Vaccine Adjuvants

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Industry Representative Member, National Vaccine Advisory Committee

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Presentation is for educational purposes only; this is not a sales, marketing or promotional presentation
Vaccine Science: Two Centuries of Continuous Research, Improvements, and Achievements

# Current Challenges for Vaccines

<table>
<thead>
<tr>
<th>Challenging populations</th>
<th>Need for booster vaccinations</th>
<th>Recombinant antigens</th>
<th>Pathogens</th>
<th>Need for antigen sparing</th>
</tr>
</thead>
<tbody>
<tr>
<td>due to impaired immune system (e.g., elderly, children, immunocompromised)</td>
<td>Increase the level of the immune response</td>
<td>Recombinant antigens generally less immunogenic than live or attenuated organism vaccine&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Pathogens that require broad and complex immune response</td>
<td>Need for antigen sparing potential supply problems (e.g., pandemic flu)</td>
</tr>
</tbody>
</table>

| Increase the level of the immune response | Prolong the duration of the immune response, improve immune memory, and protection | Overcome a weakened immunogenicity | Induce the generation of a high and broad immune response | Reduce the amount of antigen needed (dose-sparing) |

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# Examples of Novel Approaches to Vaccine

<table>
<thead>
<tr>
<th>DNA&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Live vectors&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Reverse vaccinology&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Self-amplifying RNA&lt;sup&gt;2&lt;/sup&gt;</th>
<th>Novel adjuvants and adjuvant combinations&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
</table>
| • Pathogen-derived genetic material coding for the antigens contained in a non-replicating DNA plasmid  
• Antigen is expressed by the cells of the vaccine recipient | • Targeted antigens encoded by gene(s) incorporated into the vector’s genetic material  
• Antigen is expressed by a vector (like virus or bacterium) that is non-pathogenic | • Computer analysis of the pathogen’s entire genome is conducted to find genes that may be antigenic  
• Vaccine candidate identified based on prediction of protein sequences similar to pathogen’s genome sequences | • Synthetic virus particles include antigen proteins  
• Once inside host cell cytoplasm, these self-amplify in large amounts, express antigen proteins and interact with the host immune system | • Substances included in a vaccine formulation to enhance the quality and strength of the immune response induced by the vaccine antigen(s) |

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Adjuvant\(^1,2\)

- From Latin, *adiuvare*: to aid
- Substance included in a vaccine to enhance and modulate the quality and/or strength of the immune response induced by the antigen
- Old technology, made new

Vaccines With or Without Adjuvants

- No adjuvant
- Adjuvanted

Adjuvant discovery

- Smallpox
- Plague
- Cholera
- Typhoid
- Rabies
- Pertussis
- Tuberculosis
- Yellow fever
- Influenza whole virus
- Pneumococcus
- Polio (IPV)†
- Diphtheria
- Tetanus
- Hib polysaccharide
- Meningococcus
- Influenza split,
- Influenza
- Mumps
- Meningococcus ACWY polysaccharide
- Pertussis
- Hib conjugate
- Hib polysaccharide
- Meningococcus B
- Hepatitis A
- Typhoid live attenuated
- Typhoid polysaccharide
- Meningococcus C conjugate
- Typhoid B
- Polio (OPV)
- Polio
- Tetanus
- Diphtheria, Tetanus, Pertussis-based combinations
- Varicella
- Meningococcus
- Hepatitis B
- Zoster recombinant
- Meningococcus B
- Influenza live attenuated
- Rotavirus
- Influenza
- Pneumococcus conjugate
- Meningococcus C conjugate
- Hepatitis B
- Zoster live attenuated
- HPV
- Meningococcus
- ACWY conjugate
- Varicella
- Typhoid polysaccharide
- Mumps
- Meningococcus ACWY conjugate
- Meningococcus B
- Influenza
- Pneumococcus conjugate
- Meningococcus C conjugate
- Typhoid live attenuated
- Typhoid polysaccharide
- Hepatitis B

†IPV is adjuvanted when formulated in combination with diphtheria, tetanus, pertussis-based vaccines, but is not adjuvanted when formulated as a standalone vaccine.

Hib = Haemophilus influenzae type b; HPV = human papilloma virus; IPV = inactivated polio vaccine; OPV = oral polio vaccine (live).

Antigens May Need Help: The Role of Adjuvants

- Immunogenicity
  - Native virus
  - Replicating (live attenuated)
  - Non-replicating (inactivated)
  - Subunit (e.g., split virus)
  - Purified antigens (e.g., recombinant protein)

- Tolerability
  - High
  - Low

- Adjuvants
  - Purified antigens/Adjuvants combination

Figure adapted from Di Pasquale A, et al. Vaccines. 2015;3:320-343.
Adjuvants Work by Stimulating Innate Immunity

**Innate immune system**
Required for the onset

**Adjuvant**
- Recognized by specific receptors (TLRs, NLRs)
- Stimulate antigen presentation to cells from adaptive immunity (specific T- and B-cells)

