Precision Vaccines: Using Adjuvants to Bring Precision Medicine to Vaccinology

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Many factors impact vaccine responses
Infectious Causes of Death are Most Common in Early Life

J Sepúlveda, and C Murray Science 2014;345:1275-1278
A range of interventions can confer passive and/or active immunity in early life

Kollmann, Kampmann, Mazamian, Marchant & Levy, *Immunity* 2017
### Challenges in Pediatric Vaccinology: Relative Lack of Early Immunization & Need for Multiple Booster Doses

<table>
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<tr>
<th>Vaccine</th>
<th>Birth (0 months)</th>
<th>1 mo</th>
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<th>15 mo</th>
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<th>19-23 mo</th>
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<td>Diphtheria, Tetanus, Pertussis (DTaP)</td>
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**Window of vulnerability**

**Lack of early immunization**

**Yearly seasonal dose**

**Two doses**

**For high risk groups**

Sanchez-Schmitz G, Levy O Sci Transl Med 2011
children all agree one shot is better than three
Activation of Pattern Recognition Receptors (e.g., TLRs) can enhance vaccine responses

Mills, KH Nat Rev Immunol 2011
Recently licensed adjuvanted vaccines

- **Cervarix**
  - Human papilloma virus vaccine
  - Adjuvant: MPLA (TLR4A)/Alum
  - Age: 10-64 years
  - 3 dose series

- **Heplisav**
  - Hepatitis B surface Ag
  - Adjuvant: TLR9 agonist (CpG)
  - Age: 18 years and older
  - 2 dose series (dose sparing)
Ontogeny of TLR Function

Th17 (extracellular microbes)

Th1 (intracellular)

Th1/IFN-\(\alpha\) (antiviral)

Pro-inflammatory

Anti-inflammatory

"Inflammaging"

Preterm  Term  1yr  2yr  Adult  Old  Older  Oldest
What are Precision Vaccines?

- “Precision Medicine refers to tailoring medical treatment to individual characteristics of each patient. It does not literally mean the creation of drugs ...unique to a patient, but rather the ability to classify individuals into subpopulations that differ in their ...response to a specific treatment.”
  {National Research Council}

- **Precision Vaccines:**
  - Take into account the target population
  - Formulated to selectively activate the immune system by targeting anatomic sites, cells and molecular pathways that generate a protective response
  - As needed, contain an **adjuvant** known to act optimally in the **target** population
• Boston Children’s Hospital, Division Infectious Diseases
• Support: internal/philanthropy
• Goal: Develop vaccines for vulnerable populations
• N >160: academia, government, consultants & industry
• Resources: admin, technical, bioinform, organizational, legal, & graphic
• Website: www.childrenshospital.org
• Program Coordinator Diana Vo
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• Twitter: @PrecVaccProgram
Modeling neonatal immune responses must take into account humoral & cellular differences.
BCG: proof of concept for neonatal immunization & heterologous immunity

- Live attenuated *Mycobacterium bovis*
- Activates multiple PRRs
- Most commonly administered vaccine
- >3 billion doses given (!)
- Efficacy vs disseminated dz/meningitis.
- Potential beneficial heterologous (“non-specific”) effects
- Reduces all cause mortality in 1st month of life (Aaby, *P J Infect Dis* 204:245)
- Innate training: NOD2-dependent epigenetic re-programming of monocytes (Kleinnijenhuis, *PNAS* 2012)
Age-specific adjuvant synergy for Human MoDC Activation: R848 (TLR7/8 agonist) & TDB (Mincle Agonist)

Van Haren et al., Age-specific Adjuvant Synergy: Dual TLR7/8 and Mincle Activation of Human Newborn Dendritic Cells Enables Th1-polarization, Journal of Immunology, 2016.

Age-dependent adjuvant action across *in vitro* platforms
Development of microphysiologic systems to model human vaccine responses
Creation of 3-dimensional microphysiologic tissue constructs

1. A. Primary human endothelium  B. Casting of human extracellular matrix  C. Assembly of Tissue Construct

2. A. Human mononuclear cells and intact plasma  B. Cell banking/cryopreservation  C. Magnetic cell sorting  D. Purity assessment by Flow Cytometry (QA/QC SOP)

3. Diapedesis of monocytes  Vaccine in 100% autologous plasma  Reverse transmigration of APCs

- Endothelium
- ECM cushion
- HLA-DR high
- CD86 high
- CD14neg/low
- CCR7+
- CD83+

4. Lymphocytes
Tissue constructs demonstrate age-specific differences in responses to Adjuvants.
TLR7/8 adjuvantation dramatically accelerates & enhances neonatal immune responses to Pneumococcal Conjugate Vaccine
New Adjuvant Permits Early Pneumococcal Immunization in Newborn Monkeys

Compound May Help Protect Human Infants Earlier with Fewer Doses
March 23, 2017

These preliminary results support the concept that immunization of newborn babies may be possible for certain diseases and could be lifesaving.

— Anthony S. Fauci, M.D., NIAID Director
Adjuvant Discovery Program
Systems Biology to Define Biomarkers of Newborn Vaccine Immunogenicity

Twitter: @hipcProject
Developing *Precision Vaccines*

**Develo</noscript>ing Precision Vaccines**

Hypothesis generating

Pre-clinical Targeted Human *In vitro* Models (newborn, elderly etc)

Licensed or novel vaccines

Appropriate animal models

Targeted Clinical Trial

Transcriptomics
Proteomics
Metabolomics

Systems Biology (OMICs)
Conclusions

• Need for vaccines to protect those with distinct immunity: newborns/infants, elderly, & immunocompromised.

• Current vaccine development does not fully account for age- and species-specificity.

• Novel approaches can accelerate, enhance, and de-risk vaccine development:
  – Age-specific *in vitro* systems employing primary human leukocytes and autologous plasma to model immune responses
  – Benchmarking new vs. licensed adjuvanted vaccines to accelerate translational development
  – Systems vaccinology- use of OMIC technologies to gain insight into adjuvant effects that correlate with protection
  – Age-specific adjuvants and adjuvantation systems to optimize immunogenicity and potentially to induce heterologous immunity/broad protection

• *Precision Vaccines Program* (PVP) at Boston Children’s Hospital provides administrative, intellectual, technical, biostatistical and graphic support to foster collaborative development of vaccines targeted towards vulnerable populations.

• Multi-disciplinary, collaborative efforts will inform a new generation of safe & effective targeted vaccines that protect the most vulnerable
Levy Lab

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- 3M Drug Delivery Systems (Mark Tomai)
- VentiRx (Rob Herschberg)
- Crucell (Johnson & Johnson)
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