Precision Vaccines: Using Adjuvants to Bring Precision Medicine to Vaccinology

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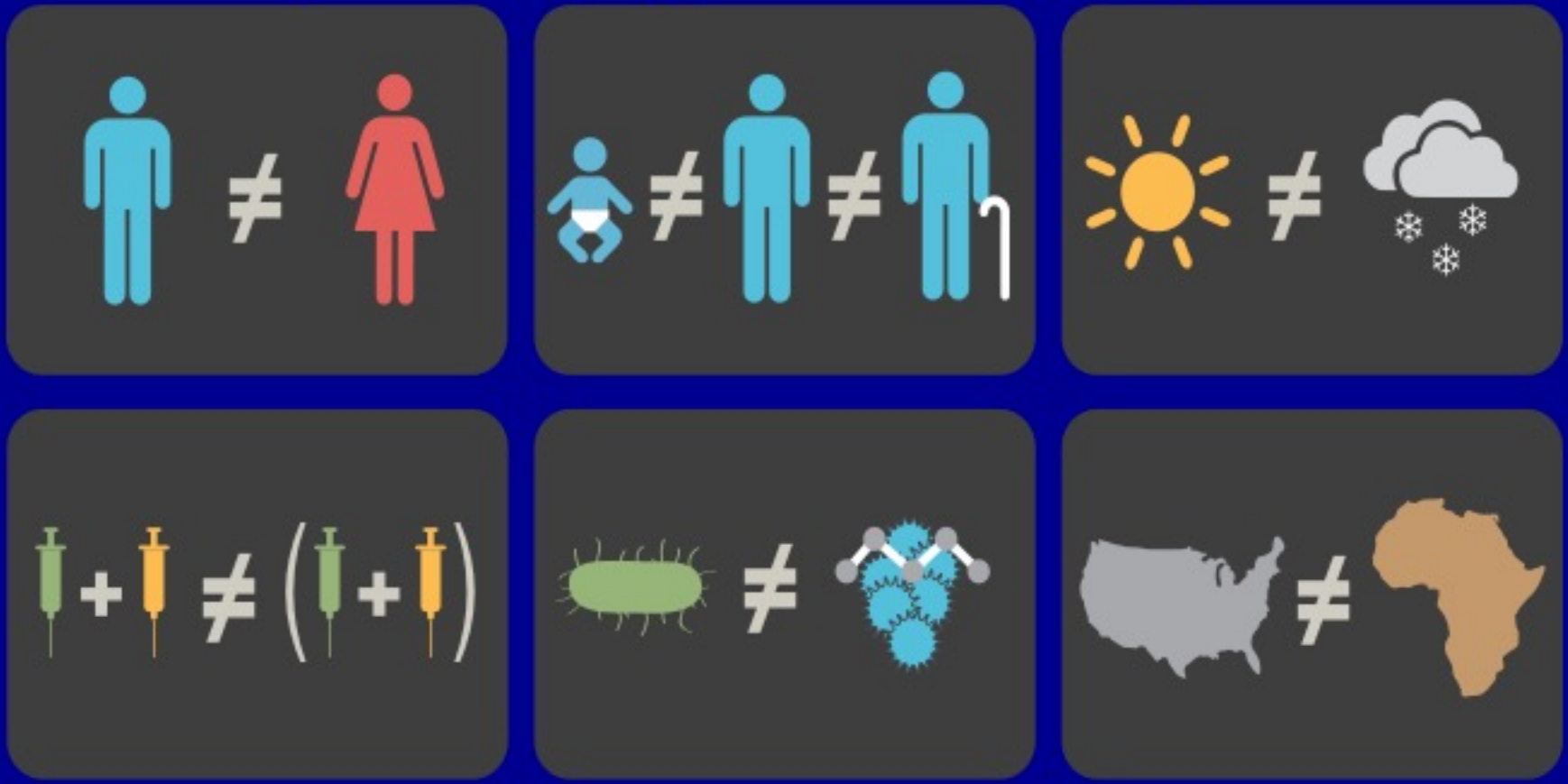
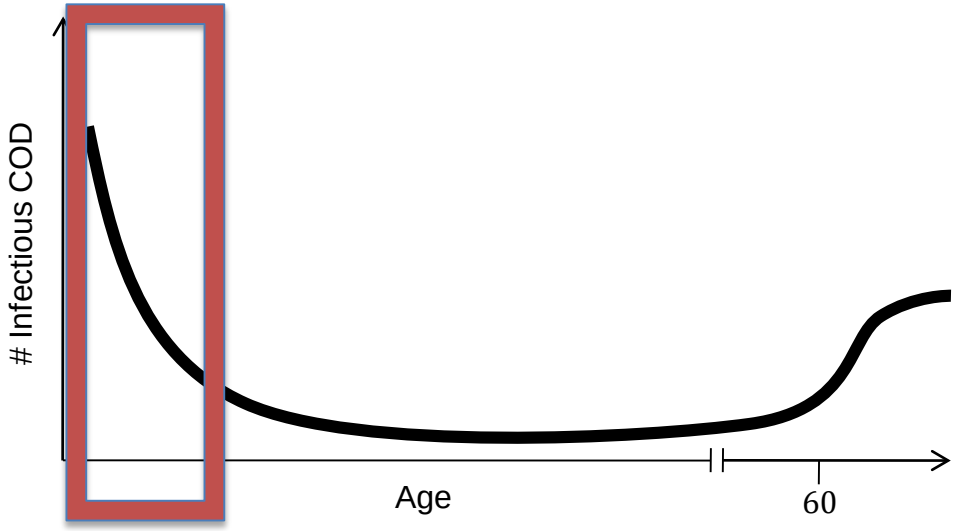
Many factors impact vaccine responses

