CHIM: Opportunities in human immunology?

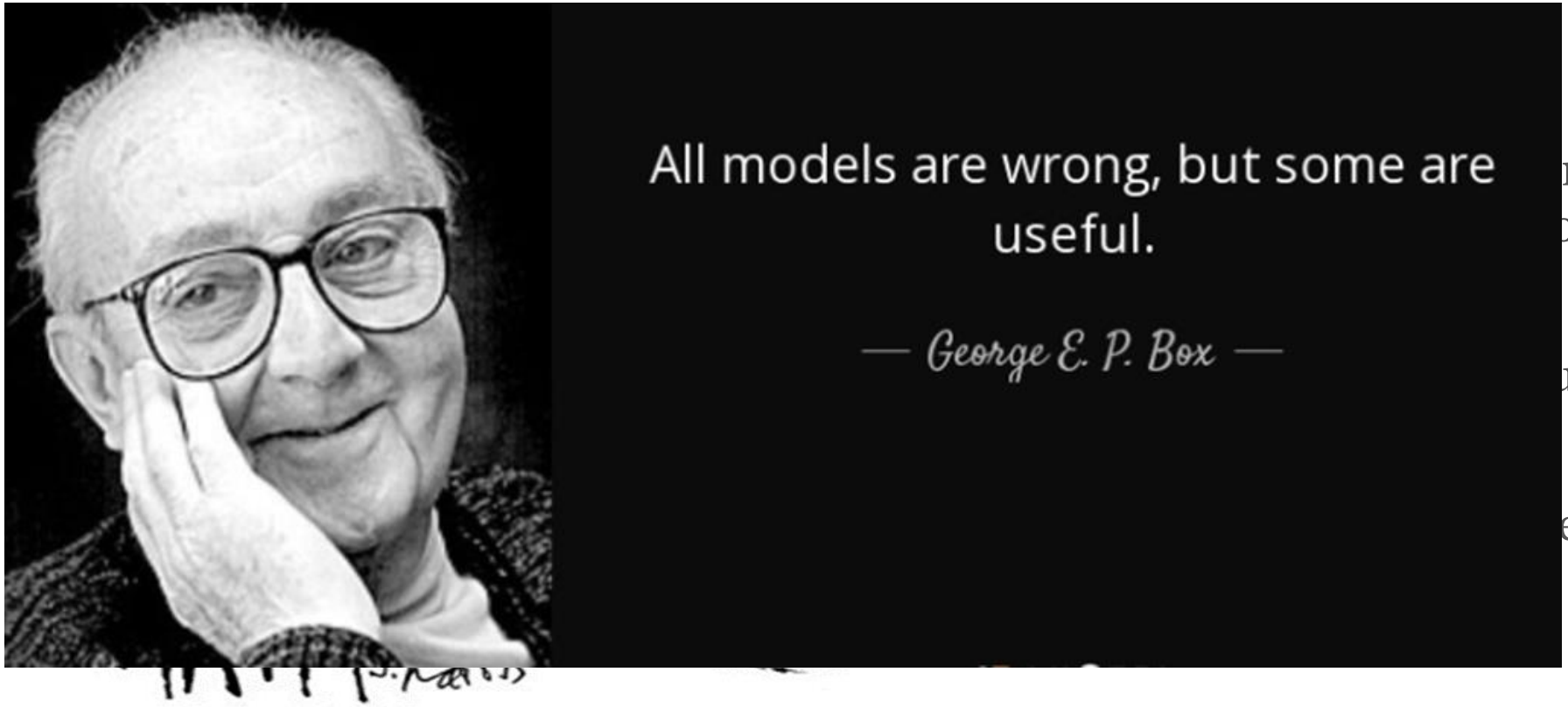
IABS 2nd Human Challenge Trials in Vaccine Development Conference

