Rotavirus immune responses and correlates of protection (CoP)

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Compartmentalization of the immune system

Intestinal compartment

Peyer’s Patch

\(\alpha 4\beta 7^+\) CCR9+ memory B cell

ASC

Polymeric IgA

LP

ExP + ExC

Blood

ExC

Sistemic compartment

Spleen

CD62L+ memory B cell

ASC

Monomeric IgG, IgA

Monomeric IgA, IgG

RV-memory B cells with an intestinal homing phenotype in vaccinees

Serum RV-IgA and RV-specific IgD-, α4β7+, CCR9+ mBc correlate weakly (rho< 0.2) with protection after D2 when vaccinees and placebo recipients are considered together

Two problems

• Frequencies of RV-specific mBc are not different between vaccinees and placebo recipients and do not correlate well with protection.

• Are we measuring the relevant cells?

• Protection is higher than frequency of children that have RV-IgA.

• Can we indirectly measure the “missing” intestinal antibodies?
RV-specific mBc are enriched in the IgM<sup>hi</sup>, IgD<sup>low</sup> subset

Can we quantify RV-specific intestinal antibodies in blood?
RV-specific SIg titers in plasma of vaccinees and placebo recipients after D1 or D2 and in protected and non protected individuals
Comparison of RV-IgA and RV-Sig as CoP

A

% of Children Protected

Log 2 Inverse Titer of Plasma RV-IgA After D2

B

% of Children Protected

Log 2 Inverse Titer of Plasma RV-Sig After D2

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# Comparison between RV-SIg and RV-IgA

<table>
<thead>
<tr>
<th></th>
<th>RV-SIg</th>
<th>RV-IgA</th>
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</thead>
<tbody>
<tr>
<td><strong>Specificity vaccination after dose 2</strong></td>
<td>74%</td>
<td>92%</td>
</tr>
<tr>
<td><strong>Sensitivity vaccination after dose 2</strong></td>
<td>48%</td>
<td>50%</td>
</tr>
<tr>
<td><strong>Differences between titers of vaccinees and placebo recipients</strong></td>
<td>Yes</td>
<td>No</td>
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<tr>
<td><strong>Higher frequencies of protected vaccinees than placebo recipients without the marker</strong></td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Specificity protection after dose 2</strong></td>
<td>85%</td>
<td>88%</td>
</tr>
<tr>
<td><strong>Sensitivity protection after dose 2</strong></td>
<td>40%</td>
<td>28%</td>
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<tr>
<td><strong>Differences in titers between protected and non protected children</strong></td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td><strong>Correlation with protection (vaccinees/placebo)</strong></td>
<td>After Dose 2</td>
<td>After Dose 2</td>
</tr>
</tbody>
</table>
Conclusions

• IgM RV-Bc are probably composed of both antigen experienced and non experienced cells.
• “Antigen experienced” IgM and switched RV-mBc that express intestinal homing receptors may be good correlates of protection.
• RV-SIg includes RV-IgM and seems more sensitive, but less specific in detecting protection.
• RV-SIg can be complementary to RV-IgA as a correlate of protection in vaccine trials.
In favor of Serum RV-IgA as a correlate of protection

• Reflects duodenal RV-IgA levels 4 months after RV natural infection.

• Correlates with protection after natural infections in children.

• Follows Prentice’s first condition as a CoP for RV1 as it correlates with the true clinical endpoint in an individual trial.

• Using meta-analysis it correlates with protection in different vaccine settings for both RV1 and RV5.
Correlation between RV-IgA and protection may vary for each type of vaccine
Against Serum RV-IgA as a correlate of protection

- It fails to fulfill Prentice’s second condition for a surrogate endpoint, as it does not “fully capture the treatment’s ”net effect “on the true clinical endpoint.” But it is “reasonably likely to predict clinical benefit”, so it is a level 3 endpoint surrogate of protection.
- It is a “non-mechanistic” CoP, hence, any vaccine change affecting this biomarker may or may not affect the clinical endpoint.
- A dose effect (likelihood of not having a RV associated-GE with each 1 log increase in RV-IgA titer) has not been observed.
- Vaccinees without serum RV-IgA have significantly less RV GE than placebo recipients, suggesting that factors other than serum RV-IgA play a role in protection.
Proposals to validate RV-IgA as a level 2 endpoint surrogate marker

• For new human attenuated vaccines: evaluate Vaccine Efficacy with a clinical endpoint (with delayed OPV), assessing serum RV-IgA with a standardized protocol and testing in “parallel” RV1. If the correlation between RV-IgA and protection induced by new RV vaccines is similar to the one observed for RV1, serum RV-IgA could be considered a practical “validated” level 2 surrogate endpoint for this type of vaccine.

• For new heterologuos vaccines: Determine if RV-IgA correlates with protection after RV5 in an individual trial. And repeat with RV5 as for RV1 above.
Prioritization of blood assays as RV correlates of protection against GE

<table>
<thead>
<tr>
<th></th>
<th>IgA</th>
<th>Slg</th>
<th>Conform VP4/7 Slg/IgA</th>
<th>Gut homing mBc</th>
<th>Antibody Lymph Sup</th>
<th>Gut homing T cells</th>
<th>Neutralize Ab</th>
<th>IgG</th>
</tr>
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<tbody>
<tr>
<td>Not present in “naïve” children</td>
<td>+++</td>
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<td>+++</td>
<td>+++</td>
<td>+++</td>
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<tr>
<td>Mechanistic</td>
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<td>++</td>
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<tr>
<td>Practical to measure</td>
<td>+++</td>
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<td>Reflects intestinal immunity</td>
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<td>Reflects long lasting protection</td>
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**IgM^hi, IgD^{low} subsets have different phenotypes**

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**Age-related aspects of human IgM^+ B cell heterogeneity**

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RV-specific IgA bound to secretory component (SIgA) in serum and secretions