National Vaccine Advisory Committee
Overview of Progress and Landscape in Adjuvants

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Why do we need adjuvants?
U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Adjuvants’ Role in a Vaccine

- Makes vaccine more cost effective (fewer doses required)
- Effective innate immune signals, including danger signals
- Good immunomodulatory capacity
- High specific antibody production
- Antigen-specific clonal expansion
- Generation of cytotoxic T cells
- Long-lasting adaptive immune response
- Makes antigen more potent (less dose required)


NATIONAL VACCINE PROGRAM OFFICE
Modern Adjuvants Discovery

William Coley (1893)
- Killed Bacteria
- MPL: AS04, AS01
- CpG

Gaston Ramon (1925)
- Oils
- MF59, AS03
- Plant Extracts
- QS21, AS01

Alexander Glenny (1926)
- Aluminum Salts

Adapted from: “M. Friede, Adjuvants for Vaccines, a Pragmatic Approach”, ADVAC, 2016
Adjuvant Experimentation in Vaccines Timeline

1930’s

- Need for a substance that when added to the antigen would improve the immune response

1980’s

- QS-21; MF59; MPL; Oligonucleotides: Need to induce proper immune response against difficult pathogens (HIV and Malaria)

1990’s

- AS01, AS02, etc.: Insufficient immune response produced by challenging vaccine candidates; to stimulate the production of an effective and long lasting immune response in certain populations
**Different Types of Adjuvants Have Distinct Effects on the Immune System**

<table>
<thead>
<tr>
<th>Adjuvant</th>
<th>Innate responses</th>
<th>Effects on DC</th>
<th>Type of immune response</th>
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<tbody>
<tr>
<td><strong>Aluminum salts</strong></td>
<td>NALP3/P2X7R-dependent neutrophil recruitment, DAMP release: (chromatin, histones, IL-1α, NETs, uric acid), TBK1/Irf3/STING dependent effects on IgE</td>
<td>↑ migration to LN (i.p.) ↑ T cell interactions ↑ antigen presentation ↓ IL-12 secretion Reorganization of membrane lipids</td>
<td>TH2 TFH ↑ IgG1/IgE</td>
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<tr>
<td><strong>Emulsions</strong></td>
<td>Increases delivery to APC ↑ phagocytosis ↑ infiltration of monocytes ↑ cytokine production</td>
<td>↑ antigen presentation</td>
<td>TH1/TH2 ↑ IgG1/IgG2a</td>
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<tr>
<td><strong>MF59</strong></td>
<td>Monocyte recruitment, NALP3 activation (not required for adjuvant effects), DAMP release: (ATP), MyD88-dependent effects on cellular immunity</td>
<td>↑ migration to LN (i.p.) ↑ expression of costimulatory molecules</td>
<td>Polyfunctional TH1 TFH ↑ IgG2a, IgG1 ↑ antibody diversity/switching</td>
</tr>
<tr>
<td><strong>MPL</strong></td>
<td>TLR4/TRIF and type I IFNs Migration of monocytes to injection site</td>
<td>↑ expression costimulatory molecules and cytokines ↑ antigen presentation ↑ phagocytosis and endosomal activity</td>
<td>TH1 TFH CTL and ↑ antibody diversity and affinity</td>
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# Type of Adjuvants Tested in Vaccines Worldwide