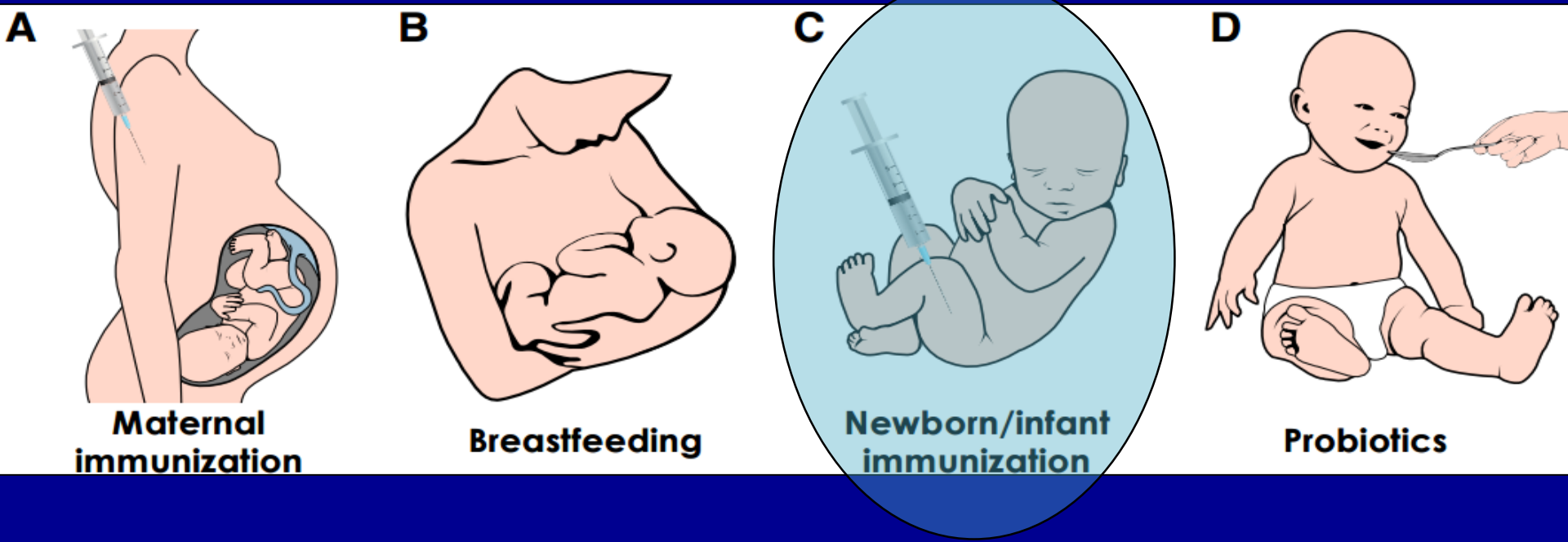


Infectious Causes of Death are Most Common in Early Life



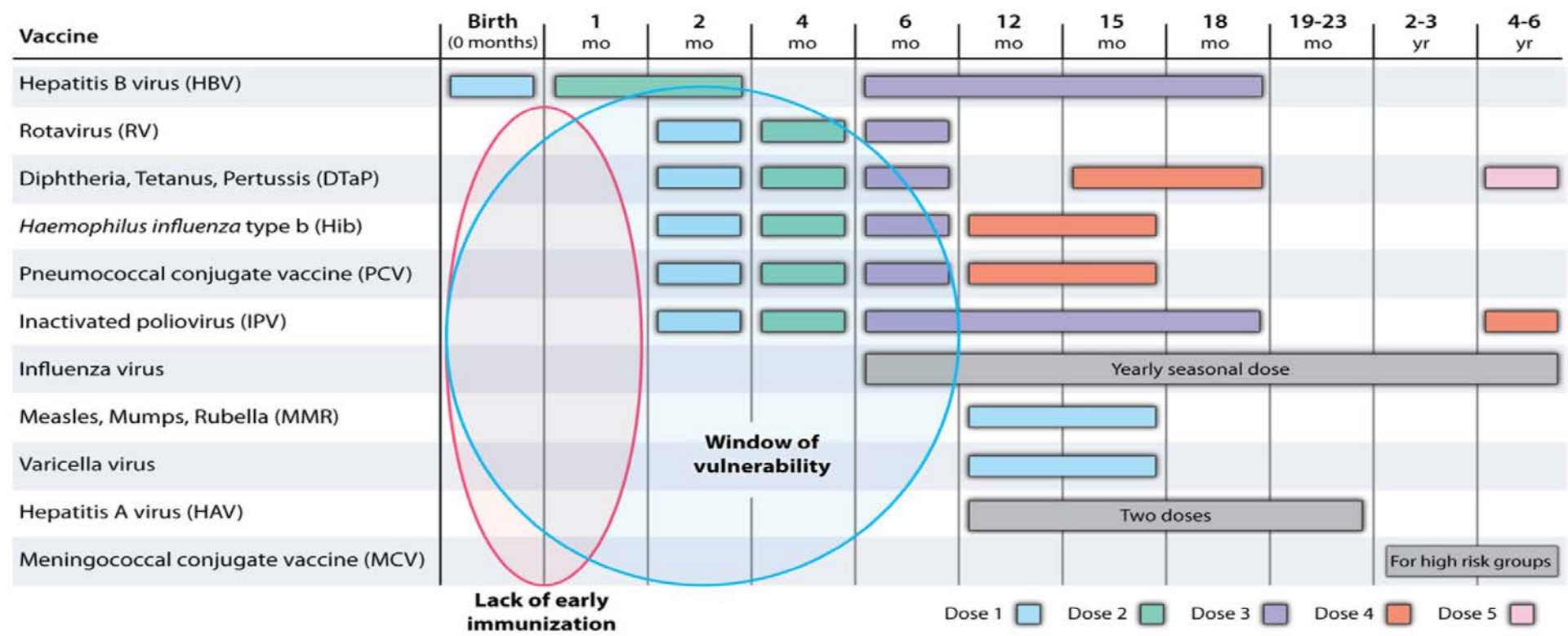
J Sepúlveda, and C Murray *Science* 2014;345:1275-1278

A range of interventions can confer passive and/or active immunity in early life



Kollmann, Kampmann, Mazamian, Marchant & Levy, *Immunity* 2017

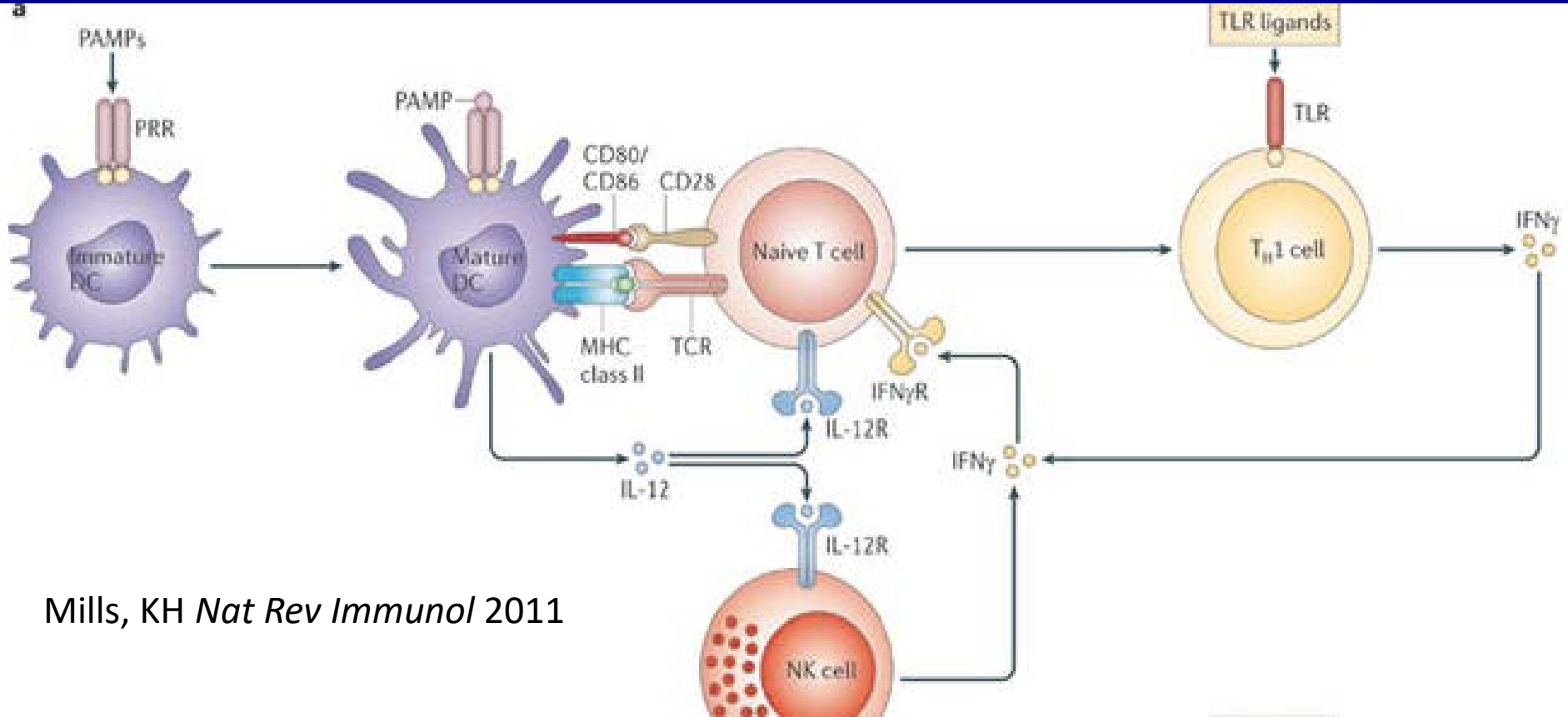
Challenges in Pediatric Vaccinology: Relative Lack of Early Immunization & Need for Multiple Booster Doses



Sanchez-Schmitz G , Levy O Sci Transl Med 2011

children all agree
one shot is better than three

Activation of Pattern Recognition Receptors (eg, TLRs) can enhance vaccine responses