Beth Kirkpatrick, MD
University of Vermont, Vaccine Testing Center

September 29, 2017

The University of Vermont

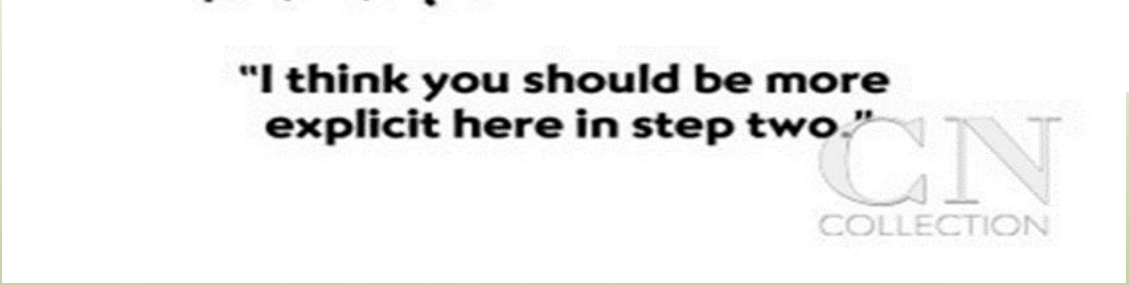
Overview

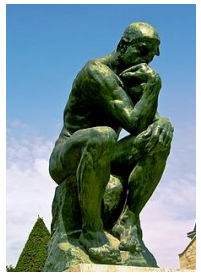


nd design CHIMs
our knowledge of

ue and

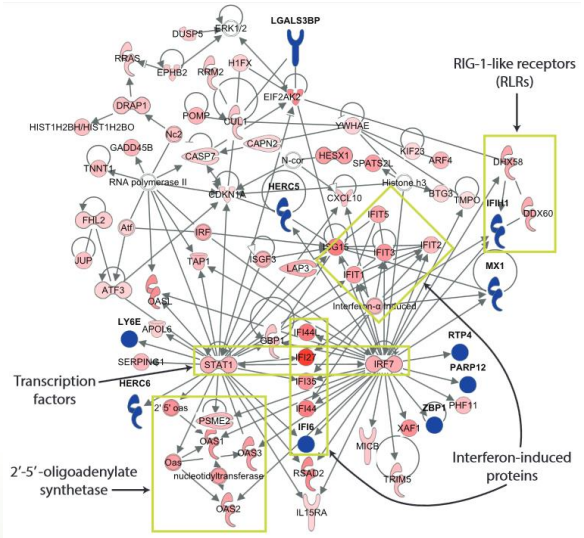
es in the field

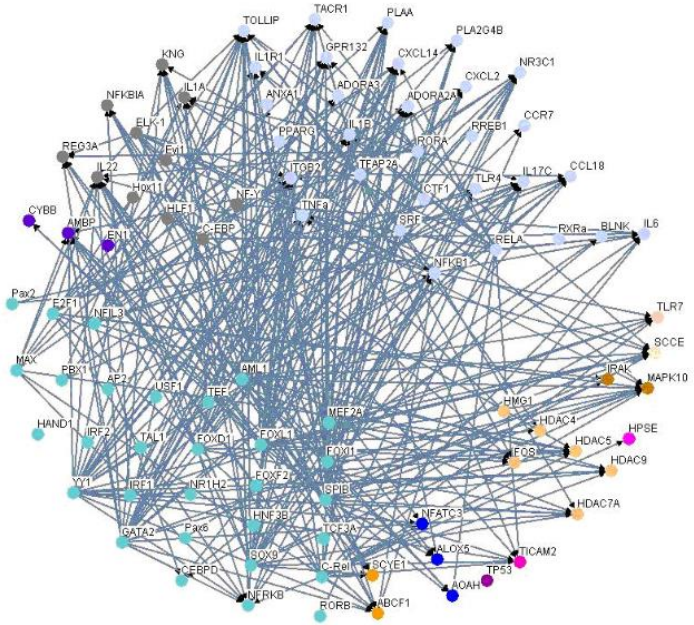


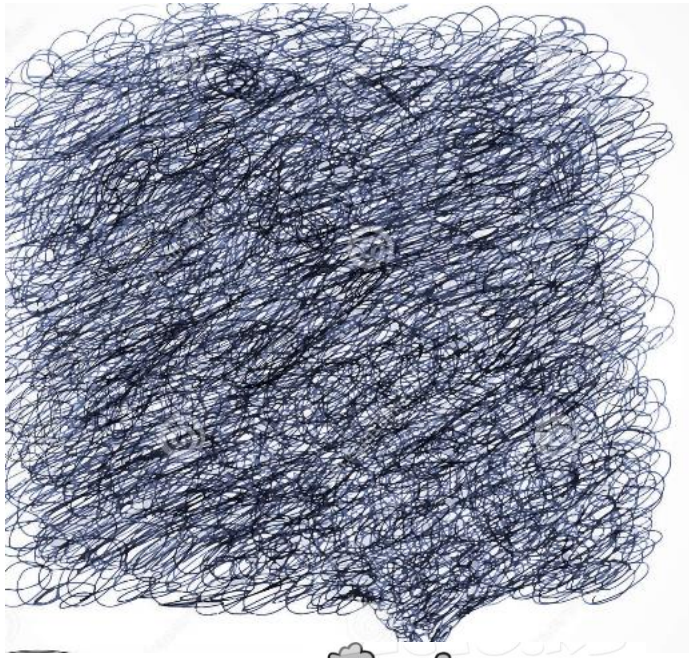


Mucosal vs. systemic
Infants vs. adults
Innate vs. adaptive

Homotypic vs. heterotypic
Isolated vs. cross-protective
Antibiotic truncated vs. not







Humoral vs. cellular
Sterilizing vs. shedding
Permanent vs. short lived

Endemic populations vs. naive
Co-infections?

What type of immunology questions might be desired from CHIM?

- Confirmation of epidemiologic or animal models
- Descriptive and comparative immunology
- Functional or mechanistic understanding of immune components
- Antigen discovery
- Identification of monoclonal antibodies for diagnosis or treatment
- Selection and standardization of immunogenicity for future bridging
- Correlates of protection

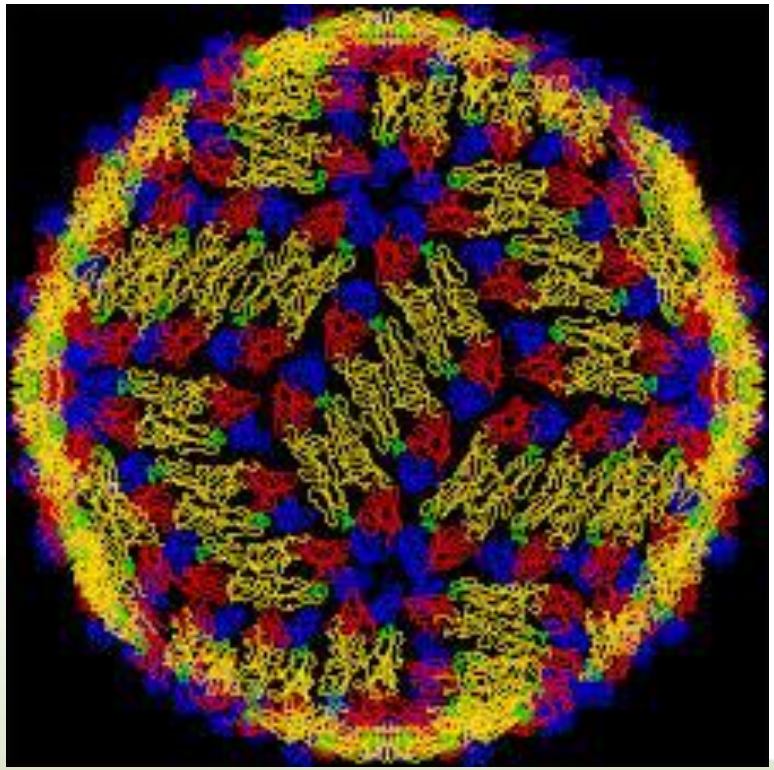
What type of immunology information might be actually learned? What might be actually valuable toward improving human health?

