Progress in the Development of a Norovirus VLP Vaccine

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Virus-Like Particles (VLPs) as Vaccines, Vectors and Adjuvants

Fondation Merieux

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Norovirus

According to the CDC, “The perfect human pathogen” (Hall AJ 2012)

• Highly contagious by:
  – Direct contact between hosts via fecal-oral transmission
  – Ingestion of contaminated foods or water
  – Contact with contaminated surfaces
  – Ingestion of aerosolized particles (rare among enteric pathogens)

• Environmentally stable
  – Survives heating and freezing
  – Persists for weeks on dry surfaces

• Rapidly and prolifically shed
  – Up to 5 billion particles of infectious virus can be shed by an ill person in uncontrolled vomiting and diarrhea episodes

• Evokes limited immunity

• While most hosts survive the illness, the infection can be fatal in young children and the elderly. Hall AJ, J Infect Dis. 2012;205:1622-1624
Norovirus

NoVs are currently recognized as the leading cause of acute gastroenteritis (AGE) worldwide:

- Responsible for approximately half of all gastroenteritis outbreaks

- Second most common cause of severe gastroenteritis in infants in countries without Rotavirus vaccination
  
  - In countries with an effective Rotavirus vaccination program, NoVs are now emerging as the most important enteric pathogen in pediatric populations
  \[\text{Payne 2013 NEJM, Hemming, 2013, Eur J Ped}\]

- Symptoms of vomiting and diarrhea can be very serious
  
  - Hospitalization rates are high in young children and the elderly worldwide
  
  - Up to 200,000 deaths per year in children under 5 (primarily in developing countries)
  \[\text{Patel 2008 EID}\]
Norovirus Burden of Illness

- 2.8 Billion cases of gastroenteritis every year\(^a\)
- 350 Million cases due to norovirus\(^a\)
- 35 Million seek medical care\(^a\)
- 2 Million hospitalized\(^a\)
- 21,000\(^a\) to 200,000\(^b\) deaths

Rotavirus\(^c\)

- 440,000 deaths
- 2 M hospitalized
- 25 M clinic visits
- 111 M cases of AGE with home care

\(^a\) Developed world only
\(^b\) Developing world <5 yrs of age
\(^c\) Worldwide children <5 yrs of age

Parashar et al, EID, 2003

Patel EID 2008; Hall, EID 2011; Lopman, CID 2011; Tam, GUT 2012; Hall CID 2012
Norovirus Cost Burden / Health Economics

• Norovirus associated with high costs
  – US: Estimated annual cost of $5.8 billion *Wobus 2013 mBio*
  – UK: annual hospital outbreak costs alone exceed £100mm *Lopman 2004 Emerg Infect Dis*
  – CDC estimates annual NoV-associated hospitalizations cost $500 million annually in the US *Payne 2013 NEJM*

• CDC has already published cost-effectiveness modeling for norovirus vaccination
  – Large burden of illness supports cost effectiveness, which is important for broad recommendation and reimbursement
  – Modeling at this early stage underscores public health interest in a vaccine
Challenges for Norovirus Vaccine Development

- Epidemiology is only now being understood
- Virus cannot be cultured \textit{in vitro}
- Limited animal models of infection and protection
- Limited understanding of protective immune responses
- Strain diversity and evolution
Norovirus (family *Caliciviridae*): Genotypes and Strains

- RNA virus classified into five genogroups based on the capsid protein sequence
  - GI and GII cause illness in humans
- Genogroups divided into 8 GI and 19 GII genotypes
  - Majority of illness is caused by genotype GII.4
- Individual strains within genotypes circulate globally
  - Recent circulating strain is “Sydney 2012” (GII.4)
- Illness due to GI and GII genotypes is similar

Norovirus Capsid Structure

- Capsid is formed by 180 copies of single VP1 protein (yellow, red & blue in diagram)
- Virus-like particles (VLPs) can be produced by expressing the capsid protein
- VLPs self-assemble within the expression cells, comprised of only the monomer protein

Advantages of VLP Vaccine Approach

• Norovirus capsid protein self-assembles into VLPs
  – Authentic conformation of important antigenic epitopes
  – Particulate ordered array

• VLPs contain no viral genetic material
  – Non-infectious
  – Potential safety advantage over live attenuated vaccines

• Proven technology for mucosal infectious disease
  – Cervarix®, Gardasil® for HPV

• Robust and reproducible manufacturing
  – High yields using recombinant cell expression system
  – Standard industrial processes for purification and adventitious agent removal
Selection of Vaccine Antigens

- GI.1 VLPs broadly cross-react with other GI strains
  - Selected as GI antigen in Takeda vaccine
- GII.4 is the natural choice for a GII antigen due to its dominance worldwide
- Takeda developed a consensus VLP from three relevant GII.4 strains
  - 2006a (Yerseke)
  - 2006b (Den Haag)
  - 2002 (Houston)

GII.4 Consensus VLP as a Vaccine Candidate
GII.4 Consensus VLPs Contain Epitopes from Multiple GII.4 Strains

Reactivity of GII.4 (2004) MAbs with GII.4 consensus VLPs

Parra et al. JVI (2012)
Parra et al. Vaccine (2012)
Vaccine:

- GI.1 and GII.4 VLPs
- Adjuvants: alum and MPL (3-O-desacyl-4’ monophosphoryl lipid A)
  - Analogous to GSK’s AS04 (Cervarix®, Fendrix®)
- Presentation: single-dose vials or syringes for intramuscular (IM) administration
- One dose administration in adolescents and adults
- Prime / boost strategy for infants
Human Experience with the Takeda IM Norovirus Vaccine Candidate

