Applicability of Adjuvants

T cell vaccines
Antibody Response Broadening
Antigen Dose Sparing
Vaccine Dosage Sparing
Immune Senescence
Vaccine Therapy
Points to Consider

Adjuvant Choice, Formulation Selection:
- Safety
- Availability
- Choice of Antigen (VLP, Soluble Protein, etc.)
- Route of Administration
- Type of Response(s) Desired
  - CD4
  - CD8
  - nAB
  - Mucosal
Adjuvants in Vaccines

Adjuvants in approved vaccines:

- **Alum**
- **MF59** (squalene emulsion)
- **AS03** (squalene/tocopherol emulsion)
- **AS04** (MPL-Alum)

Clinical Development (partial list):

- **AF3** (squalene o/w emulsion)
- **GLA** (TLR 4 agonist)
- **Flagellin** (TLR 5 agonist)
- **AS01**
- **SE** (squalene o/w emulsion)
- **CoVaccine** (TLR 4 agonist)
- **IC31** (dI:dC – TLR9 ago.)
What goes into a vaccine?

Vaccine = antigen + delivery system + adjuvant

- Antigen Mining
- Molecular Biology
- Expression Systems
- Purification
- Characterization
- TLR-agonist screening
- etc...

Mix antigen with something

- Antibody response
- CMI characterization
- Safety trials
- Efficacy trials
- Etc...

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TLR Agonist turns into an Adjuvant

- Micelle: Nanomicellar GLA
- Emulsified: GLA-SE
- Small Particle: GLA/Alum
- Liposome: GLA-LI
TLR4 Ligands: Demonstrate Ideal Adjuvant Properties

- Mature TLR4 expression restricted to macrophages and dendritic cells in humans (no direct effect on human lymphocytes)
- Transient local effects (low levels of IL-10, TGF-b; reduced inflammation leads to better central memory)
- Only TLR in approved vaccines (regulatory advantages because of familiar and approved mechanism of action)

- SYNTHETIC TLR4 L available in millions of doses, and COST EFFECTIVE
Targeted Nanostructures

Organic/inorganic Hybrid Hollow Spheres Prepared from TiO2-stabilised Pickering Emulsion Polymerization
Adjuvant Formulation Library

GLA
- Aqueous suspension
- Alum-adsorbed
- Liposome
- Niosome
- Emulsion

R848
- Aqueous solution
- Liposome
- Emulsion

QS21
- Aqueous solution
- Liposome
- Emulsion

CpG
- Aqueous solution
- Emulsion

Poly (I:C)
- Aqueous solution
- Liposome
- Emulsion

- GLA + QS21
  - Aqueous suspension
  - Liposome
  - Emulsion

- GLA + R848
  - Aqueous suspension
  - Liposome
  - Emulsion

- GLA + CpG
  - Aqueous suspension
  - Emulsion

- GLA + Poly (I:C)
  - Aqueous suspension
  - Emulsion
### IDRI Adjuvant Program: Active Clinical Support (Non-Profit Mission Partners)

<table>
<thead>
<tr>
<th>Collaborator</th>
<th>Disease Area</th>
<th>Adjuvant</th>
<th>GLA Dose (Route of Admin)</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fiocruz</td>
<td>Schistosomiasis</td>
<td>GLA-SE</td>
<td>10µg (IM)</td>
<td>Active: Participants in follow up phase</td>
</tr>
<tr>
<td>Rockefeller University</td>
<td>Adjuvant</td>
<td>GLA-AF, GLA-SE, SE</td>
<td>2µg (Sub-Q, IM, ID)</td>
<td>Active: 32 participants have been vaccinated. 16 participants to be enrolled in 2nd arm pending review of safety data.</td>
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<tr>
<td>St. George’s University of London</td>
<td>HIV</td>
<td>GLA-AF</td>
<td>5µg (IM, IVAG)</td>
<td>Active: 6 participants have been vaccinated</td>
</tr>
<tr>
<td>Sabin Institute (Brazil)</td>
<td>Hookworm</td>
<td>GLA-AF</td>
<td>2.5µg (IM)</td>
<td>Active: 12 participants have been vaccinated</td>
</tr>
<tr>
<td>IDRI- Leishmaniasis (F3)</td>
<td>Lesihi specialist</td>
<td>GLA-SE</td>
<td>2µg/5µg (IM)</td>
<td>Active: 18 participants have been vaccinated</td>
</tr>
<tr>
<td>WRAIR</td>
<td>Malaria</td>
<td>GLA-SE</td>
<td>2µg/5µg (IM)</td>
<td>Active: 8 participants have been vaccinated</td>
</tr>
</tbody>
</table>
Formulations for Memory Responses
HIV Memory Immune Responses

GLA formulations induce strong responses in HIV with memory B cell migration to the bone marrow
Ab Response Broadening

Not Just Increased Titer
GLA formulations induce immune responses in NHP that cross react with drifted strains.
### Flu-HA protein microarray analysis of antibody reactivity

- **6 different sera samples per chip**
- **140 proteins, 60 different HA proteins, ~7500 measurements/chip**
- **9 unique measurements per protein**
  - triplicate
  - 3 dilutions
- **Simultaneous measurements of IgG1 and IgG2c isotypes**
Targeting TLRs Expands the Antibody Repertoire in Response to a Malaria Vaccine