IT DEPENDS

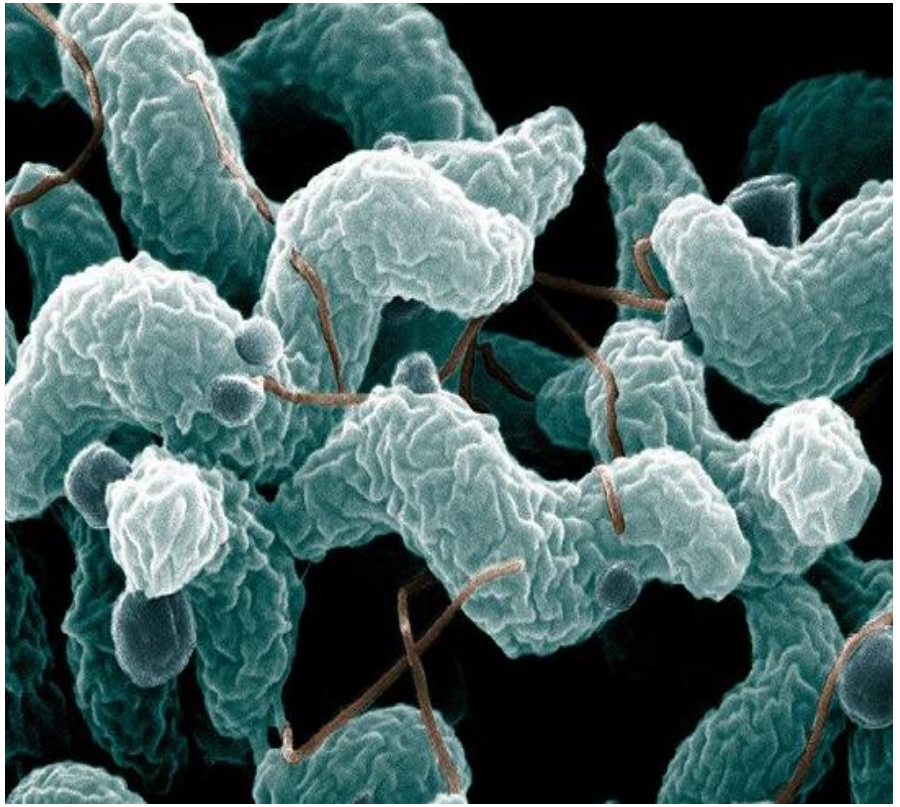
Where are you starting?

- What is known about the natural history of disease for your pathogen?
- Are robust epidemiologic data available? Populations/ages?
- Are animal models available? Do they reflect human disease?
- Does clinical immunity actually develop? Is it sterilizing/neutralizing? Does it last?
- What immune components are linked with clinical protection? Are immunodominant antigens known? Are there correlates/surrogates?
- Are immune assays with specific antigens established? Validated/Qualified?

Let's look at two examples:

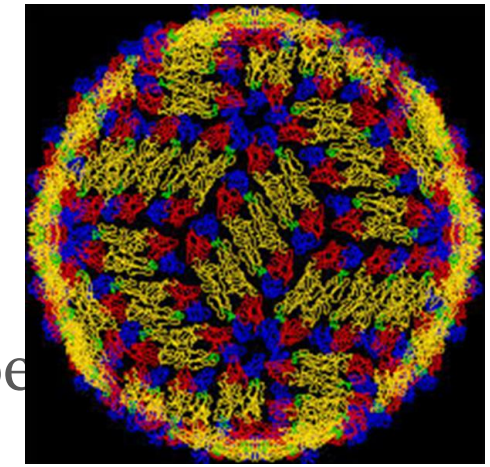


Dengue Viruses



Campylobacter jejuni

Dengue

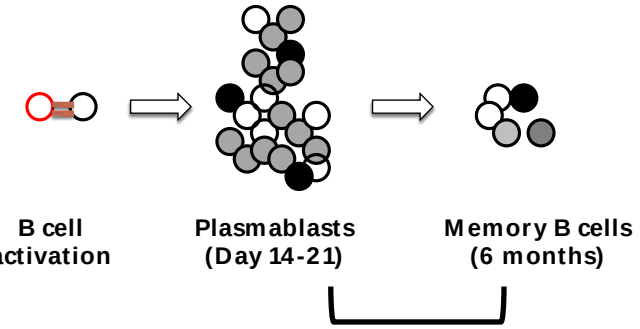


- Virus and biology well understood. Genetically stable. 4 serotype
- Viral genetics worked out, manipulable
- Natural history of clinical disease well known, lots of epidemiologic studies
- Good non-human primate model mimics human disease
- Long lasting homotypic protection. Sterilizing immunity
- Correlate of protection is probably neutralizing antibodies
  - Established functional assays (NAB), validated (mostly), cut offs
- Vaccine robust. CHIM robust. Vaccine +CHIM robust.

Immunology advances: Dengue (infection) CHIM

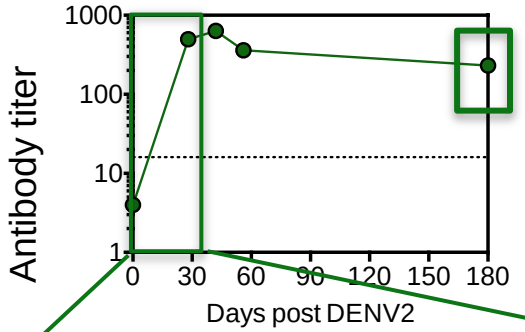
- Advanced descriptive immunology:
  - What is the relative role of CD4 vs. CD8 to structural vs. non-structural antigens?
  - How clonal is the dengue-specific B cell pool and are these antibodies all functional (neutralizing)?
  - Can we characterize memory B cells and their function?
- Identification of monoclonal antibodies with diagnostic or therapeutic potential.
- Study of dengue epitopes
- Confirmation or refinement of immune correlates of protection