Study LV03-104 (n=102)

- Safety and immunogenicity study
- Phase I, randomized, double blind, placebo-controlled, dosage-escalation, and age escalation:
  - Doses: 5 to 150 µg per VLP
  - Healthy adults, 18-85 years of age; 2 injections, 28 days apart

Results:

- All dosages equally well tolerated
- GI.1 is relatively more immunogenic than GII.4 in each formulation tested
- Five SAEs reported in 102 subjects; none were vaccine-related
LV03-104: Takeda IM Norovirus Vaccine Candidate

Total Serum Antibodies Through Day 56 by Dosage Level

50 μg / 50 μg dosage level selected for further development based upon data in 18-49 year old adults

Pan-Ig is all anti-norovirus antibody combined

Vaccine administered on Days 0 and 28
The majority of subjects in all groups seroresponded* after 1 dose of 50/50 vaccine

Vaccine administered on Days 0 and 28

LV03-104: Takeda IM Norovirus Vaccine Candidate
Immunogenicity After 2 Doses at Day 56

28 days after second dose

* ≥4-fold rise in GMTs from baseline
LV03-104: Takeda IM Norovirus Vaccine Candidate
Total Serum Antibodies Persist Through Day 393

Majority of subjects remain > 4-fold at 1 year

Pan Assay Anti-NoV GMT

<table>
<thead>
<tr>
<th></th>
<th>GI.1</th>
<th>GII.4</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>56 Days</td>
</tr>
<tr>
<td>GI.1</td>
<td>1000</td>
<td>100000</td>
</tr>
<tr>
<td>GII.4</td>
<td>1000</td>
<td>100000</td>
</tr>
</tbody>
</table>

Vaccinations: ↑↑

Vaccine administered on Day 0 and 28
LV03-104: Takeda IM Norovirus Vaccine Candidate

Breadth of Response

- Vaccination with 50mcg/50mcg intramuscular vaccine in humans induces broad functional antibody responses
  - Vaccination induces HBGA blocking antibody response against strains and types not included in vaccine
  - Consensus GII.4 antigen induced antibody response against Sydney 2012 GII.4 strain that emerged 1-2 years later

Baric et al., Fifth International Conference on Calicivirus, 2013
Takeda Norovirus Vaccine Candidate

Post-Vaccination vs Post-Infection Antibody Titers

- Serum antibody profile in vaccinated adults (study LV03-104) is similar to post-infection profile in a separate oral GI.1 challenge study
  - Responses shown to GI.1 antigen

Pan is a specific anti-norovirus ELISA assay
LV03-105: GII.4 Challenge Study
Safety and Immunogenicity

- Phase I/II randomized, double blind, multi-center, placebo-controlled human challenge trial
- Endpoints: safety, immunogenicity, and efficacy
- Conducted in 132 healthy adults, 18-50 years
- Subjects received two IM injections of bivalent vaccine 28 days apart or placebo
- GII.4 challenge on study day 56 (or asap thereafter)
- Results
  - No attributable SAEs throughout the observation period
  - Increase in challenge strain blocking antibody titers following vaccination
  - Higher GMTs following vaccination than after challenge in placebo subjects
  - GMTs not increased in vaccinees post challenge
LV03-105: GII.4 Challenge Study
HBGA GMT’s Through Day 30 after Challenge

Vaccination:  
Challenge:  

Vaccine administered on Day 0 and 28
### LV03-105 Human Challenge Study Results

**Inpatient Phase, all Challenged subjects, Per Protocol Population**

<table>
<thead>
<tr>
<th>Gastroenteritis Symptom (post-hoc analysis)</th>
<th>Vaccine (%) N = 50</th>
<th>Placebo (%) N = 48</th>
<th>Rate Difference (95% CI)</th>
<th>% Reduction (95% CI)</th>
<th>p value (Fisher’s Exact)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe vomiting AND/OR diarrhea</td>
<td>0 (0.0%)</td>
<td>4 (8.3%)</td>
<td>-8.3 (-16.2, -0.5)</td>
<td>100% (-,-)</td>
<td>0.054</td>
</tr>
<tr>
<td>Moderate or severe vomiting AND/OR diarrhea</td>
<td>3 (6.0%)</td>
<td>9 (18.8%)</td>
<td>-12.8 (-25.6, 0.1)</td>
<td>68% (-11.2, 90.8)</td>
<td>0.068</td>
</tr>
<tr>
<td>Mild, moderate or severe vomiting AND/OR diarrhea</td>
<td>10 (20.0%)</td>
<td>20 (41.7%)</td>
<td>-21.7 (-39.5, -3.8)</td>
<td>52% (8.3, 74.9)</td>
<td>0.028</td>
</tr>
</tbody>
</table>

**Bernstein et al, ID Week 2013, Oct 2-6 2014**

- Severity of illness by modified Vesikari score reduced in subjects receiving vaccine vs placebo (p=0.023)
- Composite primary endpoint (any illness, positive by norovirus assay in stool) not met, results inform design of efficacy trial

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Takeda Pharmaceutical Company Limited
Secondary Endpoint: Challenge Virus Shedding

- 9 placebo recipients who met the predefined illness definitions continued to shed virus at day 10 post-challenge vs 4 vaccinees.
- Mean viral load in stool samples following illness were observed to be 2 logs lower in vaccinees (not tested for infectivity).
Conclusions

• Norovirus illness is widespread and potentially severe

• VLP vaccines are associated with reduction in major symptoms of norovirus gastroenteritis in humans after live virus challenge

• Reduction of illness symptoms and observed impact on viral load may have favorable impact on global burden of illness

• Data support evaluation of norovirus VLP vaccines in large field studies