Advances in Vaccine and Immunization Technologies

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May 6, 2013

Conflict of Interest Statement

Presenter Disclosure Information

Cristina Cassetti, Ph.D.

Title: Advances in Vaccine and Immunization Technologies

- The presenter has no financial conflicts of interest.
- The lecture was prepared as part of the presenter's official capacity as a U.S. government employee.

Considerations for vaccine development

- Breadth of immunity
- Durability of immunity
- Ease of dosing
- Cost
- Temperature stability
- Target population

Approaches to Vaccine Development

- Design
- Manufacturing
- Delivery
- Stabilization
- Evaluation

Vaccine Design

Conventional Approaches to Vaccine Design

- Killed/inactivated vaccines
  - rabies, Salk polio
- Attenuated vaccines
  - MMR, Sabin polio
- Subunit vaccines
  - Hep B
- Conjugate vaccines
  - *Haemophilus influenzae* type B–Hib, Pneumoccocal conjugate vaccine

Replicate the type of immunity elicited by natural infection and disassociate it from pathogenic events.

Example of vaccines resistant to conventional approaches

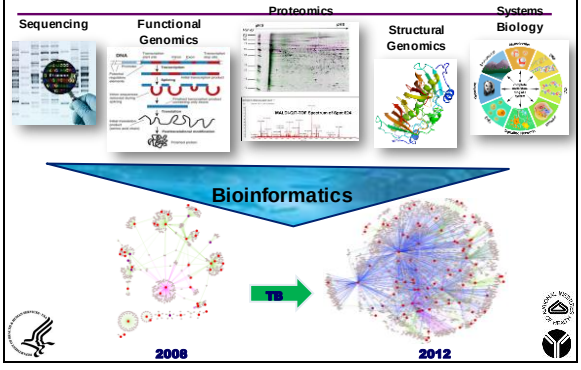
- HIV
- Malaria
- Dengue
- HSV

Experimental Approaches to Vaccine Design

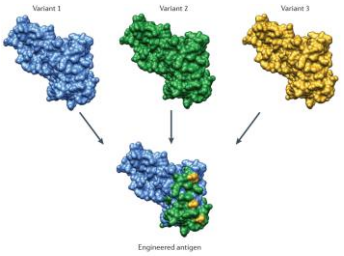
- Antigen identification
- Synthetic peptide vaccines
- Vector-based vaccines
- Recombinant subunit vaccines
- DNA and RNA vaccines
- Combination vaccines (prime/boost)

Rational vaccine design such as *de novo* constructs which optimize immune responses and/or target delivery.

Antigen Identification in the Genomics Era



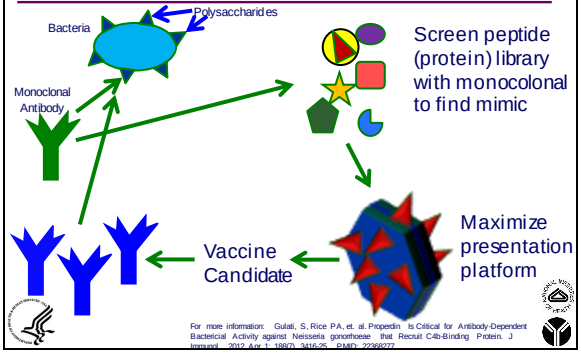
Structural vaccinology



Nature Reviews | Microbiology

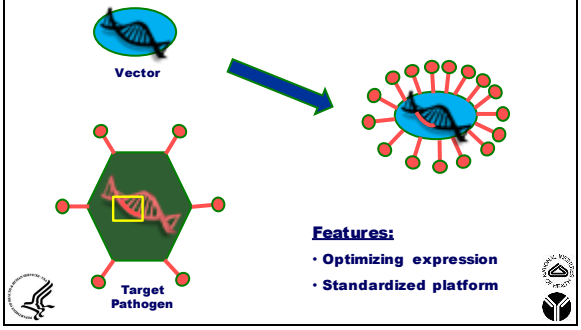
Philip R. Dormitzer, Guido Grandi & Rino Rappuoli
December 2012

Peptide "mimic" vaccine



For more information: Gulati, S, Rice PA, et. al. Properdin Is Critical for Antibody-Dependent Bactericial Activity against Neisseria gonorrhoeae that Recruit C4b-Binding Protein. J Immunol. 2012 Aug 1; 189(3): 3416-25. PMID: 22908277

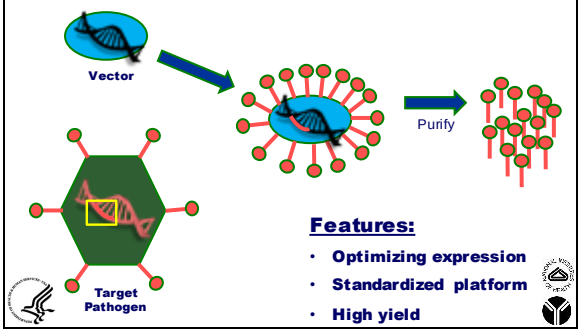
Vector-Based Vaccines



Features:

- **Optimizing expression**
- **Standardized platform**

Recombinant Subunit Vaccines



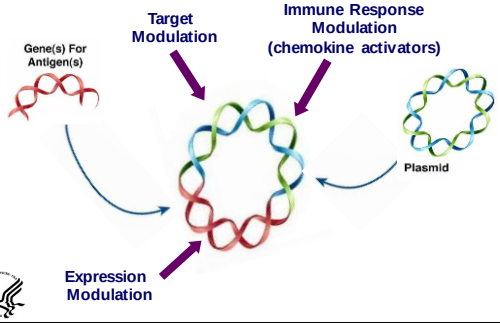
Features:

- Optimizing expression
- Standardized platform
- High yield

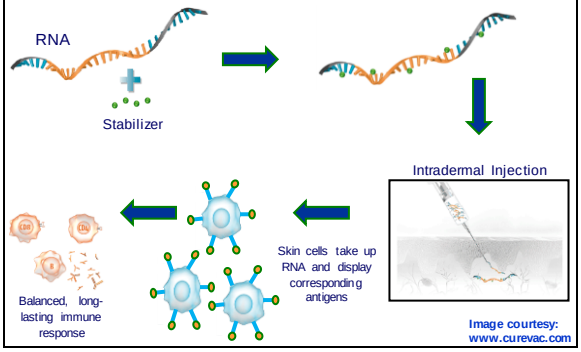
Examples of recombinant subunit vaccines

Expressed with recombinant insect viruses (baculovirus)

DNA Vaccines: Maximizing Delivery and Expression

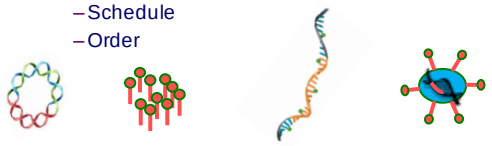


RNA Vaccine



Prime-Boost

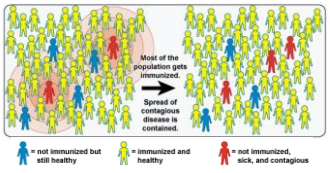
- Individual
  - Which combination maximizes immune response?
    - Considerations:
      - Dose
      - Schedule
      - Order



For more on prime-boost strategy, see: Belshe RB, Frey SE, et. al., Safety and immunogenicity of influenza A H5 subunit vaccines: effect of vaccine schedule and antigenic variant. J Infect Dis. 2011 Mar 1;203(5):666-73. PMID: 21282194

Prime-Boost

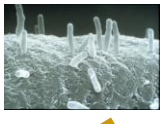
- Population
  - What are the implications of priming a population to prepare for a potential pandemic?



Vaccine manufacturing

Current manufacturing practices: eggs or cultured cells

Vaccine Manufacturing: Plant-based



- Transfection process with agrobacterium
- Produces high yield of protein
  - Pilot yields of protein >200mg/kg fresh leaf weight
  - Goal: 1kg of purified vaccine protein, which equates to about 10 million doses, in one month
- Project GreenVax video: **http://tinyurl.com/ctl2wes**

On an Industrial Scale

www.caliberbio.com

Malaria Vaccine in Goats' Milk

Photo courtesy: Houston Chronicle/Texas A&M Reproductive Sciences Laboratory

- Transgenic female goats express malaria antigen in their milk
- A single goat typically produces 3 liters of milk per day, and will yield about 3 kilograms of protein per year

For more information: http://www.chron.com/news/houston-texas/article/A-amp-M-goats-modified-to-carry-malaria-vaccine-3378385.php

Vaccine Manufacturing: *Agaricus* Mushroom

- Untapped resource for rapid recombinant protein expression
- Can be grown underground
- 2.5 million fold replication from single spore within 17 days

Single use bioreactor

- Portable manufacturing
- Single-use technologies
- 50-2000 liters
- Automated
- Eliminates clean- and steam-in-place and clean room infrastructure
- Simplifies facility design
- Reduces mfg footprint

www.xcellerex.com

Vaccine Delivery

Cutaneous delivery

- Electrode array
- Patch
- Needle-free

Photo credit Pharmajet

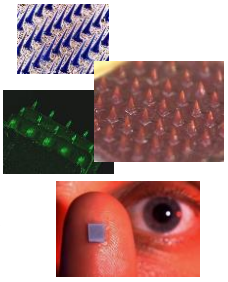
Photo Credit Ichor: TriGrid™

Photo Credit Zosano: Macroflux®

Photo credit Iomai Corp.

Photo Credit Biovalve: Mini-ject

Microneedles



- Stage: Preclinical development
- Features
  - Length formulated to be long enough to penetrate the stratum corneum and viable epidermis but short enough to avoid pain.
  - Needles are dip-coated in vaccine that dries and then rapidly dissolves in skin.

