Systems Vaccinology

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Global Vaccine Research and Immunization Forum
Hyatt Regency, Bethesda, Washington DC, March 4 – 6, 2014
1. Systems Vaccinology: using the tools of systems biology to identify predictors of vaccine efficacy, and to discover new insights about protective immunity.

2. Gnostic predictors: extracting biological meaning from signatures.

3. Relevance for clinical trials
Vaccines as tools to probe the human immune system

- Young Healthy adults
- Infants
- Elderly
- Malnourished
- Immunocompromised

Measuring vaccine immunity

- Serologic response
- Flow cytometry
  - CyTOF
- Cytokine assays
- Transcriptomics
  - Micro RNAs
  - Metabolomics

Vaccines:
- Yellow Fever vaccine
- Influenza vaccines
- Shingles vaccine
- Pneumococcal vaccines
- Meningococcal vaccines
- Malaria vaccine
- Tularemia vaccine
Systems biology approach predicts immunogenicity of the yellow fever vaccine in humans


Systems biology of vaccination for seasonal influenza in humans


VOLUME 12 NUMBER 8 AUGUST 2011 NATURE IMMUNOLOGY
Is there a “universal correlate” of antibody responses to any vaccine?
Day 3/0 antibody correlation

Li et al – Nature Immunology, 2014
Systems Immunology Consortium

Goal:
Create a unified research platform for the analysis of vaccine trials and natural history studies
We are drowning in a sea of data and thirsting for knowledge.

Low input, High throughput, No output Biology?

Sydney Brenner
What are we learning?

1. The impact of nutrient sensing and metabolic control on vaccine immunity

2. Control of vaccine immunity by the intestinal microbiome
Systems biology approach predicts immunogenicity of the yellow fever vaccine in humans

The yellow fever vaccine YF-17D is one of the most successful vaccines ever developed in humans. Despite its efficacy and widespread use in more than 500 million people, the mechanisms by which it stimulates protective immunity remain poorly understood. Recent studies using systems biology approaches in humans have revealed that YF-17D–induced early expression of general control nonrepressible 2 kinase (GCN2) in the blood strongly correlates with the magnitude of the later CD8+ T cell response. We demonstrate a key role for virus-induced GCN2 activation in programming dendritic cells to initiate autophagy and enhanced antigen presentation to both CD4+ and CD8+ T cells. These results reveal an unappreciated link between virus-induced integrated stress response in dendritic cells and the adaptive immune response.
Early expression of TLR5 is positively correlated with productive antibody responses against influenza HA following vaccination with the seasonal inactivated flu vaccine.

Natural Ligand for TLR5 is Flagellin
Antibody Response to vaccination with flu vaccination is dependent on TLR5

BUT, the flu vaccine itself lacks the capacity to stimulate TLR5 signaling
Is there a role for commensal microflora in mediating vaccine responses?

20 µg TIV s.c.

Antibiotics (ATB)

Cocktail:
- Neomycin (1 g/L)
- Ampicillin (1 g/L)
- Vancomycin (0.5 g/L)
- Metronidazole (0.5 g/L)

Serum ELISA

Day 7 14 28

WT B6

p < 0.0001
***

p < 0.0001
***

p < 0.0001
***
Implications for Human Vaccination Programs?

Stop the killing of beneficial bacteria

Antibiotics

n = 15

0 3 7 28 days

Untreated

n = 15

0 3 7 28 days

HAI d0 and d28
NGS – Microbiome (stool)

Vaccine Efficacy

TLR5 polymorphisms
Potential applications for clinical trials
A framework for Systems Vaccinology

Clinical trials

Discovery based science

Human vaccination

New biological insights guide vaccine design

Mechanistics studies (e.g. animal model, in vitro experiments, challenging)

Generation of new hypotheses

Bioinformatics analyses

Systems biology approaches applied to vaccinology

Immunity 2010
Acknowledgements

Emory Vaccine Center

Troy Querec
Helder Nakaya
Jason Oh
Rajesh Nair
Noor Khan
Sudhir Kasturi
Sai Duraisingham
Shuzhao Li
Dmitri Kazmin

Rafi Ahmed

Jens Wrammert
Gui-Mei Li
Megan McCausland
Mark Mulligan
Rouphael Nadine

Francois Villinger
Traci Legere
Zarpheen Jinnah Sher

Eric Hunter

Cynthia Derdeyn

Pam Kozlowski
Peng Xiao
Sharmila Reddy

Georgia Tech
Eva K. Lee

Dana-Farber
Nick Haining

NIAID-NIH
Kanta Subbarao

Yerkes Veterinary Staff:
Christopher Souder
Robert Sheffield
John Wambua
Carmen Nash
Stephanie Ehnert

National Institutes of Health
HIPC U19, CCHI U19 and IPIRC Flu center

Bill & Melinda Gates Foundation