Mills, KH *Nat Rev Immunol* 2011

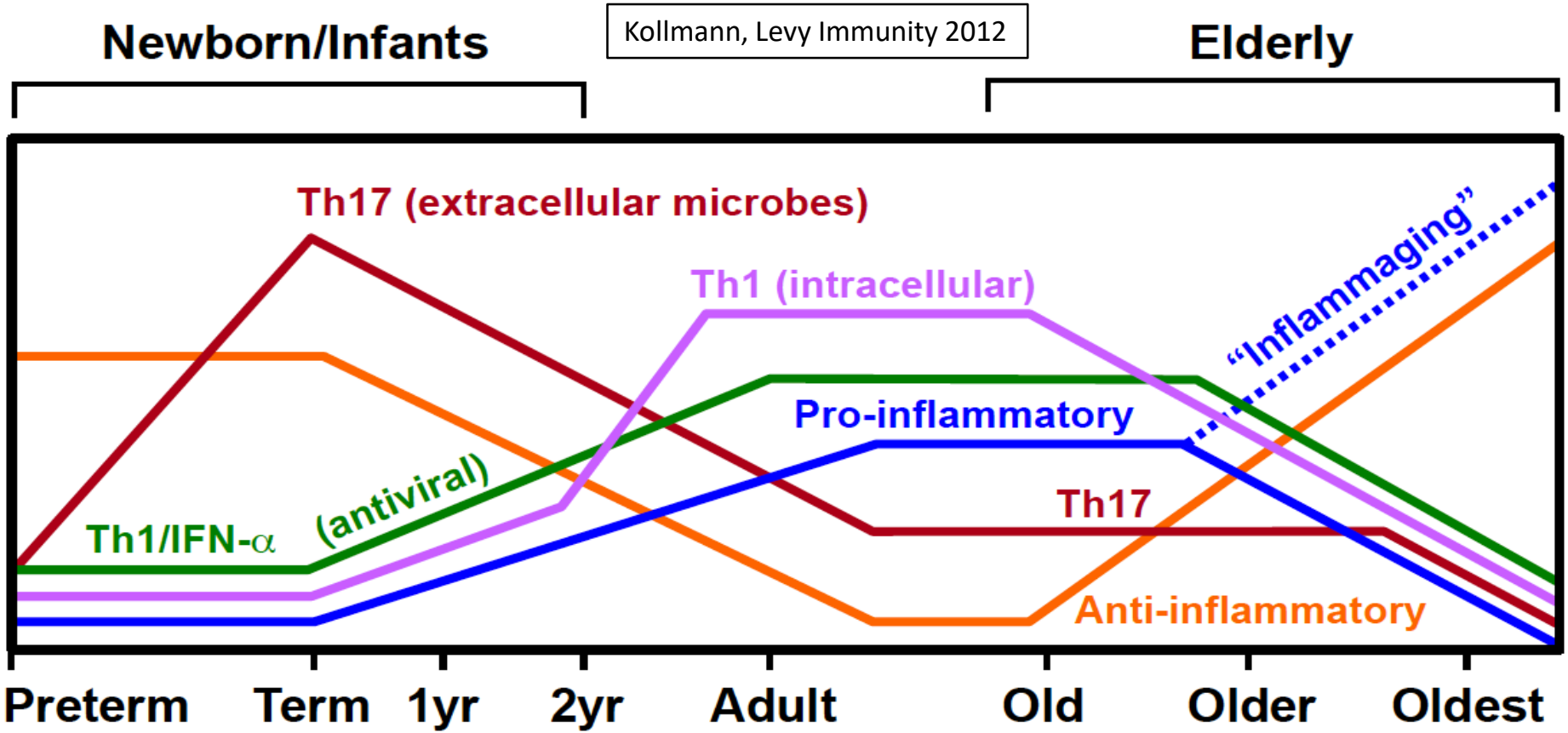
Recently licensed adjuvanted vaccines

- **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)

HEPLISAV-B™
Hepatitis B Vaccine (Recombinant), Adjuvanted

Ontogeny of TLR Function



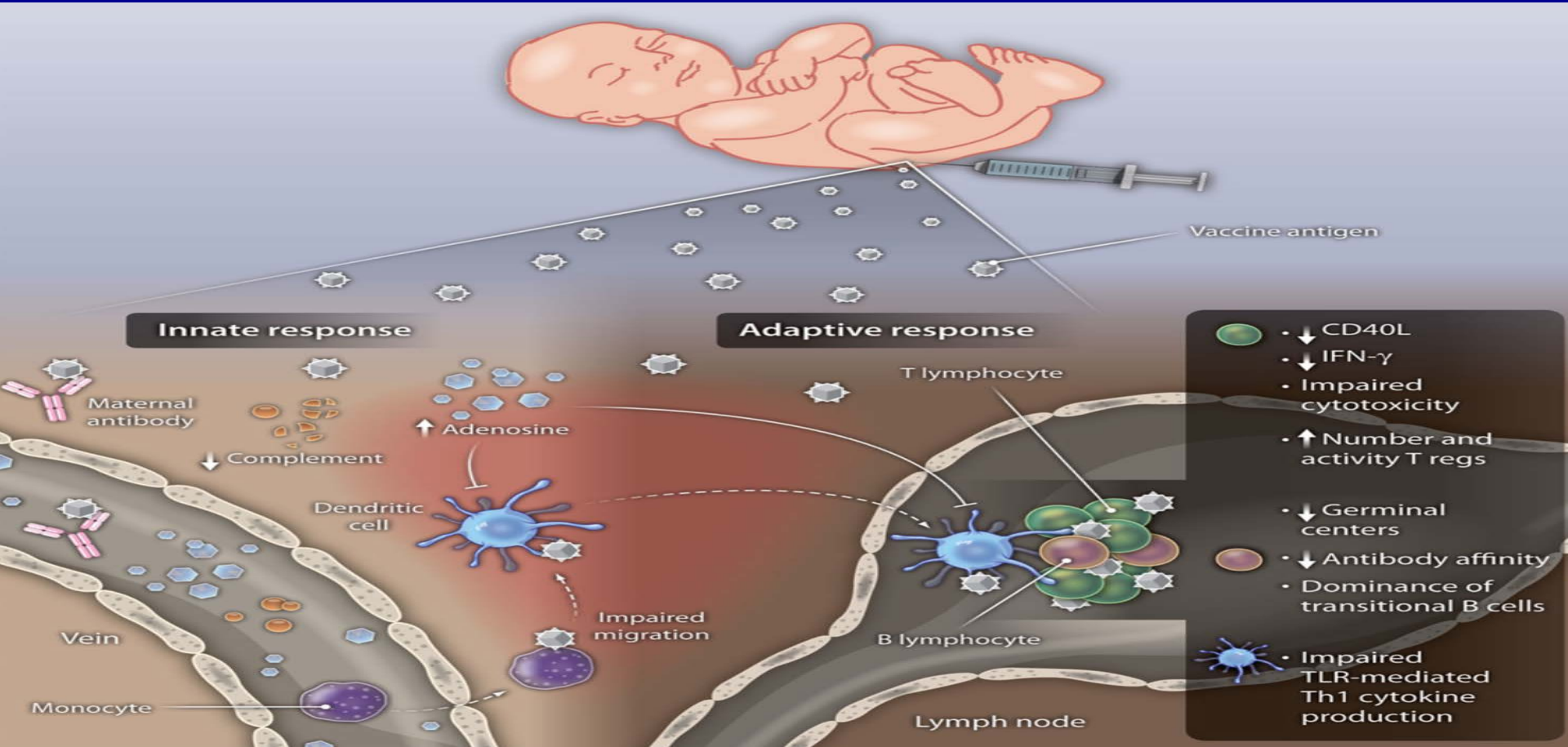
What are Precision Vaccines?