Photo Credits: Mark Prausnitz, Ph.D., Georgia Tech
Richard Compans, Ph.D. Emory University

For more information, see: Koutsonanos, DG, Vassilieva, EV, et. al., Delivery of a subunit influenza vaccine to skin with microneedles improves immunogenicity and long-lived protection. Scientific Reports. 2012, April 12; Article number 357, doi: 10.1038/srep 00 35 7

Mucosal Delivery

- Edible vaccines
- Spray injectors
  - new adjuvants, mucoadhesiv
- Intranasal
- Sublingual

Photo Credit Optinose
www.optinose.com/products/technical-overview

Photo Credit: MedImmune

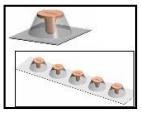


Photo credits Mystic Pharmaceuticals: VetiDoser

Nanoparticles

Schematic of Particle Replication in Non-wetting Templates (PRINT) micro-molding methodology

"Particle Engineering for Inhalation Formulation and Delivery of Biotherapeutics"; Mack, P at al. *Inhalation*, August 2012.
www.inhalationmag.com; www.liquidia.com

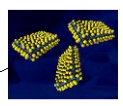
Vaccine stabilization

Benefits of thermostable vaccines

- Low er cost of cold chain
- Less vaccine w astage due to expiration
- Reach the unreachable populations
- Few er or no turnovers of stockpiled vaccines
- Ensure the potency of vaccines w hen cold chain breaks

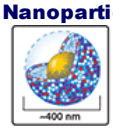
Excipient enhanced Lyophilization

Protein coated microcrystals



Stabilization

Nanoparticles



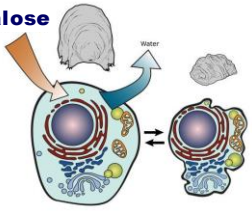
Glassification

Sugar to stabilize vaccines

Tardigrades

- **Extremophile**
- **Dehydrated (3% water) can live up to 10 years**

trehalose



Silk protein to thermo stabilize vaccines

www.vaxess.com

Vaccine evaluation

Plaque Reduction Neutralization Assays

Multi-parametric Flow cytometry

- For analy zing multiple cell markers in single specimen
- Application of genomics/proteomics for potential correlates/surrogate markers
- Robotics for large scale/assay evaluations- ELISPOT and ICC

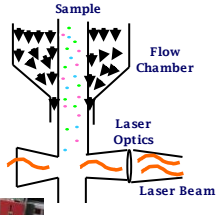
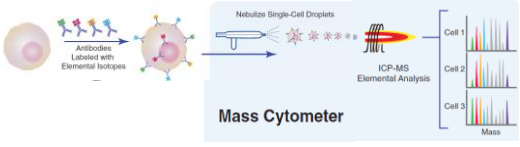


Photo Credit: NIAID

Single cell Mass-cytometry (CyTOF)



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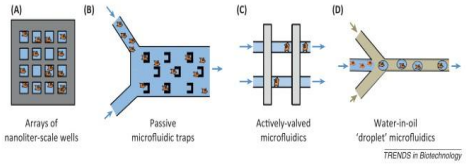
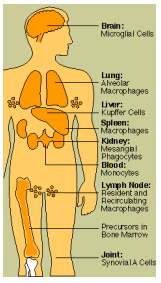
Tools for single cell analysis



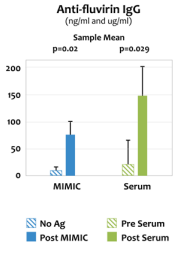
- **sample sparing (10^2-10^5 cells/assay)**
- **cost sparing**
- **time sparing**

Trends in Biotechnology Volume 31, Issue 5, 2013, 280 – 286C

Evaluation: Modular Immune In Vitro Construct (MIMIC™)

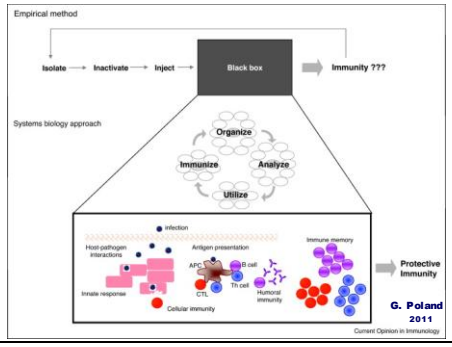


Immune systems in vitro- Clinical trial in a test tube for Influenza vaccines

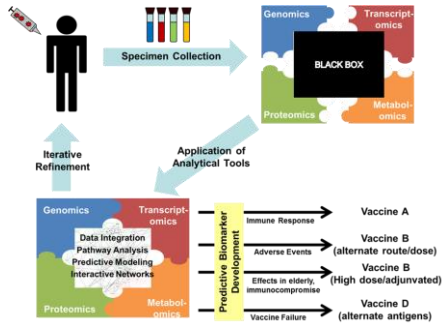


From: vaxdesign.com

Systems biology and vaccine evaluation



Personalize vaccines: the future of medicine?



Conclusions

- Many exciting advances in vaccine technologies
- Many technologies are available to design vaccines with desired features
- Advances in immunology, bioinformatics and systems biology should help us better understand what immune responses are protective and how to design better vaccines