Probing the B cell response to find new protective measures

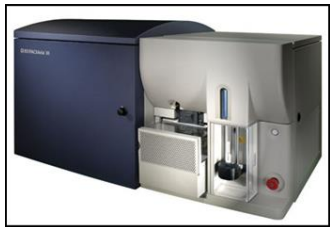


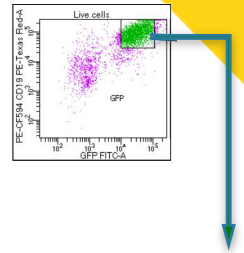
Gap in knowledge

Dengue antibody response

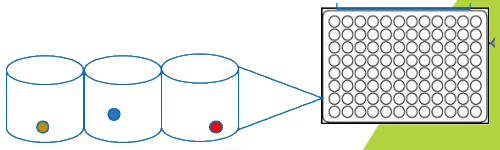


High throughput memory B cell sorting

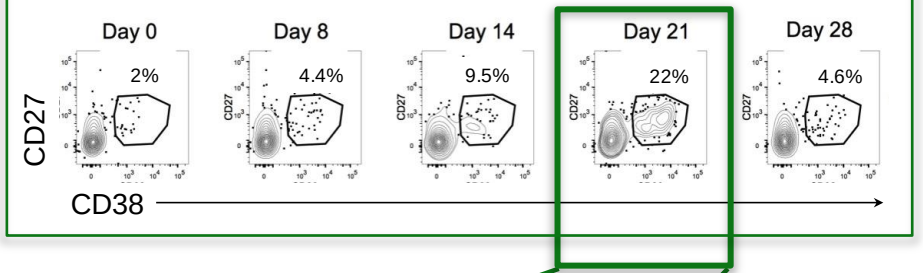




Immortalized MBC (1 cell per well)

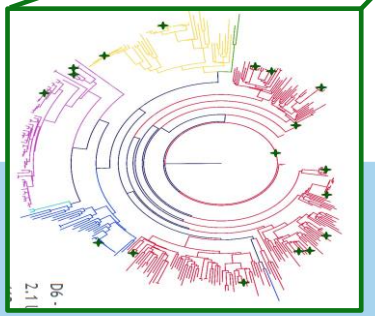


Plasmablast response



Screen antibodies for antigen binding and activity

Next-gen sequencing
Antibody phylogeny(Atreca)



Select test Aff Mat Abs based on bioinformatics

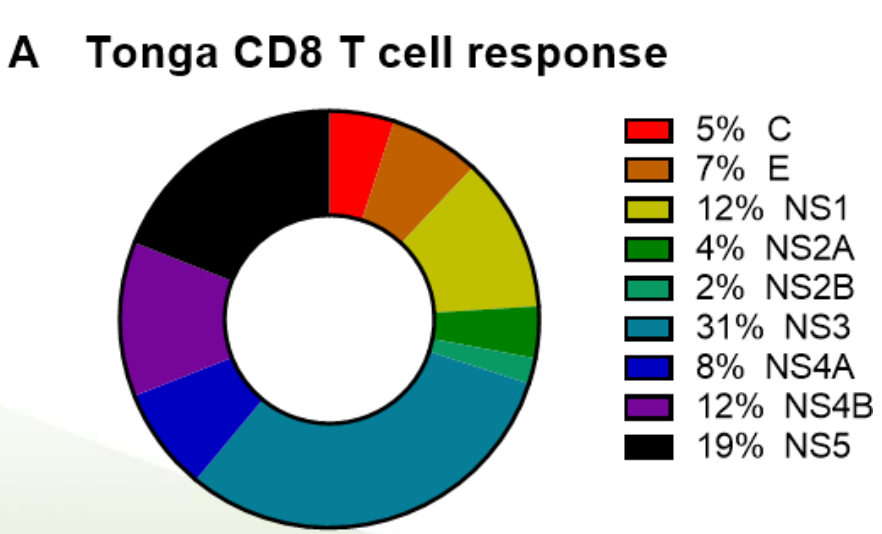
Key Antibodies & Antigens

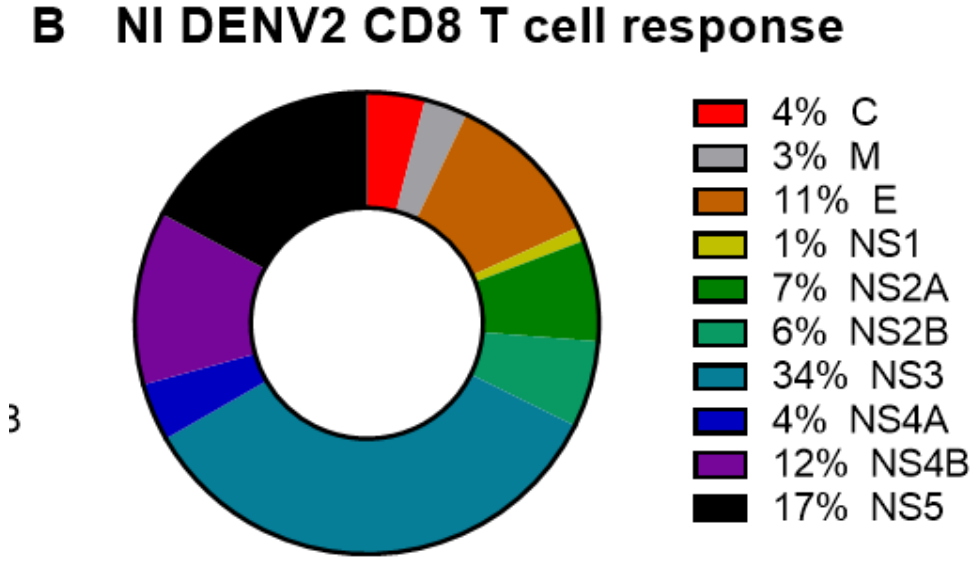
Partners: Atreca, JHU, NIAID, UNC

The Robert Larner, M.D. College of Medicine
THE UNIVERSITY OF VERMONT

Cellular responses to the DENV2 challenge strain?