- "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

Precision Vaccines Program

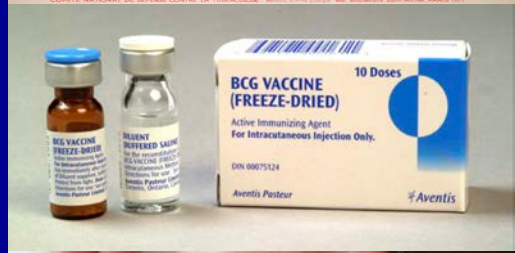
- Boston Children's Hospital, Division Infectious Diseases
- Support: internal/philanthropy
- Goal: Develop vaccines for vulnerable populations
- N >160: academia, government, consultants & industry
- Resources: admin, technical, bioinform, organizational, legal, & graphic
- Website: www.childrenshospital.org
- **Program Coordinator Diana Vo**
- **diana.vo@childrens.harvard.edu**
- **Twitter: *@PrecVaccProgram***

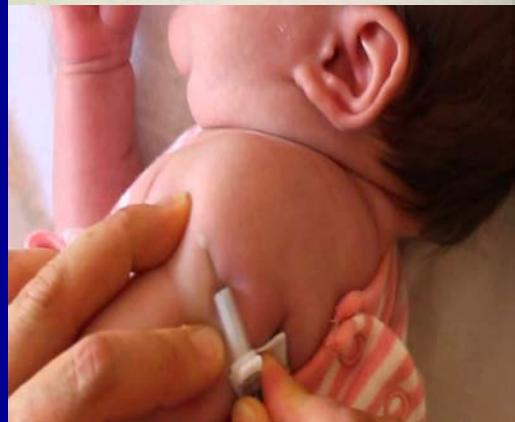
Modeling neonatal immune responses must take into account humoral & cellular differences



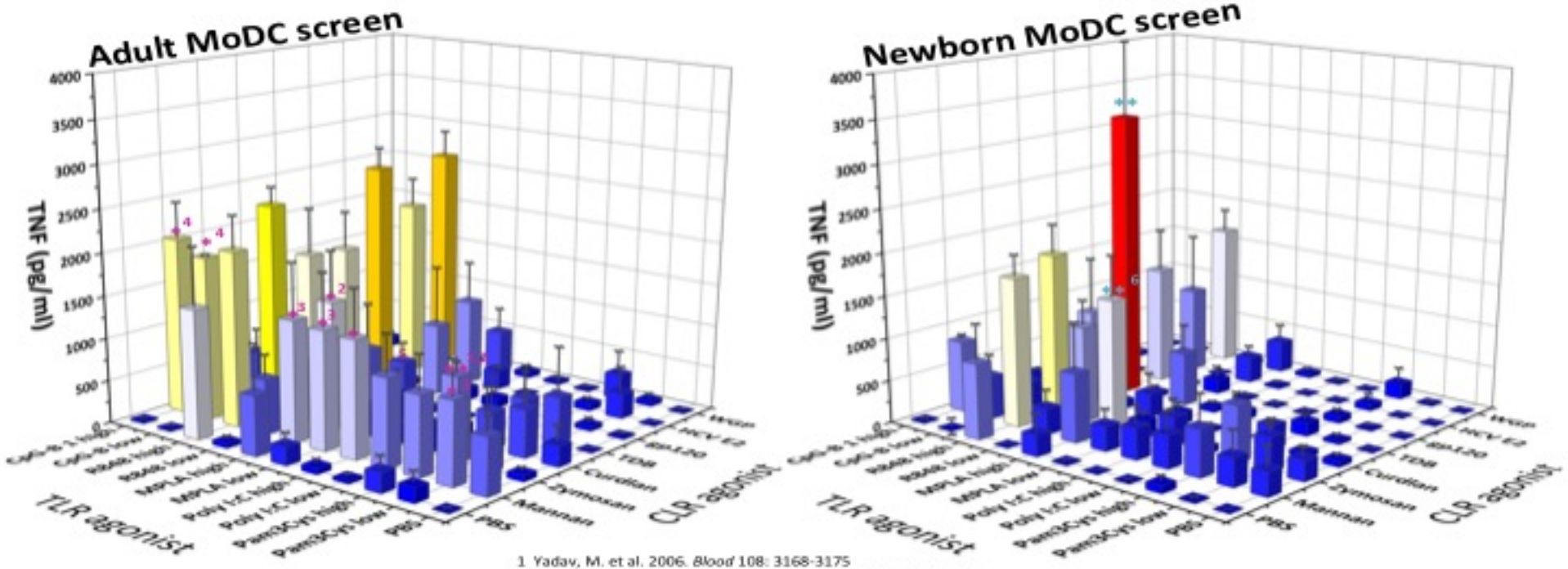
BCG: proof of concept for neonatal immunization & heterologous immunity

- 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)





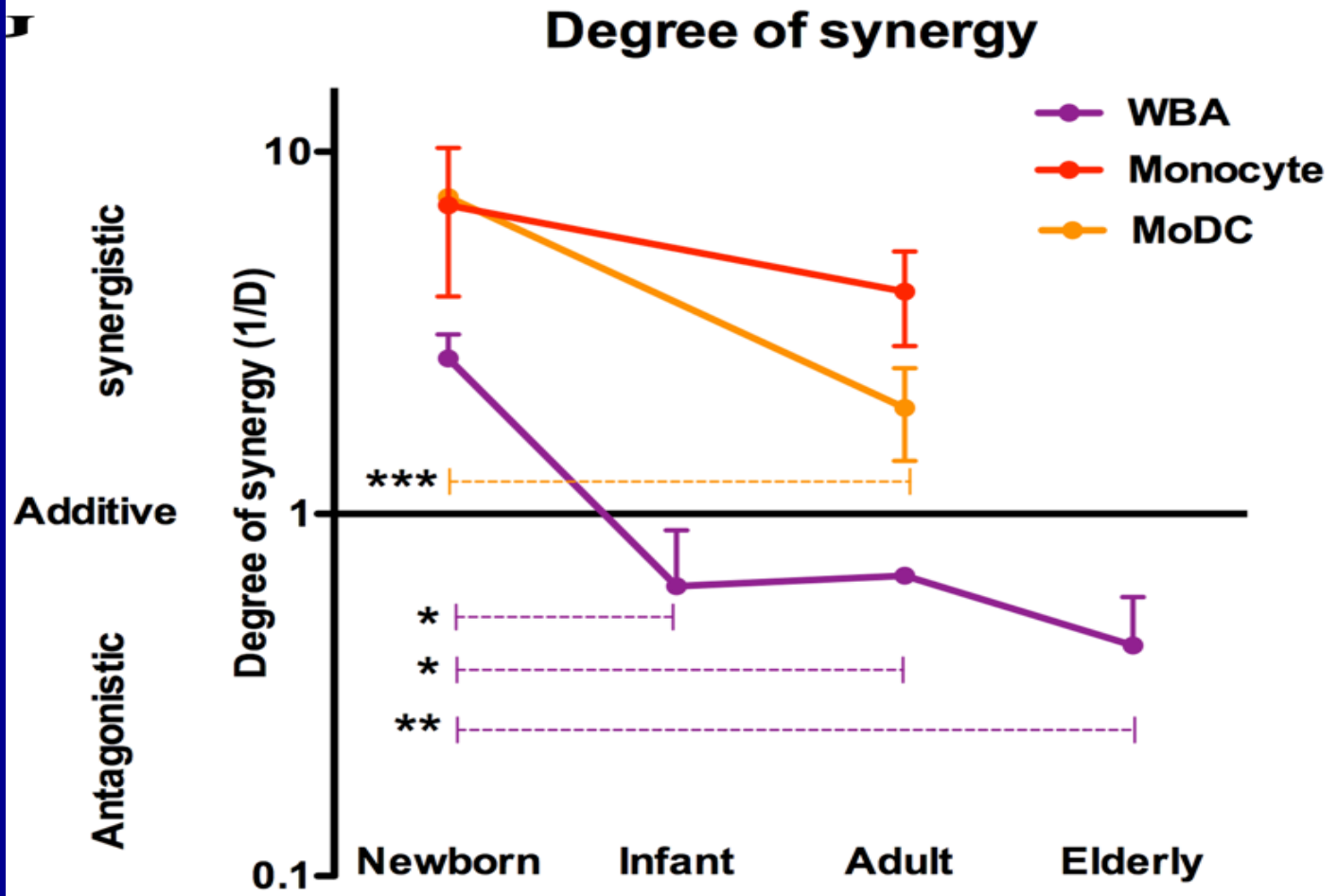
Age-specific adjuvant synergy for Human MoDC Activation: R848 (TLR7/8 agonist) & TDB (Mincle Agonist)