**Adjuvanted vaccine**

**Adaptive immune system**
Specific, provide memory

**Antigens**
- Antigen-specific T- and B-cells provide the specificity to the vaccine
- Memory T- and B-cells confer long-term protection against disease

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Expected Impact of Adjuvants on Vaccine Immune Response

Different Categories of Adjuvants Have Been Developed

- Mineral salts
- Emulsions
  - Oil droplet
  - Oil/Water surfactant
  - Water
- Particulate Formulations
  - Phospholipid bilayer
  - Aqueous core
  - Liposomes
  - Saponin complexes

## Adjuvants in Licensed Products

<table>
<thead>
<tr>
<th>Adjuvant</th>
<th>Mechanism or Receptor</th>
<th>Licensed product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aluminum salts</td>
<td>NaIp3, ITAM, antigen delivery</td>
<td>Numerous (e.g., pertussis, hepatitis, pneumococcal)</td>
</tr>
<tr>
<td>AS04</td>
<td>TLR4</td>
<td>HPV</td>
</tr>
<tr>
<td>Emulsions (MF59, AS03)</td>
<td>Immune cell recruitment, antigen uptake</td>
<td>Influenza</td>
</tr>
<tr>
<td>AS01</td>
<td>TLR4, inflammasome</td>
<td>Zoster</td>
</tr>
<tr>
<td>CpG ODN</td>
<td>TLR9</td>
<td>Hepatitis B</td>
</tr>
</tbody>
</table>

## Adjuvants in Development

<table>
<thead>
<tr>
<th>Adjuvant</th>
<th>Mechanism or receptor</th>
<th>Clinical phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>ISCOMs (Matrix-M)</td>
<td>Unknown</td>
<td>2</td>
</tr>
<tr>
<td>dsRNA analogues</td>
<td>TLR3</td>
<td>1</td>
</tr>
<tr>
<td>Flagellin</td>
<td>TLR5</td>
<td>1</td>
</tr>
<tr>
<td>C-type lectin ligands</td>
<td>Mincle, NaIp3</td>
<td>1</td>
</tr>
<tr>
<td>CD1d ligands</td>
<td>CD1d</td>
<td>1</td>
</tr>
<tr>
<td>GLA-SE</td>
<td>TLR4</td>
<td>1</td>
</tr>
<tr>
<td>IC31</td>
<td>TLR9</td>
<td>1</td>
</tr>
<tr>
<td>CAF01</td>
<td>Mincle, antigen delivery</td>
<td>1</td>
</tr>
</tbody>
</table>

Observed Benefits of Adjuvants in Candidate or Licensed Adjuvanted Vaccines

- Efficacy demonstrated for different antigens: split (influenza)\(^1\), parasite-derived (malaria)\(^2\), viral glycoprotein (herpes zoster)\(^3\), viral particles (HPV)\(^4\)
- Persistent increase in T-cell and antibody response in magnitude and quality (antibody breadth and cross-reactive T-cells)\(^1,5\)
- Benefits shown across the entire age spectrum (6-month-old infants to >80-year-old-adults)\(^3,6\) with the possibility to adapt dosage to age (eg, use of lower dose in pediatric formulation)\(^6\)
- Being used in vaccines in special populations, such as in immunocompromised or HIV+, with acceptable safety outcomes\(^7\)

Safety Is of Primary Importance From the Start of Development and Throughout the Entire Life of a Vaccine

- Vaccines are carefully evaluated under tight process controls and overseen by regulatory authorities
- Safety monitoring designed to rapidly identify rare and/or serious adverse events temporally linked to vaccination

General Reactogenicity and Safety

• Adjuvanted vaccines often have increased reactogenicity, especially at the injection site

• Local symptoms are usually mild/moderate, short-lasting and do not impact compliance

The safety profile of aluminum salt adjuvants has been well established through the use of billions of doses, in different populations, over more than 80 years

Licensed, adjuvanted vaccines have clinically acceptable benefit-risk ratios

No universal adjuvant to cover all vaccine needs

Different diseases may require different immune responses to elicit protection through vaccination

Appropriate selection of adjuvant-antigen combination is key to the formulation of novel and efficacious vaccines

Among All the Possibilities, How Is An Adjuvant Selected?\textsuperscript{1,2}

Understand:
- Host-pathogen interaction
- Antigen selection and production
- Optimized immunological tools

Tools to Develop the Next Generation of Adjuvants

**KNOWLEDGE-GENERATION MODEL**

- Study of adjuvanted vaccines with established safety & effectiveness
- Adjuvant “signature”

**DISCOVERY**

- New molecules (SMIPs)
- New/improved adjuvants
- Selection based on targeted signature
- New delivery systems

**IMPROVED ADJUVANTED VACCINES**

• More efforts are needed to highlight the importance of novel adjuvants in ongoing vaccine research and their potential to prevent many more infectious diseases through vaccination. As industry, we often say, "the low hanging fruit has been picked." Remaining vaccine targets are exceptionally difficult.

• Advances in understanding how adjuvanted vaccines interact with the immune system should help in mitigating health risks and in better analyzing those events when they occur. Considering the increasing importance of vaccine confidence, public perceptions of adjuvants should be assessed.