Are the CD8 protein targets the same? Yes





La Jolla Institute FOR ALLERGY AND IMMUNOLOGY | Life Without Disease.™

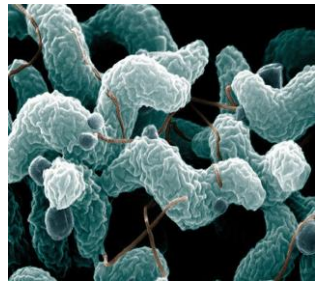
Sette, Weiskopf

The University of Vermont

DENGUE

- Incredibly rich opportunity to advance natural history "immunology" and compare vaccine to natural disease.
- Can move immune correlates of protection forward (easier if vaccine was less than 100% effective!)
- Opportunities for everyone!
- Four serotypes of dengue
- Difficult to tease out issue of cross-reactive components of immunity
- Vaccine works "too well"!
- "Correlates of Protection"…is a process not a slam dunk.
- Iterative improvements of standardized assays
  - PRNT→microneut (96 well MTP)

Campylobacter jejuni



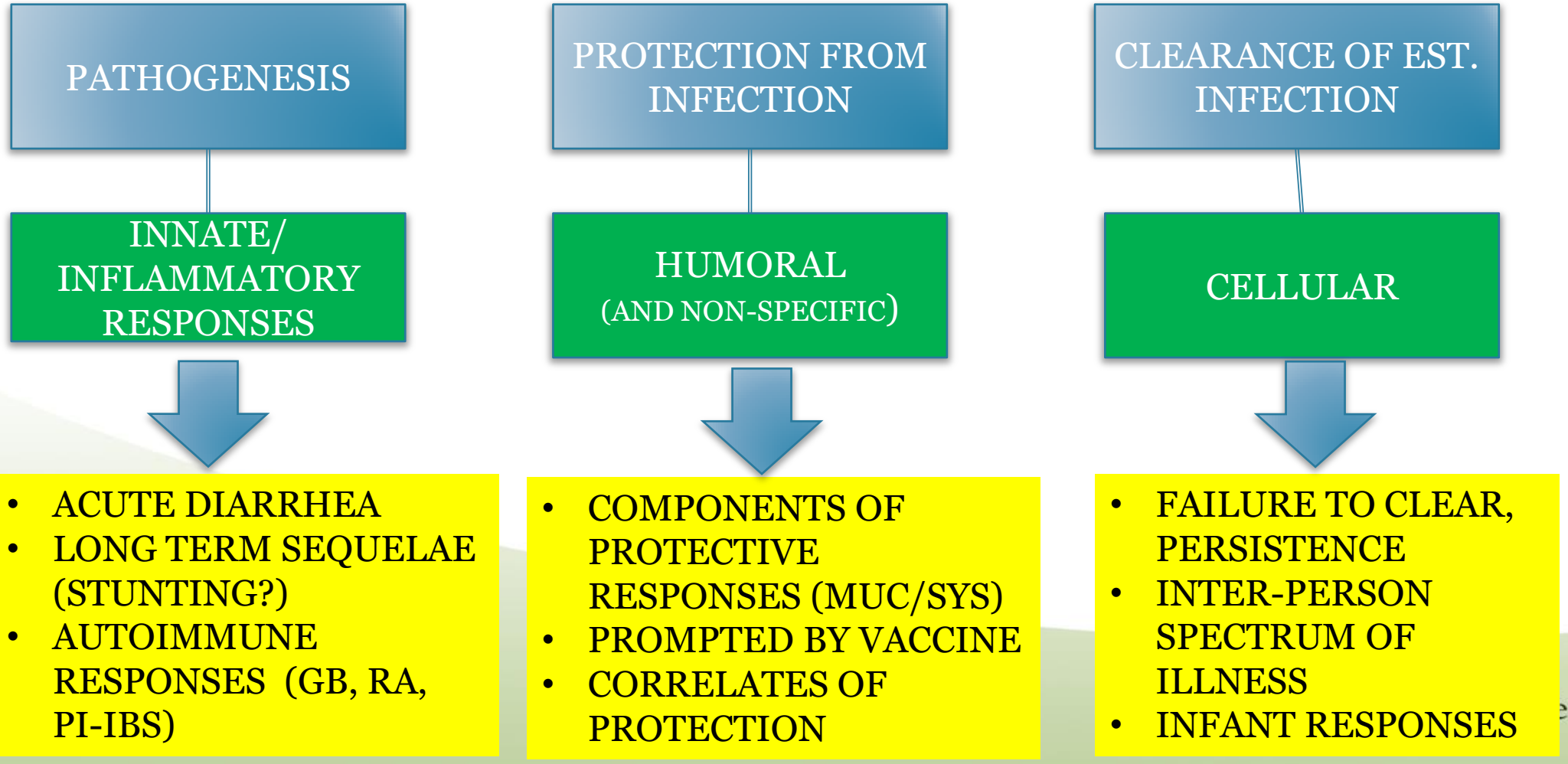
- Enteric microaerophilic enteric pathogen. Many subtypes. Large amount of capsular phase variation (antigenic changes)
- Clinical spectrum known, epidemiology strong.
- Epi studies show clinical protection (no diarrhea), but no sterilizing immunity. Short lived protection.
- Post-infectious sequelae, molecular mimicry.
- Mechanisms of protection unclear. Components of immune protection assumed from epi and immunocompromised patients.
- Unknown role of the microbiome
- No great animal models
- Human Immunologic assays mostly not functional.

CHIM: *Campylobacter* immunology

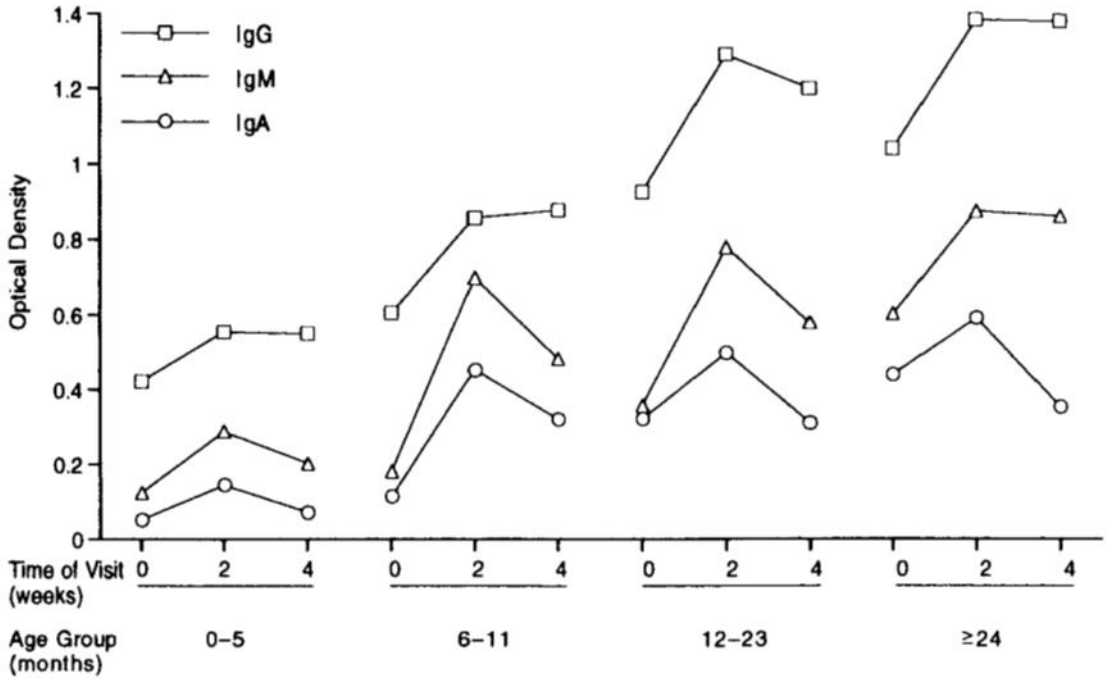
- Comparative immunology vs. epidemiologic observations/natural disease
  - Except issue of antibiotic truncation of full response?
- Descriptive immunity: components of the immune response, effector molecules, involvement of systemic and mucosal compartments.
- Kinetics of immune responses (vs. pre-exposure baselines)
- Confirmation of critical antigens and identification of new antigens
- Understanding composite pattern associated with clinical protection.

