

Panel 1: Encouraging scientific innovation.

## **National Vaccine Plan (Draft) -**

**Goal 1: Develop New and Improved Vaccines.**

**(ties to Goal 3: Support informed vaccine decision-making by the public, providers, and policy-makers.)**

**Edward Mocarski, Distinguished Fellow**

**MedImmune Vaccines, wholly owned by AstraZeneca.**

**Emory Vaccine Center, Emory University (on leave)**

**Stanford University (Professor Emeritus)**



# What are the research challenges of bringing new vaccines to the public?

1. Public health awareness - perceived risk.
2. Economic plan - willingness to invest in R&D.
3. Understanding the natural immune control of disease.
4. Design - antigen, adjuvant, vector, attenuated pathogen.
5. Pre-clinical evaluation - safety/immunogenicity in animals.
6. Clinical evaluation - safety/immunogenicity in humans.
7. Protective immunity - experimental or natural challenge.

Where is the bottle neck?

1. Public health awareness - perceived risk.

*(Public and professional awareness needs to be increased in advance of any vaccine initiative to muster support.)*

1. Economic plan - willingness to invest in R&D.

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3. Design - antigen, adjuvant, vector, attenuated pathogen.

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6. Protective immunity - experimental or natural challenge.

*(Protective immunity in humans does not necessarily follow from success in animal models - too few natural immunity studies in humans)*

# Public health awareness.

Understanding of infectious disease risk varies dramatically within the society, among lay public as well as professionals.

News accounts increase awareness (outbreaks).

Philanthropic organizations, professional societies and CDC hold the responsibility for dissemination of information.

Advocacy groups increase awareness for some diseases.

Visibility of affected populations influences awareness.

# Vaccine Innovation Requires Sound Information about Human Immunity

Immunological control of infectious diseases - getting better for those agents controlled by cellular immunity.

Quality of the T cell response.

Mechanisms of clearance.

Collaboration of Innate and Adaptive Responses.

Vaccine design requires identification of relevant antigen and a means to make it immunogenic.

Adjuvants effect on antigen presenting cells may be cytokine activation or broader effects including cell death.

Continued inability to reproduce natural immunity.

# Existing IOM Recommendations include Prophylactic ID Vaccine approaches with non-ID Therapeutic Vaccines.

## Most Favorable

- \* Cytomegalovirus vaccine given to 12-year-olds.
  - \* Influenza virus vaccine given to the general population.
  - \* Insulin-dependent diabetes mellitus therapeutic vaccine.
  - \* Multiple sclerosis therapeutic vaccine.
  - \* Rheumatoid arthritis therapeutic vaccine.
  - \* Group B streptococcus vaccine to be administered to pregnant women and high-risk adults.
    - \* Streptococcus pneumoniae vaccine to be given to infants and 65-year-olds.

## More Favorable

- \* Chlamydia vaccine given to 12-year-olds.
  - \* Helicobacter pylori vaccine given to infants.
  - \* Hepatitis C virus vaccine given to infants.
  - \* Herpes simplex virus vaccine given to 12-year-olds.
  - \* Human papillomavirus vaccine given to 12-year-olds.
  - \* Melanoma therapeutic vaccine.
  - \* Mycobacterium tuberculosis vaccine given to high-risk populations.
  - \* Neisseria gonorrhoeae vaccine given to 12-year-olds.
  - \* Respiratory syncytial virus vaccine given to infants and 12-year-olds.

## Favorable

- \* Parainfluenza virus vaccine given to infants and women in pregnancy.
- \* Rotavirus vaccine given to infants.
- \* Group A streptococcus vaccine given to infants.
- \* Group B streptococcus vaccine given to high-risk adults and either 12-year-old girls or women during their first pregnancy.