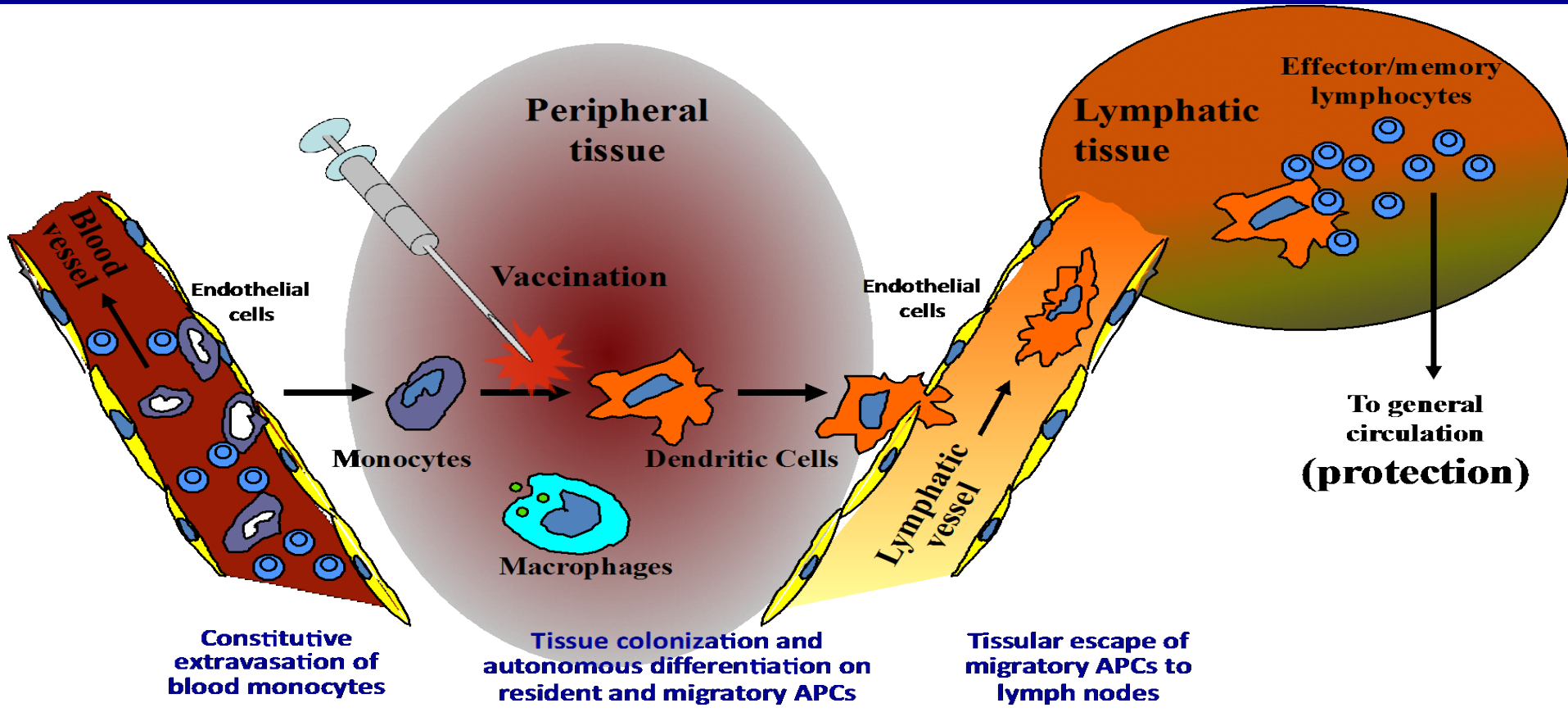
1 Yadav, M. et al. 2006. *Blood* 108: 3168-3175
2 Ferwerda, G. et al. 2008. *Cell. Microbiol.* 10: 2058-20663 Nakaira
4 Moseman, A. P. et al. 2013. *J. Immunol.* 191: 5615-5624
5 Dragicevic, A. et al. 2012. *Cytotherapy*.
6 Lemoine, S. et al. 2015. *J. Allergy Clin. Immunol.* 136: 1355-1368 e1351-1315

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.

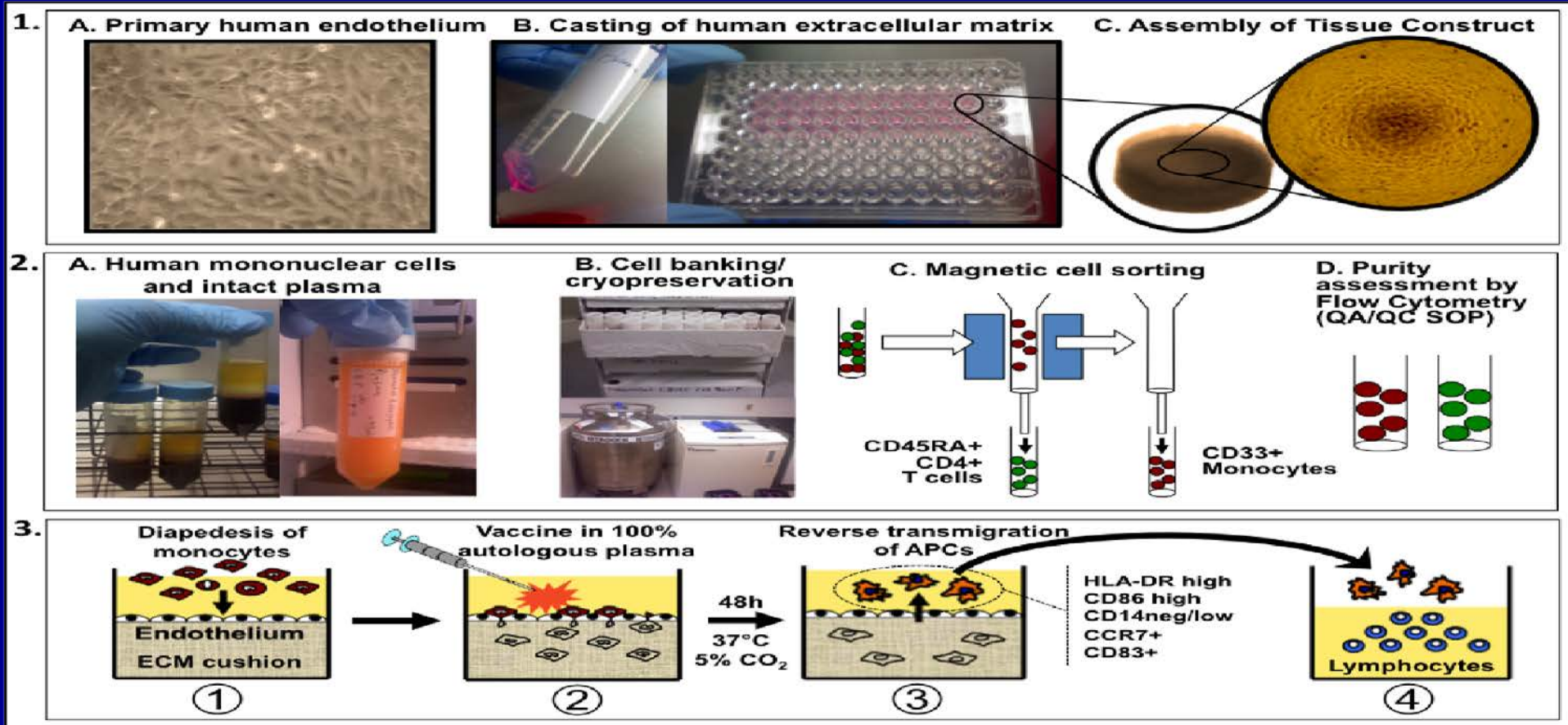
Age-dependent adjuvant action across *in vitro* platforms