Note: Campy CHIM endpoint is disease (campylobacterosis/ diarrhea)

Why do we need to understand *Cj* human immunology? A simplified view.



Protective immunity: Cohort Studies (developing world)



In conclusion, in a Thai population in which enteric infections are frequent, *Campylobacter* infections are hyperendemic. As children age, their *Campylobacter* infections become milder, they excrete fewer organisms, and *Campylobacter*-specific serum antibodies rise progressively. All of these findings are consistent with the development of immunity, which suggests that development of a vaccine against *Campylobacter* infections should be possible.

Campylobacter Immunity and Quantitative Excretion Rates in Thai Children

JID 1993;168 (September)

DAVID N. TAYLOR,[1†*] PETER ECHEVERRIA,[1] CHITTIMA PITARANGSI,[1] JITVIMOL SERIWATANA,[1] LADAPORN BODHIDATTA,[1] AND MARTIN J. BLASER[2]

Immunologic findings w/o protection (CG 8421, 3-month re-challenge)

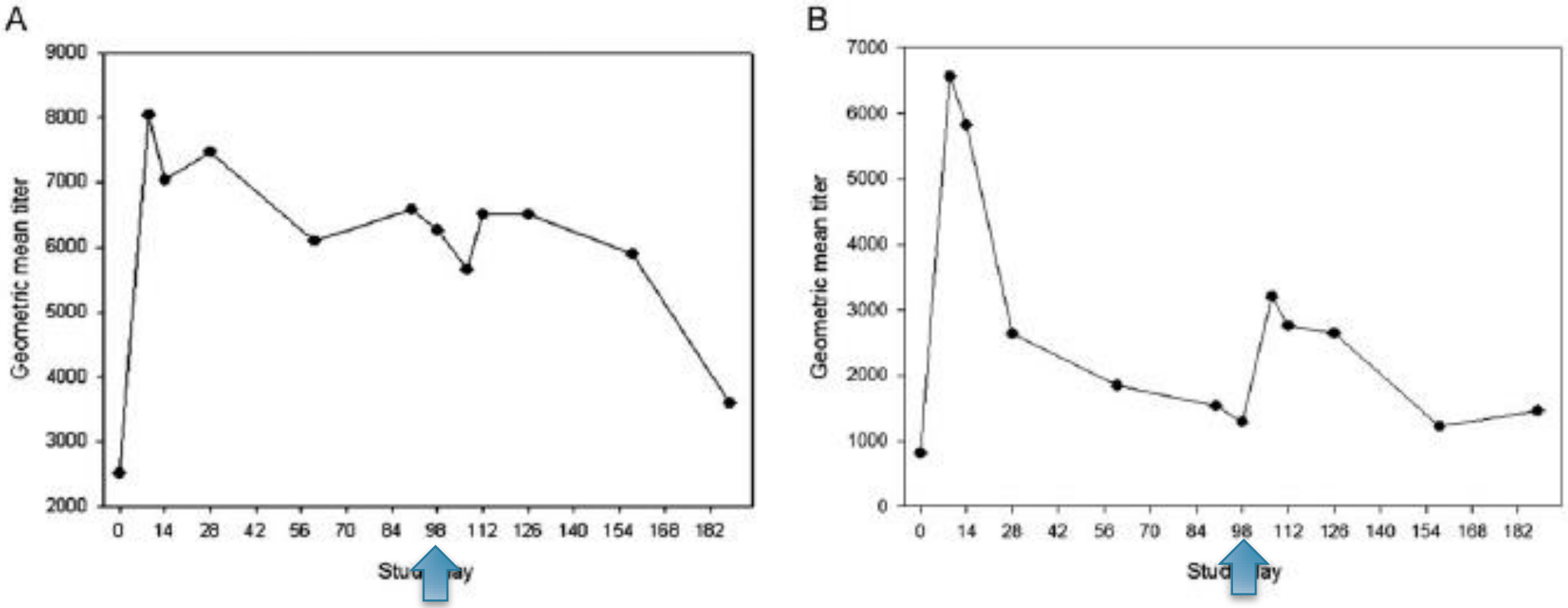


Figure 2 Serum immunoglobulin G (IgG), immunoglobulin A (IgA), and fecal IgA responses after challenge (day 0) and secondary challenge (day 98) with *Campylobacter jejuni* CG8421. *A*, Serum IgG responses after primary (day 0) and secondary (day 98) challenge with *C. jejuni* CG8421. *B*, Serum IgA responses after primary (day 0) and secondary (day 98) challenge with *C. jejuni* CG8421. *C*, Fecal IgA responses after primary (day 0) and secondary (day 98) challenge with *C. jejuni* CG8421. Hatched lines represent total fecal IgA. Solid lines represent *C. jejuni* antigem-specific fecal IgA. Abbreviation: IgA, immunoglobulin A.