## Less Favorable

- \* *Borrelia burgdorferi* vaccine given to resident infants and migrants of any age in high-risk geographic areas.
- \* *Coccidioides immitis* vaccine given to resident infants and migrants of any age in high-risk geographic areas.
- \* Enterotoxigenic *Escherichia coli* vaccine given to infants and travelers.
- \* Epstein-Barr virus vaccine given to 12-year-olds.
- \* *Histoplasma capsulatum* vaccine given to resident infants and migrants of any age in high-risk areas.
- \* *Neisseria meningitidis* type b vaccine given to infants.
- \* *Shigella* vaccine given to infants and travelers, or travelers only

# Balance Prophylactic ID Vaccine approaches with Therapeutic Vaccines.

NOT ON LIST (gut likely to be highly valuable based on success of HBV and HPV prophylactic vaccines):

HCV therapeutic vaccine (to reduce chronic disease). *(Use existing HBV and HPV vaccines in therapeutic mode)*

CMV therapeutic vaccine (to reduce transplacental transmission and opportunistic infection).

EBV therapeutic vaccine (to reduce proliferative disease and malignancies).

*Helicobacter pylori* therapeutic vaccine (to reduce gastric ulcers and malignancy).



# Immune Control of Cytomegalovirus Infection.

## Primary Infection:

Mucosal Exposure to CMV

ê |—T cells

Replication (amplification)

ê |—T cells

1° Dissemination (via blood stream)

ê |—T cells

Seed Lymphoid Organs

ê |—T cells

2° Dissemination (via blood stream)

ê |—T cells

ê |—Ab or T cells

Seed S.G./M.G./Kidney

Placenta

ê |—T cells

ê |—Ab or T cells

Shedding

Transmission

(infect newborn)

(infect fetus)

Adaptive immune control within weeks following infection.

- Antibody (Ab)

high avidity

neutralizing

- T lymphocytes

CD4 (helper T cells)

CD8 (cytotoxic T cells)

- NK cells

# Immune Control of Cytomegalovirus Infection.

## Recurrent Infection:

Mucosal Re-exposure to CMV or

Reactivation from Latency (BM)

ê-Ab      ê      |-T cells

Replication (amplification)

|-T cells      ê

1° Dissemination

ê-T cells      ê

Seed Lymphoid Organs

ê-T cells      ê

2° Dissemination (via blood stream)

|eT cells      ê      |-Ab/T cells

Seed S.G./M.G./Kidney

Placenta

|êT cells      ê      |-Ab/T cells

Shedding

Transmission

T cells play an predominant role in resolving primary or recurrent infection.

- Adoptive T cell transfer
- Immunosuppression of T cells (not Ab) leads to CMV disease
- Differences at maternal-fetal interface?
- Passive Ab therapy or prophylaxis

# What type of CMV vaccine is achievable?

A vaccine should be able to prime and/or boost immunity, and *must* be safe.

- Live attenuated - how balance safety and efficacy?
- Subunit/Adjuvant - success in preventing other infectious diseases has given this strategy the highest likelihood (gB vaccine candidates).

- Vectored:

Inert/inactivated - a vector that provides adjuvant activity (e.g. Baker's yeast-vectored HCV vaccine).

Virus-like particle - a vector based on another virus particle (HBV, HPV)

Replication defective - a vector that can infect cells and express antigens without forming progeny (e.g adenovirus)

Replication competent - a vector that is already used as a vaccine for another infectious disease. (e.g. VZV, measles).

# How to assess immune correlates of protection

Animal Models certainly provide insights into vaccine design but have not been valuable for evaluating protection from CMV (species restriction of viral replication).

Preclinical characterization in animal models is therefore restricted to measuring the production of antibodies or T cells with biological properties that correlate with expected immune mechanisms.

*Need better ways to evaluate the priming and boosting potential of candidate vaccines using human immune cells.*

Immune cross section evaluation (Quality of immunity):

Neutralizing Ab.

Multiple cytokine production by CD4 and CD8 cells.

T cell function (killing, inhibition of viral replication).

*Can evaluation correlates of protection in different viral diseases become a science?*