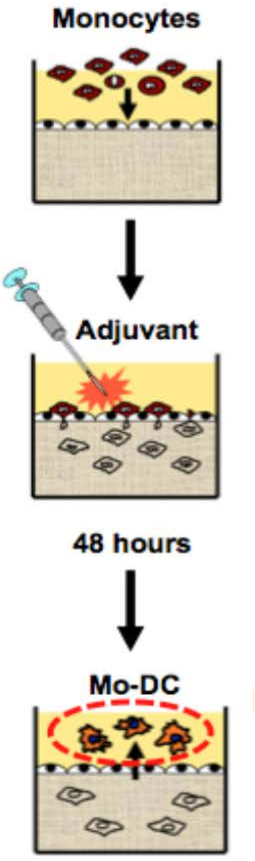
Development of microphysologic systems to model human vaccine responses

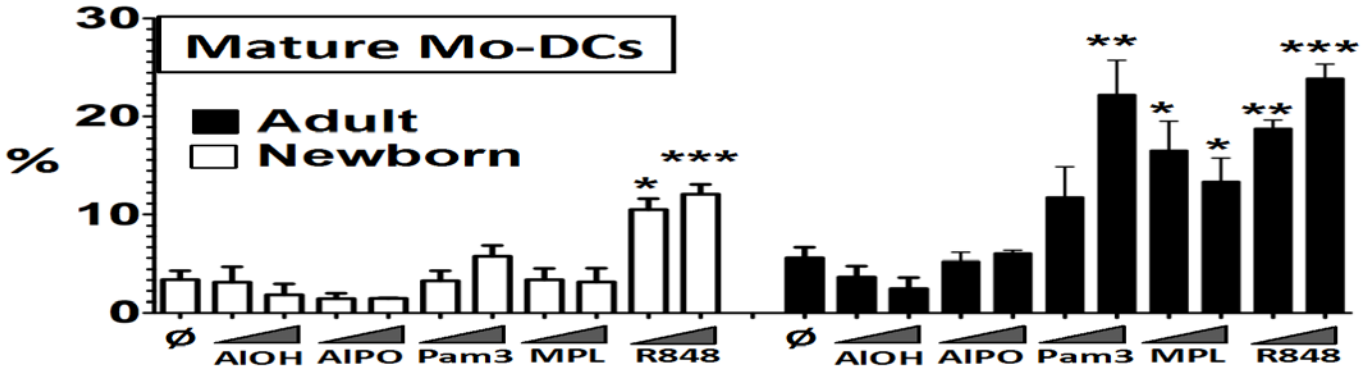


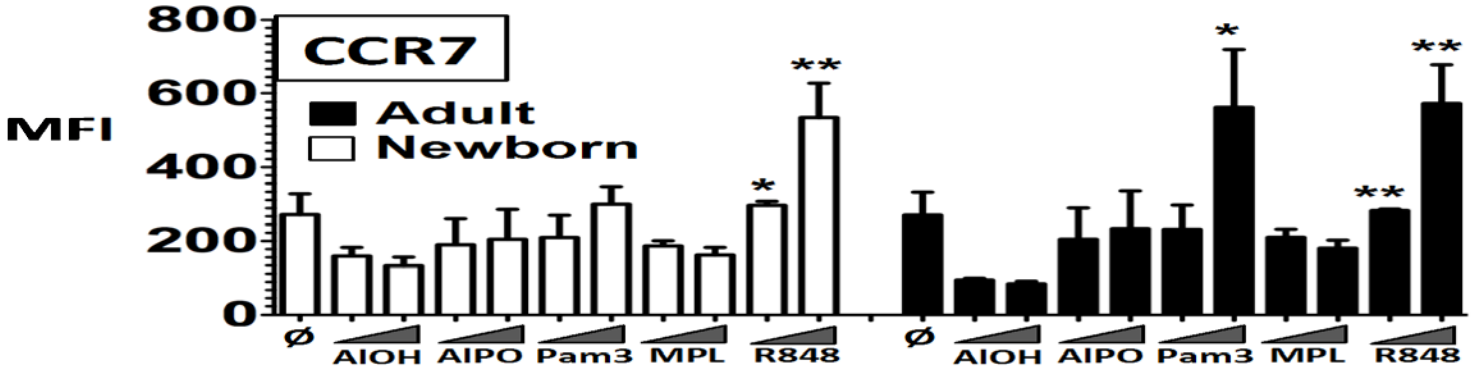
Creation of 3-dimensional microphysiologic tissue constructs



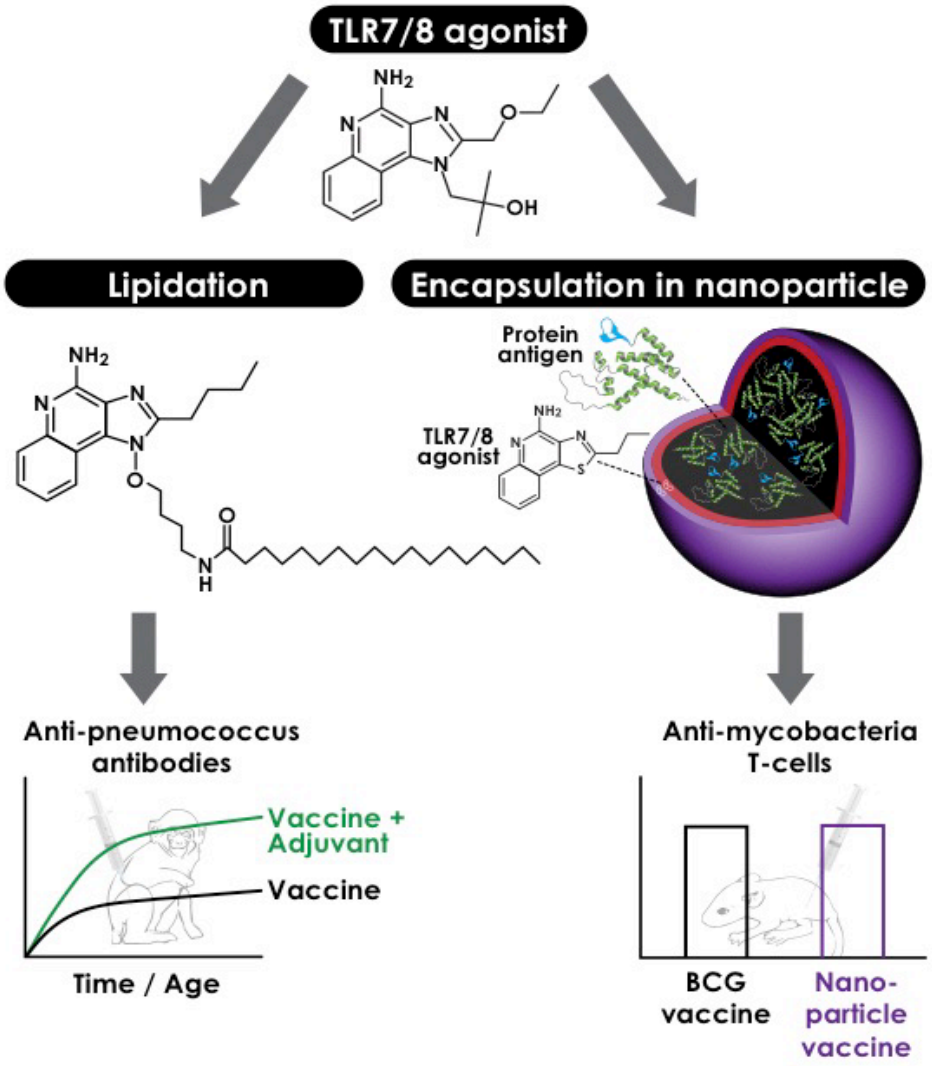
Tissue constructs demonstrate age-specific differences in responses to Adjuvants







