

Clinical Trial Design

- **High-risk groups**
  - **IV drug users and sex workers (poor compliance)**
  - **Health-care workers and public servants (low incidence of infection)**
  - **Sexual contacts of HCV-infected persons (low incidence of infection)**
  - **HIV infected persons with above risk factors (lower vaccine response)**
- **High-endemic areas**
  - **lack of infrastructure, ethical and regulatory concerns**

Sample size: prevalence, exposure frequency, infectivity, chronicity, vaccine efficacy; 500 - 10,000 people (Strickland et al, Lancet Infect Dis 2008)

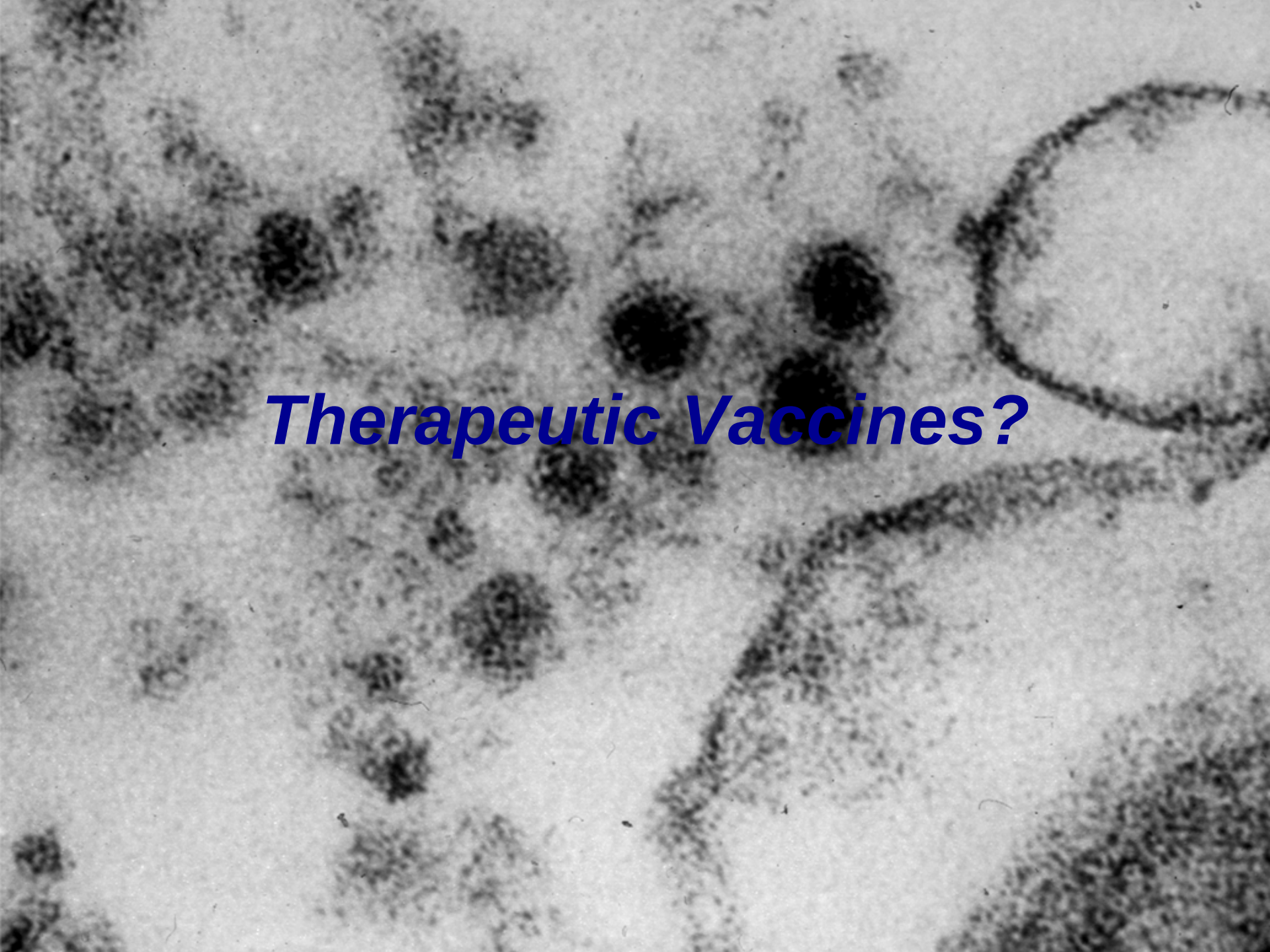


Liang, Nature Medicine 2013

Cost-Effectiveness of HCV Vaccine

Populations at risk:	Cost-effectiveness
IV drug users	High
Health-care workers	Medium
Public servants	Low to medium
Sex workers & MSM	Medium
Sexual partners of HCV infected persons	Low to medium
Children born to HCV infected mothers & household contacts	Low to medium
HIV infected persons with above risk factors	High

Strickland et al, Lancet Infect Dis 2008; Krahn et al, Vaccine 2005


Therapeutic Vaccines?

HCV Vaccines: Summary

- **Sterilizing immunity probably not possible**
- **Prevention of chronicity and disease**
- **May need to target both T and B cell immunities**
- **Clinical trials difficult to design and conduct**
- **Probably cost-effective in high-risk populations**