Adjuvants Used in Vaccines

National Adult and Influenza Immunization Summit

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This presentation on the Adjuvants Used in Vaccines and was created at the request of Bruce Gellin, MD, MPH, Deputy Assistant Secretary for Health, Director National Vaccine Program, Office US Department of Health and Human Services; Carolyn Bridges, MD, Associate Director for Adult Immunizations, Immunization Services Division, Centers for Disease Control and Prevention; and Litjen Tan, PhD, MS, Chief Strategy Officer, Immunization Action Coalition.

This is not a sales, marketing or promotional presentation.
Vaccines are Complex Biological Mixtures of Several Components

- **Antigens**
- **Adjuvant**
- **Stabilizers**
- **Diluents**
- **Trace components**

**Adjuvant**

From Latin, *adiuvare*: to aid

Pharmacological/immunological agent that modifies the effect of other agents

Compounds that enhance or shape the immune response

Immunological adjuvants added to vaccines stimulate the host immune system's response to target antigen, but do not themselves confer immunity

Old technology, made new
Antigens May Need Help: Role for Adjuvants

CURRENT CHALLENGES FOR VACCINES

- Challenging population: due to impaired immune system (e.g., elderly, children, immunocompromised)
- Need for booster vaccinations
- Recombinant antigen: Generally less immunogenic than live or attenuated organism vaccine
- Pathogen: that requires broad and complex immune response
- Need for antigen sparing: Potential supply problems (e.g., pandemic flu)

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)

Need for antigen sparing
Potential supply problems (e.g., pandemic flu)
Need for booster vaccinations
Challenging population: due to impaired immune system (e.g., elderly, children, immunocompromised)
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Adjuvants Activate Innate Immunity

Innate immunity
Adaptive immunity

Antigen-presenting Cell (APC)
MHC-peptide
TCR

An adjuvant can activate the innate immune system by acting like pathogen-associated molecular patterns and thus can enhance or restore the ability of the immune system to identify a vaccine antigen as a pathogen with subsequent activation/maturation of APCs and activation of the adaptive immune system.

MHC = major histocompatibility complex; TCR = T-cell receptor.

Microbial Structures\textsuperscript{1,2,3}

Defense triggers
(danger signals), e.g. PAMPs act as intrinsic immune-triggers

Alert immune system | Stimulate/direct immune response | Specific immune response

PAMPs = pathogen-associated molecular patterns

1. Dougan G & Hormaeche C. Vaccine 2006;24(S2):S13–S19
3. Garçon N, et al. Understanding modern vaccines, Perspectives in vaccinology, Vol 1, Amsterdam: Elsevier; 2011; Chapter 4:89-113

Selecting From Nature: Right Antigens and Well Characterized Adjuvants\textsuperscript{1,2}

- Vaccine antigens alone may exhibit insufficient immunogenicity
- Some selected adjuvants act as substitutes for natural immune-defense signals, enhancing and directing the immune response

Defense triggers

Adjuvants act as substitutes for natural immune-defense triggers

1. Dougan G & Hormaeche C. Vaccine 2006;24(S2):S13–S19
Antigens May Need Help: Why and When? The Role of Adjuvants¹,²

Illustrative figure based on concepts from:

Adjuvant: Expected Impact on Vaccine Immune Response

Illustrative figure based on concepts from:
Garçon N et al. Understanding modern vaccines, Perspectives in vaccinology, Vol 1, Amsterdam: Elsevier; 2011; Chapter 4:89-113

Adjuvants in Clinical Trials/Licensed Vaccines

<table>
<thead>
<tr>
<th>Adjuvant name</th>
<th>Mechanism or receptor</th>
<th>Clinical phase or licensed product</th>
</tr>
</thead>
<tbody>
<tr>
<td>dsRNA analogues (for example, poly(I:C))</td>
<td>TLR3</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Lipid A analogues (for example, MPL, R5529, GLA, E6020)</td>
<td>TLR4</td>
<td>Cervarix®</td>
</tr>
<tr>
<td>Flagellin</td>
<td>TLR5</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Imidazoquinolines (for example, Imiquimod, R848)</td>
<td>TLR7 and TLR8</td>
<td>Aldara</td>
</tr>
<tr>
<td>CpG ODN</td>
<td>TLR9</td>
<td>Phase 3</td>
</tr>
<tr>
<td>Saponins (for example, QS21)</td>
<td>Immunostimulatory</td>
<td>Phase 3</td>
</tr>
<tr>
<td>C-type lectin ligands (for example, TDB)</td>
<td>Mincle, NaIp3</td>
<td>Phase 1</td>
</tr>
<tr>
<td>CD1d ligands (for example, α-galactosylceramide)</td>
<td>CD1d</td>
<td>Phase 1</td>
</tr>
<tr>
<td>Aluminum salts (for example, aluminum oxyhydroxide, aluminum phosphate)</td>
<td>NaIp3, ITAM, Ag delivery</td>
<td>Numerous license products</td>
</tr>
<tr>
<td>Emulsions (for example, MF59, AS03)</td>
<td>Immune cell recruitment, ASC, Ag uptake</td>
<td>Fluad®, Pandemrix®</td>
</tr>
<tr>
<td>AS01 (MPL, QS21, liposomes)</td>
<td>TLR4, Immunostimulatory</td>
<td>Phase 3</td>
</tr>
<tr>
<td>AS04 (MPL, aluminum salt)</td>
<td>TLR4</td>
<td>Cervarix</td>
</tr>
<tr>
<td>AS15 (MPL, QS21, CpG, liposomes)</td>
<td>TLR4, TLR9, immunostimulatory</td>
<td>Phase 3</td>
</tr>
<tr>
<td>GLA-SE (GLA, emulsion)</td>
<td>TLR4</td>
<td>Phase 1</td>
</tr>
<tr>
<td>IC31 (CpG, cationic peptide)</td>
<td>TLR9</td>
<td>Phase 1</td>
</tr>
<tr>
<td>CAF01 (TDB, cationic liposomes)</td>
<td>Mincle, Ag delivery</td>
<td>Phase 1</td>
</tr>
<tr>
<td>ISCOMs (saponin, phospholipid)</td>
<td>Immunostimulatory</td>
<td>Phase 2</td>
</tr>
</tbody>
</table>

Ag = antigen; ASC= apoptosis-associated speck-like protein containing caspase recruitment domain; dsRNA = double-stranded RNA; ITAM = immunoreceptor tyrosine-based activation motif; TDB = trehalose dibehenate. Some particulate formulations (such as aluminum salts and emulsions) also generate immunomodulatory activity.

Cervarix and Pandemrix are trade marks of the GlaxoSmithKline group of companies; Fluad is trade mark of Novartis Vaccines and Diagnostics Limited

Adapted from Reed SG et al, Nature Med 19: 1597-1608, 2014

Pearl Of Wisdom

Adjuvants, acting as substitutes for natural immune defense signals, enhancing and directing the immune response, have the potential to help antigens overcome challenges including:\(^1,^2\)

- challenging populations
- need for booster vaccination
- poorly immunogenic recombinant antigens
- complex pathogens
- antigen sparing