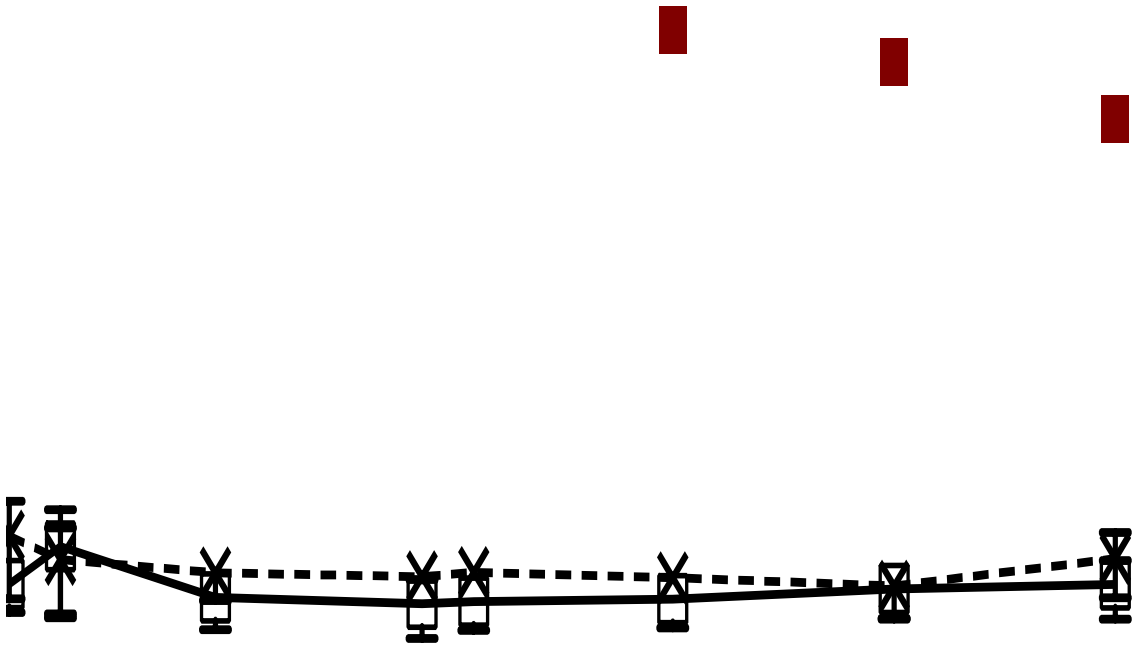
Dowling, DJ et al
J Clin Invest 2017



Dowling, DJ et al
J Allerg Clin Immunol 2017

TLR7/8 adjuvantation dramatically accelerates & enhances neonatal immune responses to Pneumococcal Conjugate Vaccine

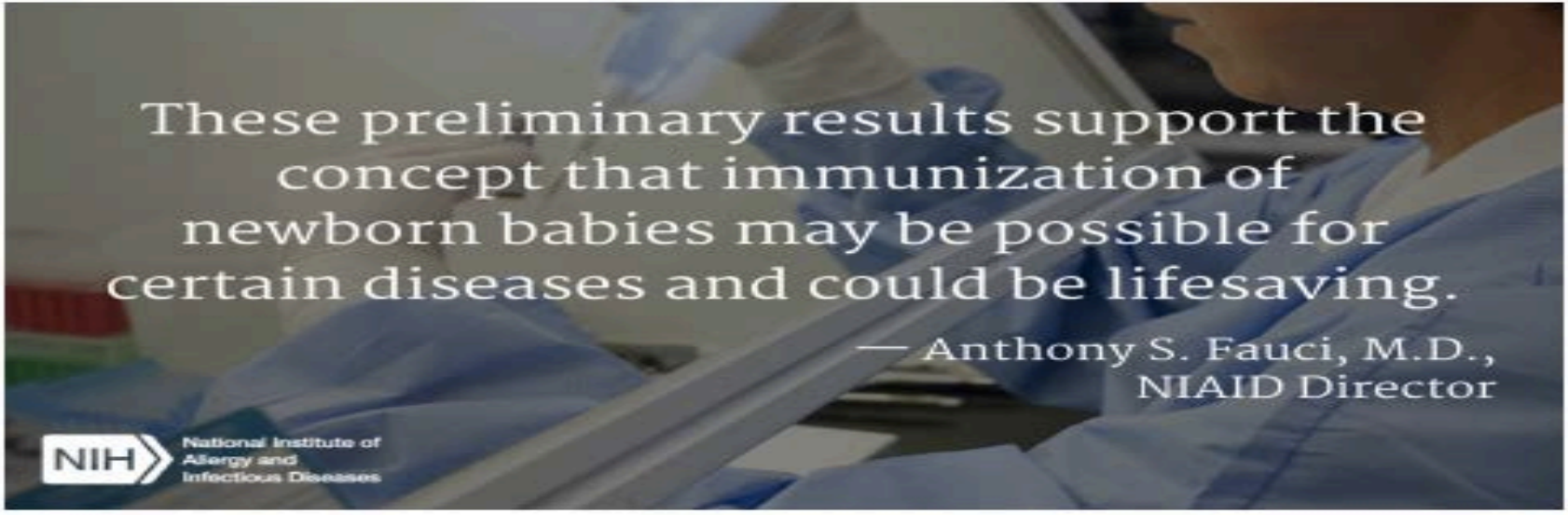
Serotype 9V



New Adjuvant Permits Early Pneumococcal Immunization in Newborn Monkeys

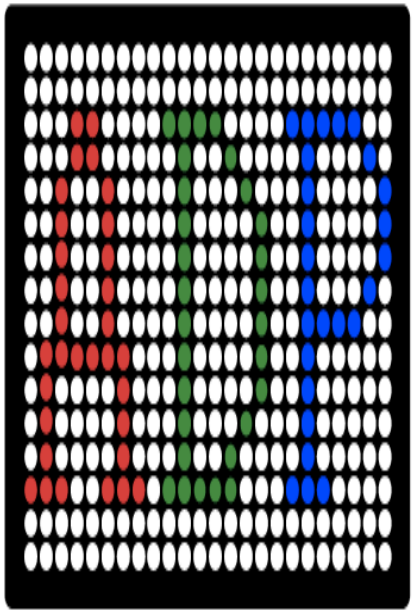
Compound May Help Protect Human Infants Earlier with Fewer Doses

March 23, 2017

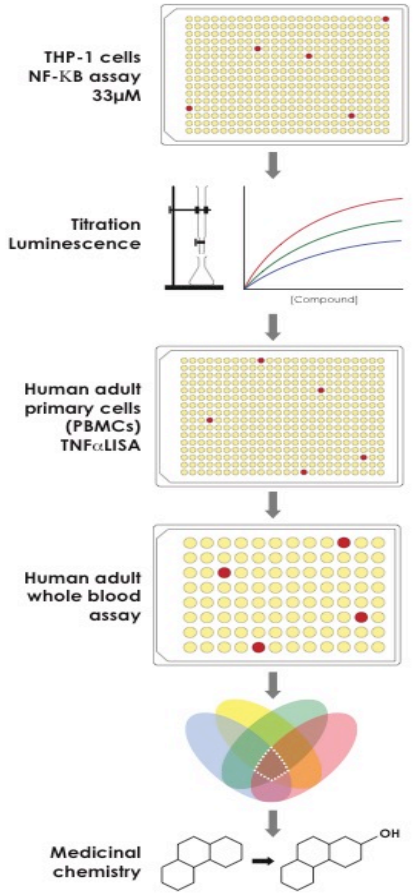


National Institute of Allergy and Infectious Diseases

Leading research to understand, treat, and prevent infectious, immunologic, and allergic diseases.