<table>
<thead>
<tr>
<th>Adjuvant</th>
<th>Vaccines</th>
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<tbody>
<tr>
<td><strong>Mineral salts</strong></td>
<td></td>
</tr>
<tr>
<td>Aluminum salts AS04 (alum + MPL)</td>
<td>DT, DTaP, HVA, HBV, HPV (AS04 — see below), HiB, Meningococcus, Pneumococcus, IPV, HAV, HPV</td>
</tr>
<tr>
<td>Calcium phosphate</td>
<td>DT, DTaP, IPV</td>
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<tr>
<td><strong>Delivery systems</strong></td>
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<tr>
<td>Viral-like particles</td>
<td>HBV, HPV, in clinical trials for HAV, HCV, malaria, HIV, HPV, malaria, norovirus</td>
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<tr>
<td>Liposomes</td>
<td>HBV, HPV, in clinical trials for Hepatitis A, C, malaria, HIV, HPV, malaria, Norovirus</td>
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<tr>
<td>Microparticles (PLA/PLGA)</td>
<td>Malaria HPV, HBV</td>
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<tr>
<td><strong>Emulsions</strong></td>
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<tr>
<td>IFA (water-in oil emulsion)</td>
<td>Influenza (1950s)</td>
</tr>
<tr>
<td>AS02 (MPL + QS21 in oil-in water emulsion)</td>
<td>Malaria</td>
</tr>
<tr>
<td><strong>Squalene</strong></td>
<td></td>
</tr>
<tr>
<td>MF59</td>
<td>Influenza</td>
</tr>
<tr>
<td>AS03</td>
<td>AS03 — in clinical trial for HPV and malaria</td>
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<tr>
<td><strong>TLR agonists</strong></td>
<td></td>
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<tr>
<td>MPL-SE</td>
<td>Influenza (MPL)</td>
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<tr>
<td>AS04 (MPL + alum)</td>
<td>HPV, HBV</td>
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<tr>
<td>AS01 (MPL + QS21 in liposomes)</td>
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</tr>
<tr>
<td>AS02 (MPL + QS21 in oil-in water emulsion)</td>
<td>Malaria</td>
</tr>
</tbody>
</table>

# Adjuvants in Clinical Development/Licensed Worldwide

<table>
<thead>
<tr>
<th>Adjuvant</th>
<th>Description</th>
<th>Vaccine</th>
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</thead>
<tbody>
<tr>
<td><strong>Licensed</strong></td>
<td></td>
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<tr>
<td>Aluminum salts (Alum)</td>
<td>Insoluble particulates of hydroxide, phosphate or hydroxyphosphate sulfate</td>
<td>Included in licensed products for routine childhood vaccines and many others</td>
</tr>
<tr>
<td></td>
<td>salts</td>
<td></td>
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<tr>
<td>Oil-in-water emulsions (MF59, AS03)</td>
<td>Oil dispersed nanoemulsions (mainly squalene) stabilized with non-ionic surfactants</td>
<td>Included in licensed products for seasonal influenza vaccine (MF59) or pandemic influenza vaccines (MF59, AS03)</td>
</tr>
<tr>
<td>Virosomes</td>
<td>Dispersed lipid vesicles including viral membrane (influenza) proteins</td>
<td>In licensed products for influenza vaccine (Inflexal) and HAV vaccine (Epaxal)</td>
</tr>
<tr>
<td>AS04</td>
<td>Natural product TLR4 ligand (MPL) adsorbed on to alum</td>
<td>Licensed products for HBV vaccine (Fendrix) and HPV vaccine (Cervarix)</td>
</tr>
<tr>
<td>MPL</td>
<td>Natural product TLR4 ligand</td>
<td>Approved products for tree pollen and grass pollen allergies on a named patient basis in Europe (Pollinex)</td>
</tr>
<tr>
<td>RC-529</td>
<td>Synthetic TLR4 ligand adsorbed to aluminum hydroxide</td>
<td>Was a licensed product in Argentina for HBV (Supervax)</td>
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<tr>
<td><strong>Phase III</strong></td>
<td></td>
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<tr>
<td>Liposomes (AS01)</td>
<td>Dispersed lipid vesicles containing TLR4 ligand (MPL) and saponin QS-21</td>
<td>Phase III, submitted for licensure for malaria vaccine (RTS,5) and for approval for herpes zoster vaccine (HZ/su)</td>
</tr>
<tr>
<td>CpG ODN (1018 ISS)</td>
<td>Soluble TLR9 ligand (oligonucleotide) co-administered with HBV vaccine</td>
<td>Submitted for licensure for HBV vaccine</td>
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<tr>
<td>Topical cream with TLR7 ligand</td>
<td>Topical ointment of TLR7 ligand (imiquimod) applied in conjunction with</td>
<td>Influenza vaccine</td>
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<tr>
<td></td>
<td>intradermal vaccination</td>
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<tr>
<td><strong>Phase II</strong></td>
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<tr>
<td>EGVac system</td>
<td>Bacterial polysaccharide/bacterial DNA</td>
<td>Therapeutic HPV vaccine</td>
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<tr>
<td>Saponin complexes (ISCOM, Matrix-M)</td>
<td>Lipid, purified saponins and cholesterol cage-like nanocomplexes</td>
<td>Influenza vaccine</td>
</tr>
<tr>
<td>GLA-SE</td>
<td>Oil-in-water nanoemulsion with synthetic TLR4 ligand (GLA)</td>
<td>Tuberculosis vaccine, RSV vaccine, and Leishmania vaccine</td>
</tr>
<tr>
<td>IC31</td>
<td>Cationic peptide complexed with TLR9 ligand (oligonucleotide)</td>
<td>Tuberculosis vaccine</td>
</tr>
<tr>
<td>Oil-in-water emulsion (ISA51)</td>
<td>Oil dispersed nanoemulsion (mainly squalene) stabilized with non-ionic surfactant</td>
<td>Included in licensed seasonal influenza vaccine</td>
</tr>
<tr>
<td>AS02</td>
<td>Oil-in-water nanoemulsion with TLR4 ligand (MPL) and saponin, QS-21</td>
<td>Malaria and HIV vaccines (withdrawn after Phase II)</td>
</tr>
<tr>
<td>VAX2012Q, VAX125</td>
<td>TLR5 ligand protein (flagellin) linked to antigen</td>
<td>Influenza vaccine</td>
</tr>
<tr>
<td>Poly I:C (Ampligen, rintatolimod)</td>
<td>Double-stranded RNA polymer analogue and TLR3 ligand</td>
<td>Influenza vaccine Rabies vaccine</td>
</tr>
<tr>
<td>PIKA</td>
<td>Cationic liposome</td>
<td>Genital herpes vaccine based</td>
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</tbody>
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Timeline of Adjuvants and Adjuvant Systems Use in the U.S.