Beth D. Kirkpatrick,[1] Caroline E. Lyon,[1] Chad K. Porter,[2] Alex C. Maue,[2] Patricia Guerry,[2] Kristen K. Pierce,[1] Marya P. Carmolli,[1] Mark S. Riddle,[2] Catherine J. Larsson,[1] Douglas Hawk,[2] Elizabeth A. Dill,[1] A. Fingar,[1] Frederic Poly,[2] Kelly A. Fimlaid,[1] Fahmida Hoq,[2] and David R. Tribble[3]

Immunogenicity≠Immunity

Table 1. Clinical Outcomes of Subjects After Challenge With *Campylobacter jejuni* CG8421

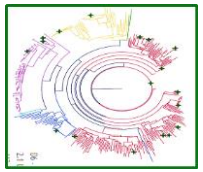
Outcome	All Naive	Veteran
No.	15	8
Met primary endpoint of campylobacteriosis, No. (%)	14 (93)	8 (100)
Any diarrhea, No. (%)	14 (93)	8 (100)
Severe diarrhea, No. (%)	8 (53)	7 (88)
Time in hoursto campylobacteriosis, median (IQR)	52.3 (46.9–56.1)	53.7 (48.3–73.7)

Next steps for Campylobacter

- Need to understand the role of the microbiome (+/- inflammation, biofilms) in immunologic development.
- Back to the field?-more nuanced study of the development of protective/clinical immunity in children. Including the role of heterologous infections in protection and the “ideal” durability of protection
- Not yet ready for a correlate or surrogate of protection
- Need to understand the function of the immune components.
  - How are those antibodies working (opsonization?)
  - Assay standardization will help with if bridging needed
  - Hypothesis generating

Overall: Context needed

- Overall, only rare pathogens have comprehensive “natural history” human immunology
  - Most are viruses (e.g. Yellow Fever)
  - The mucosal/gut pathogens are the most difficult (personal bias) due to complexity of the mucosal environment and difficulty evaluating these compartments.



- Trouble with data relevance:
  - Immunology assays are often not standardized or harmonized, making it difficult to build on historical data.
  - Data analysis plans for immunology require attention to correction for multiple variable.
  - CHIM power calculation may be insufficient for inter-personal ranges of immunologic parameters.
- Even without infection, the understanding of normal immune parameters is in its infancy
  - http://10kimmunomes.org/
  - Ten thousand immune gnomes?

About Visualize Download

The 10,000 Immunomes

The 10,000 Immunomes Project is a reference dataset for human immunology, derived from over 10,000 control subjects in the NIAID ImmPort Database .

Available data include flow cytometry, CyTOF, multiplex ELISA, gene expression, HAI titers, clinical lab tests, HLA type, and others. Check out the Visualize page to view the available data. Visit the Download page to download a subset of the data or the entire dataset for your own use.

UCSF

About | Visualize | Download

Select Data Type:

Flow Cytometry: PBMC

Select Analyte:

Effector_memory_CD4_T_cells

Normalized

Age Range:

0 100

0 10 20 30 40 50 60 70 80 90 100

Sex:

Female

Male

Ethnicities:

White

Black or African American

Asian

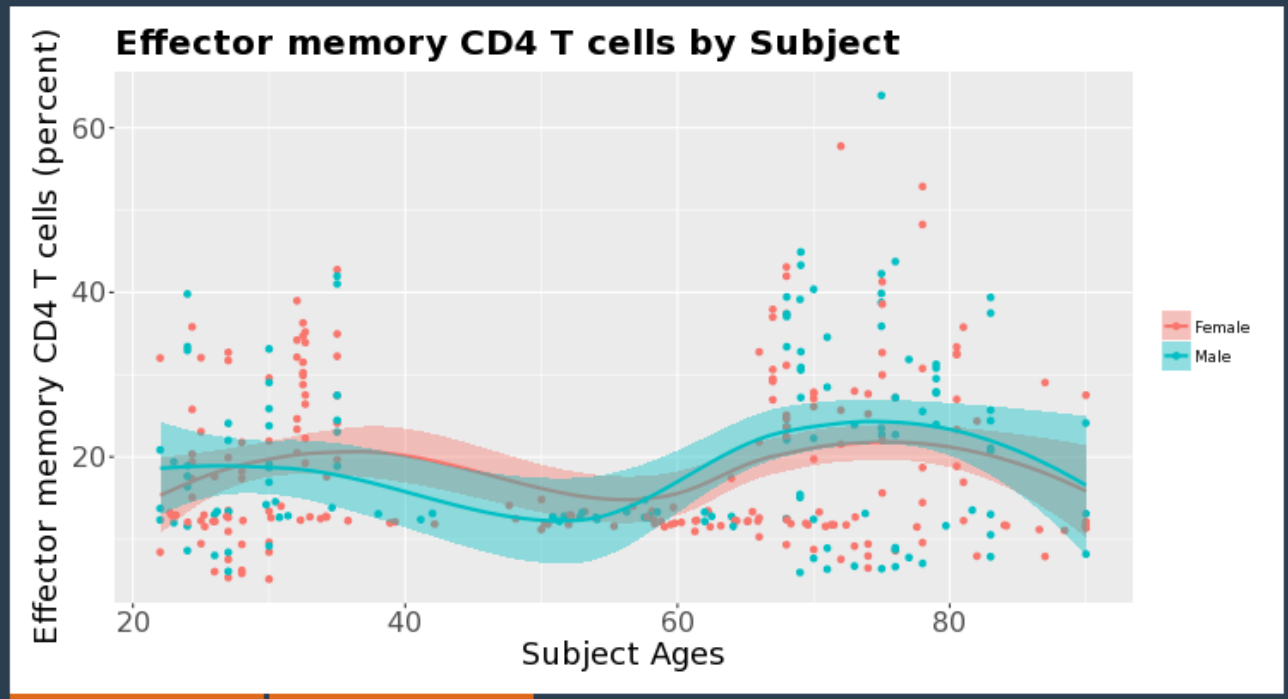
Other

Plot By:

Age & Sex

Ethnicity

Study



Download Plot | Download Data

Distinct Subjects: 330

sity of Vermont

Conclusion

- CHIMS offer unparalleled opportunities to advance human immunology,
  - Especially if re-challenges are done.
  - We shouldn't be surprised if the data makes our life more difficult.
- We might consider as a group what immunologic data is needed from natural disease populations before CHIM is started.
- Minimal standardization of assays would permit use of historical controls.
- Functional immune assays
- Statistics, modeling, bio-informatics will be more important than ever and analytic packages must meet these challenges.