Steven R. Wiley,1* Vanitha S. Raman,2* Anthony Desbiens,2 Hilton R. Bailor,2 Rukmini Bhardwaj,3 Ahmed Rushdi Shakir,3 Steven G. Reed,2,4 Chetan E. Chitnis,3† Darrick Carter2,5†

Vaccination with an isolated antigen is frequently not sufficient to elicit a protective immune response. The addition of adjuvants to the antigen can increase the magnitude and breadth of the response generated, but quantification of this increase as a function of adjuvant has been intractable. We have directly determined the variation of the immunoglobulin G variable-chain repertoire of an entire organism as a function of vaccination. Using the well-established Plasmodium vivax antigen, PvRll, and massively parallel sequencing, we showed that the use of a Toll-like receptor (TLR) agonist in the vaccine formulation increased the diversity of the variable region sequences in comparison to the use of an oil-in-water emulsion adjuvant alone. Moreover, increased variable domain diversity in response to the use of TLR agonist–based adjuvants correlated with improved antigen neutralization. The use of TLR agonists also broadened the range of polymorphic variants against which these antibodies could be effective. In addition, a peptide microarray demonstrated that inclusion of adjuvants changed the profile of linear epitopes from PvRll that were recognized by serum from immunized animals. The results of these studies have broad implications for vaccine design—they may enable tailored adjuvants that elicit the broad spectrum of antibodies required to neutralize drifted and polymorphic pathogen strains as well as provide a method for rapid determination of correlates of adjuvant-induced humoral immunity.

Malaria
Families of Antibodies Induced

Ag Dose Sparing
Flu Clinical Dose Sparing

PanBlok® H5 + GLA-SE Phase 1 Clinical Study Results

GLA-SE adjuvant provides 30-fold dose sparing

HAI titer fold-increase

<table>
<thead>
<tr>
<th>Dose Group</th>
<th>HAI</th>
</tr>
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<tbody>
<tr>
<td>135</td>
<td>2.6</td>
</tr>
<tr>
<td>45</td>
<td>2</td>
</tr>
<tr>
<td>45+</td>
<td>6.4</td>
</tr>
<tr>
<td>15+</td>
<td>6.2</td>
</tr>
<tr>
<td>7.5+</td>
<td>4</td>
</tr>
<tr>
<td>3.8+</td>
<td>3.8</td>
</tr>
<tr>
<td>Placebo</td>
<td>1</td>
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</tbody>
</table>

Seroconversion rate at 21 days post 2nd dose
Selective Th1 Induction; Correlates with Protection (TB, Leishmania)
Emulsions/GLA Dose Effect

- GLA-SE enhances Th1 responses
- while SE promotes Th2 cytokines
TB;

Formulations Affect Responses

![Graph showing IFN-γ secreting cells/million for different formulations]

- Saline
- ID93 i.m.
- ID93 + GLA-AF i.m.
- ID93 + GLA-SE i.m.
- ID93 + GLA/Niosomes i.m.
- ID93 + GLA/Liposomes i.m.

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TB: Formulation Differences Are Critical (mouse protection)
TB

Altered burden affects outcome

- (A) Saline
- (B) BCG
- (C) ID93/SE
- (D) ID93/GLA-SE

\[ P < 0.05 \]
\[ \text{n.s.} \]
GLA-SE stimulates Th1 immune responses; Emulsion alone stimulates Th2
Boosting BCG or Natural Infection

Adjuvant Selection Is Critical
ID93+GLA-SE and ID83+GLA-SE: Increased Protection in BCG primed Guinea Pigs
Mice were infected with LDA of Mtb. Fifteen days later mice were treated for 90 days with a combination of antibiotics. A subset of mice in each group were immunized three times, three weeks apart with the candidate fusion vaccine one day after chemotherapy was completed. Protection was assessed by monitoring animal survival.
Brazil Clinical Trial – Leishmaniasis

Time to Relapse-Free Cure, through Day 336
Per-Protocol Population (n = 41)

Proportion Cured

- **Vaccine + CTX**: 96%
- **Adjuvant + CTX**: 75%
- **CTX Alone**: 63%

Logrank test p-value = 0.03
Therapeutic Vaccination: Lessons Learned

• Safe in Infected, Diseased Individuals
  • Applications for PEP, Therapy
• In Human Leishmaniasis, Poor Responses to Vaccine Antigens Prior to Vaccination
• However, Strong Ag-Specific Responses Are Induced Post-Vaccine
• Immune Response Quality Can Be Re-Directed With Protein/Adjuvant
TLRL Synergy (4 + 9)
Cross Cutting Lessons to Accelerate Clinical Development

- Common Platforms Useful For Multiple Vaccine Candidates
  - Adjuvant/Formulation Selection is Critical
- More Adjuvant is Not Better
  - MPL; 40ug vs. 10ug
  - GLA Formulations: 2ug < 5ug > 20ug
- Lower Hurdles for Development
  - Build on Known Adjuvants When Possible
  - Use Minimal Amounts
  - Induce Rather Than Administer Cytokines, Cytokine Genes
Funding the Development

BMGF  NIAID
BARDA  DARPA  Murdock Trust  ALM