GENERAL DISCUSSION – ENTERIC BACTERIA-

Key Points

Identification of Research Gaps

Going Forward

Cholera

- Is vibriocidal titer a good correlate?
  - Vibriocidal response to vaccination is useful and correlates with risk of disease.
  - Facilitates dose finding for a given vaccine.
  - Has limitation when comparing vaccine categories (live vs killed vs injectable), but is useful when comparing different forms of a type.
  - Limitations:
    - <3 year olds respond but may not be protected
    - Methods need to be standardized / validated (This is possible with standardized reagents)

How to bridge to new cholera vaccines

- **Comparing new killed vaccine with Shanchol**
  - Volunteer studies to show comparable dose response vibriocidal and ALS titers
  - LPS content
- **Comparing new live oral vaccine with CVD103HgR**
  - Volunteer studies to show comparable dose response vibriocidal and ALS titers
  - Challenge studies
- **New injectable vaccines**
  - Volunteer immunogenicity and efficacy in challenge studies
  - Could be suitable for EPI
  - Since Shanchol has limited efficacy in young children <3 years, efficacy in field trials may be possible.

ETEC

- Much more complex than cholera because of the multiple LPS, toxin and CFA types
- Vaccine induced immunity will hopefully prime and natural exposure will boost.
- ALS is more sensitive than serum titers to CFA, but serum responses may be more reassuring.
- Functional assays needed but are more difficult to standardize
- ST immune response are now possible (in animals), but protection in humans is not known
- ALS useful for antigen discovery

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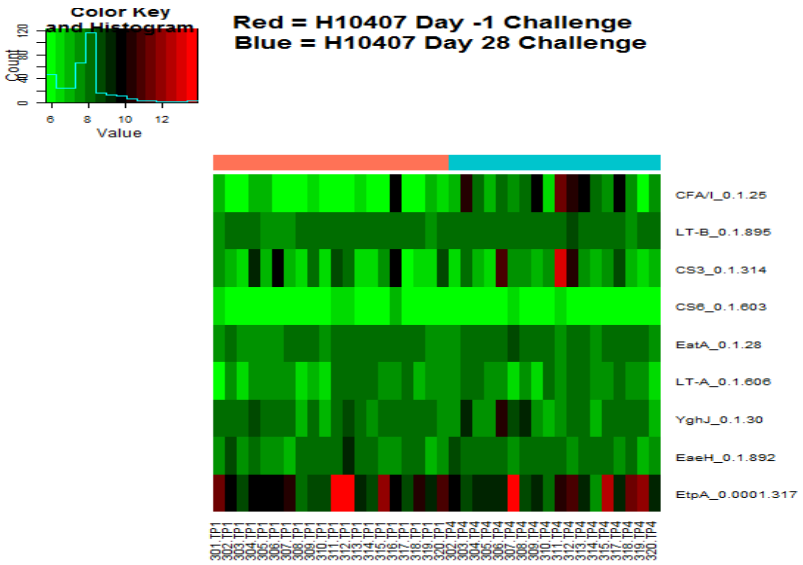

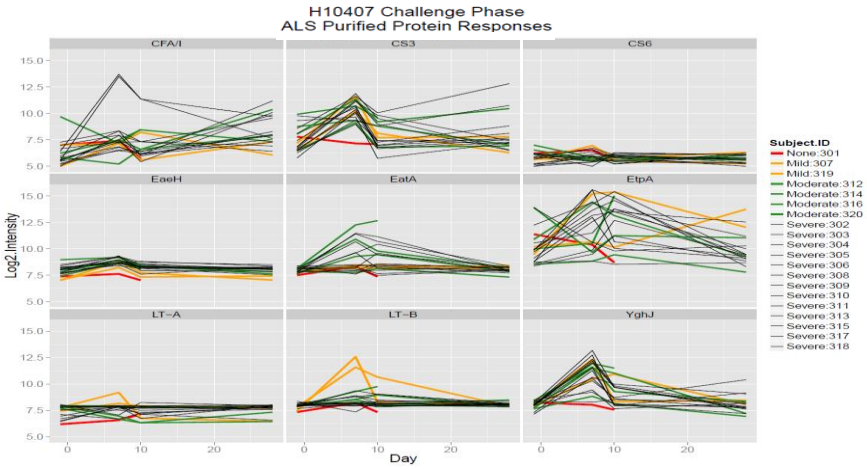

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- Will the same immune responses be useful for oral vaccines and injected?
- Tip adhesin
- Multi-epitope fusion antigen (MEFA) protein

Typhoid

- Live oral vaccine (Ty21a)
  - Many B and T cell responses
  - Challenge studies have helped to elucidate the immune events, but correlates of protection is likely multi-factorial
  - ASC responses useful in optimizing responses and searching for cross reactivity
- Vi
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- Vi + Live vaccine?
  - Both vaccines give good / not great protection
  - Completely different mechanism of protection
  - If both are given, would they protect in a synergistic manner?

Implications of ASC (ALS) response to Typhoid vaccine

- The ALS assay is a reflection of the immune response to an infection that has occurred recently.

- Can the ASC response be used to develop a new generation of diagnostic
  - Infections when blood culture is not sufficiently sensitive (e.g. typhoid or pneumococcus)
  - Infections when multiple pathogens are detected (e.g. diarrhea)
  - Could ALS sample be applied to micro spot methods to detect recent infections?

Shigella

- Serotype specificity

  ⇨ LPS immunity

  - *S. sonnei* + *S. flexneri* 2a, 3a, 6

- Several types of vaccine under development:
  - Oral live attenuated
  - Oral killed
  - Conjugate

- Correlates of protection will depend on proof of efficacy – not all candidates have protected

Campylobacter

- Vaccine is under development
- Association with GBS limits ability to carry out challenge studies with a variety of strains
- Natural history suggests development of immune protection but inconsistent protection against re-challenge limits our understanding of immune protection