Thank you

The University of Vermont

8421 re-challenge.
No ASC boost. No protection

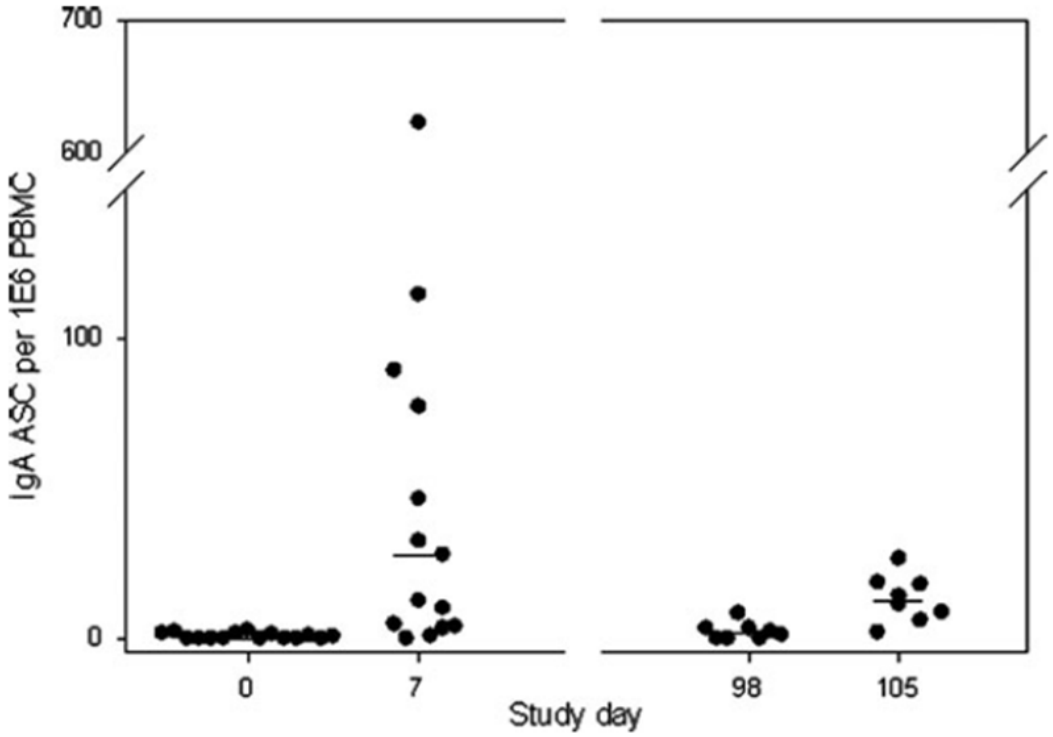
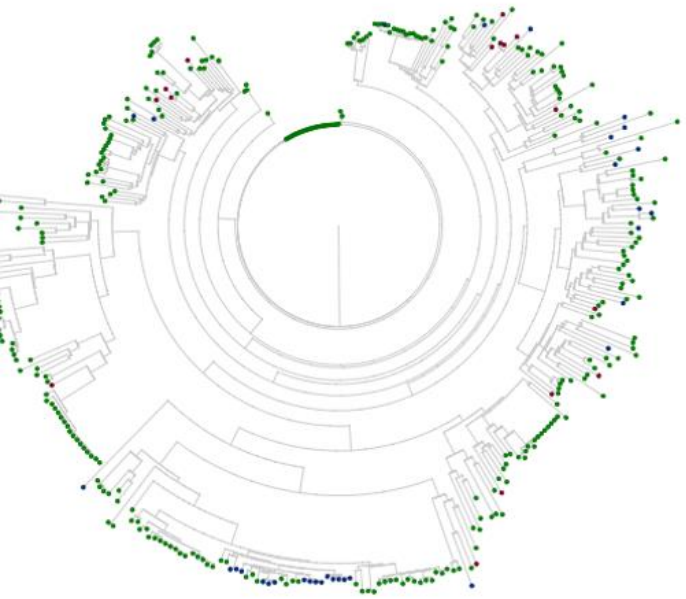


Figure 3. Immunoglobulin A antibody-secreting cell responses after primary and secondary challenge with *Campylobacter jejuni* CG8421. Horizontal lines denote the median number of antibody-secreting cells for each day. Abbreviations: ASC, antibody-secreting cell; IgA, immunoglobulin A; PBMC, peripheral blood mononuclear cell.

Antibody Immune Repetoire



IgG Isotype

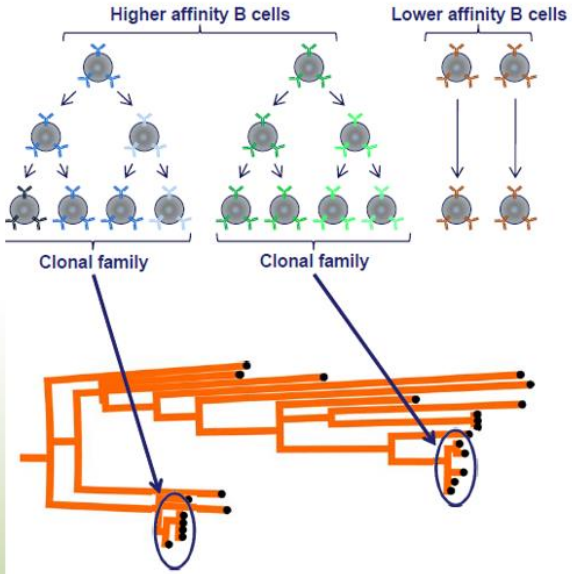
- G1
- G2
- G3

- Viremic D6 – D7 post-challenge
- 2.1 $\log_{10}$ PFU/ml peak titer
- 412 pairs

Courtesy of Daniel Emerling, Atreca

ATRECA

Clonal Family Analysis Identifies Affinity Matured Antibodies



Affinity maturation of B cells in germinal centers leads to clonal expansion

Clonal families

- Contain antibodies with shared HC V(D)J and LC VJ
- Identify high-affinity and functional antibodies

ATRECA, INC.