1930’s
- Aluminum Salts
- hepatitis A, hepatitis B, diphtheria-tetanus-pertussis (DTaP, Tdap), Haemophilus influenzae type b (Hib), human papillomavirus (HPV) and pneumococcus infection

2009
- AS04 (MPL/Alum)
- HPV (Cervarix)

2017
- AS01 (TLR4 ligand: MPL, and saponin: QS-21)
- MF59
- CpG ODN
New Adjuvanted Vaccines Licensed in 2017: Influenza Virus

• **FLUAD™** is a standard-dose, three-component (trivalent) inactivated flu vaccine that contains an adjuvant. It is manufactured using an egg-based process (like most flu vaccines), and is formulated with the adjuvant MF59.

• **FLUAD™** is only licensed and approved for persons aged 65 years and older

• Study conducted in Canada among adults 65 years of age and older during the 2011-2012 flu season found that **FLUAD™** was significantly more effective in preventing laboratory-confirmed influenza compared with an unadjuvanted standard-dose inactivated influenza vaccine
New Adjuvanted Vaccines Licensed in 2017: Hepatitis B Virus

- **Heplisav-B** is a combination of HBV surface antigen with Dynavax’s proprietary Toll-like receptor 9 (TLR9) agonist

- Indicated for prevention of infection caused by all known subtypes of hepatitis B virus in adults 18 years of age and older, as a **two dose series**
New Adjuvanted Vaccines Licensed in 2017: Herpes Zoster Virus

- **Shingrix** is a non-live, recombinant subunit vaccine approved in the United States and Canada to help prevent shingles (herpes zoster) in people aged 50 years or older. It combines an antigen, glycoprotein E, and an adjuvant system, AS01B.

- CDC recommends **Shingrix®** (recombinant zoster vaccine) as *preferred over Zostavax* (zoster vaccine live) for the prevention of herpes zoster (shingles) and related complications. CDC recommends two doses of **Shingrix** separated by 2 to 6 months for immunocompetent adults age 50 years and older.

- Zoster Vaccine Live (ZVL) **Zostavax**, a 1-dose live attenuated strain of VZV, recommended by the ACIP for use in immunocompetent adults aged ≥60 years.
The NIAID Vaccine Adjuvant Program: A Pipeline Of Novel Compounds To Safely Enhance Vaccine Efficacy

Dr. Wolfgang Leitner, NIH

Precision Vaccines: Using Adjuvants to Bring Precision Medicine to Vaccinology

Dr. Ofer Levy, Boston Children’s Hospital

Vaccine Adjuvants

Dr. Leonard Friedland, NVAC Member/BIO