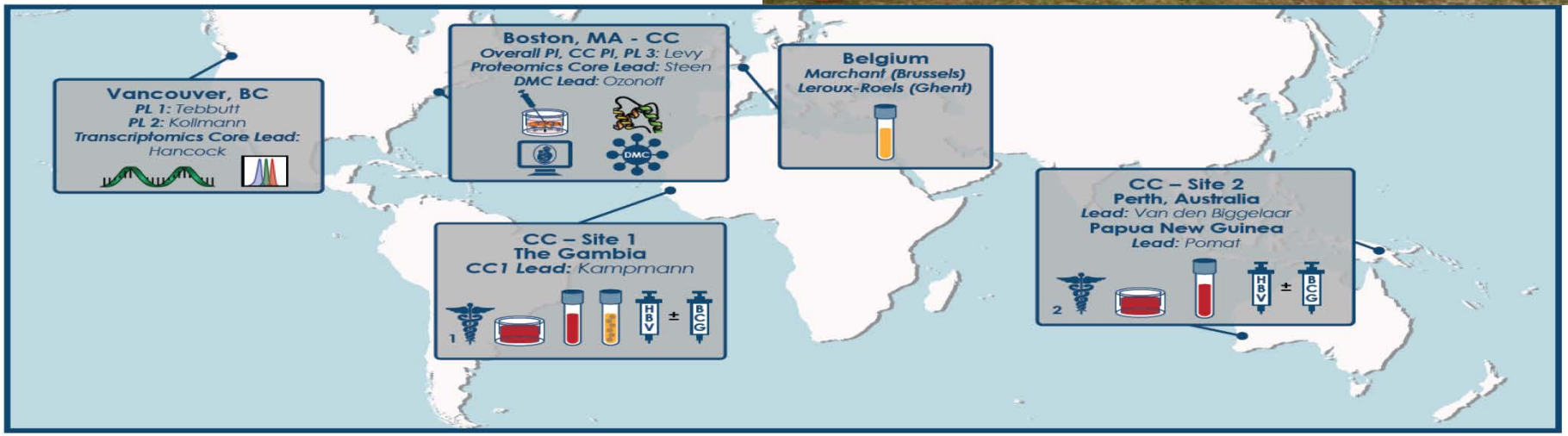


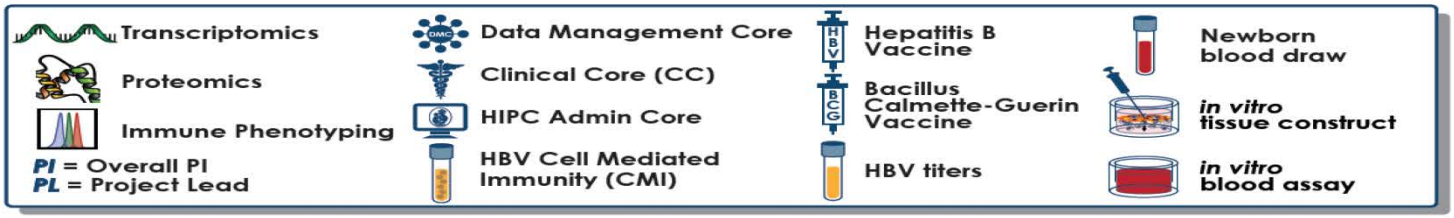
Adjuvant Discovery Program



epic

Twitter: *@VaccinesEPIC*



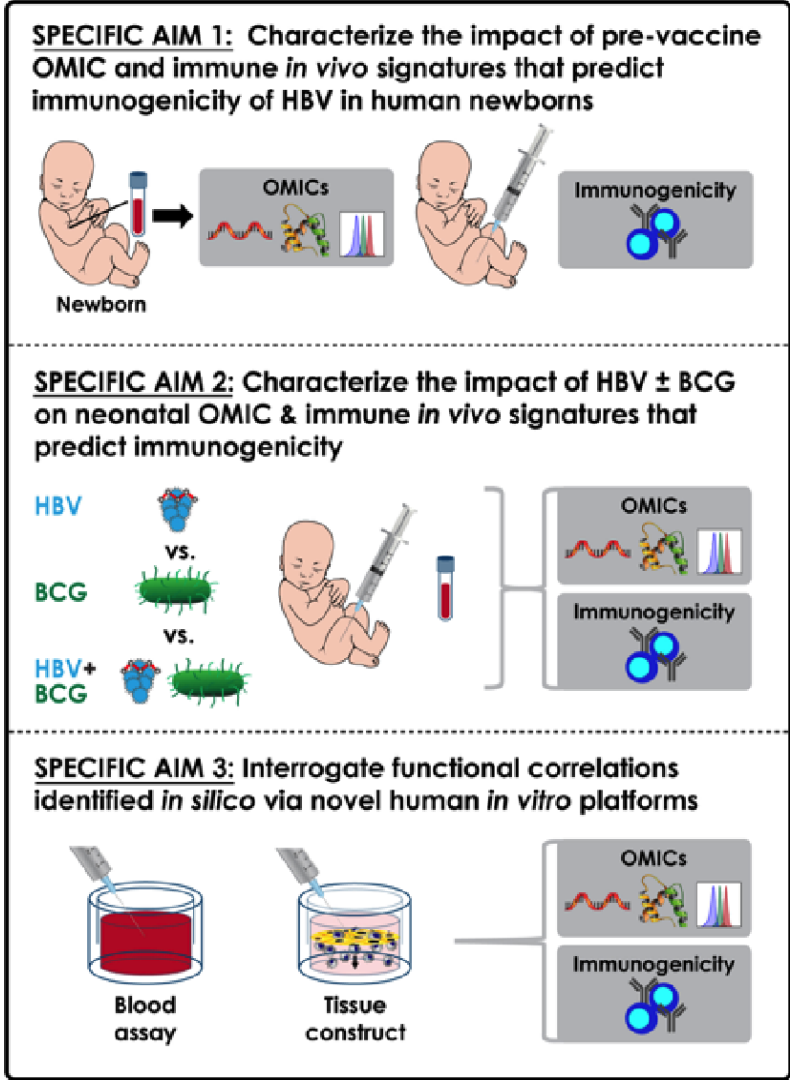


Systems Biology to Define Biomarkers of Newborn Vaccine Immunogenicity

HIPC

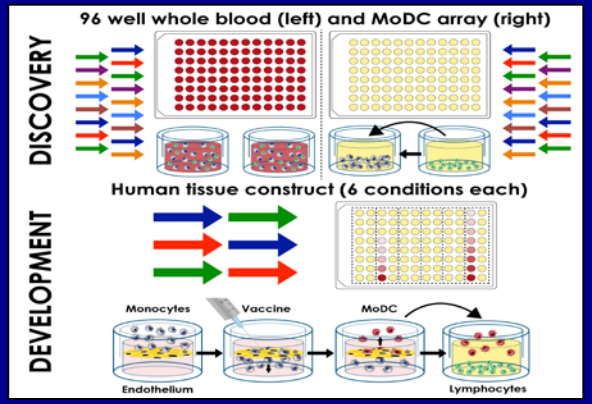
Human Immunology Project Consortium

Twitter: *@hipcProject*



Developing *Precision Vaccines*

Hypothesis generating



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

Licensed or novel vaccines

Appropriate animal models

Targeted Clinical Trial

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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- Bill & Melinda Gates Foundation
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- IDRI (Steve Reed & Chris Fox)
- 3M Drug Delivery Systems (Mark Tomai)
- VentiRx (Rob Herschberg)
- Crucell (Johnson & Johnson)

Open to collaboration:

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