National Vaccine Advisory Committee

Overview of Progress and Landscape in Adjuvants

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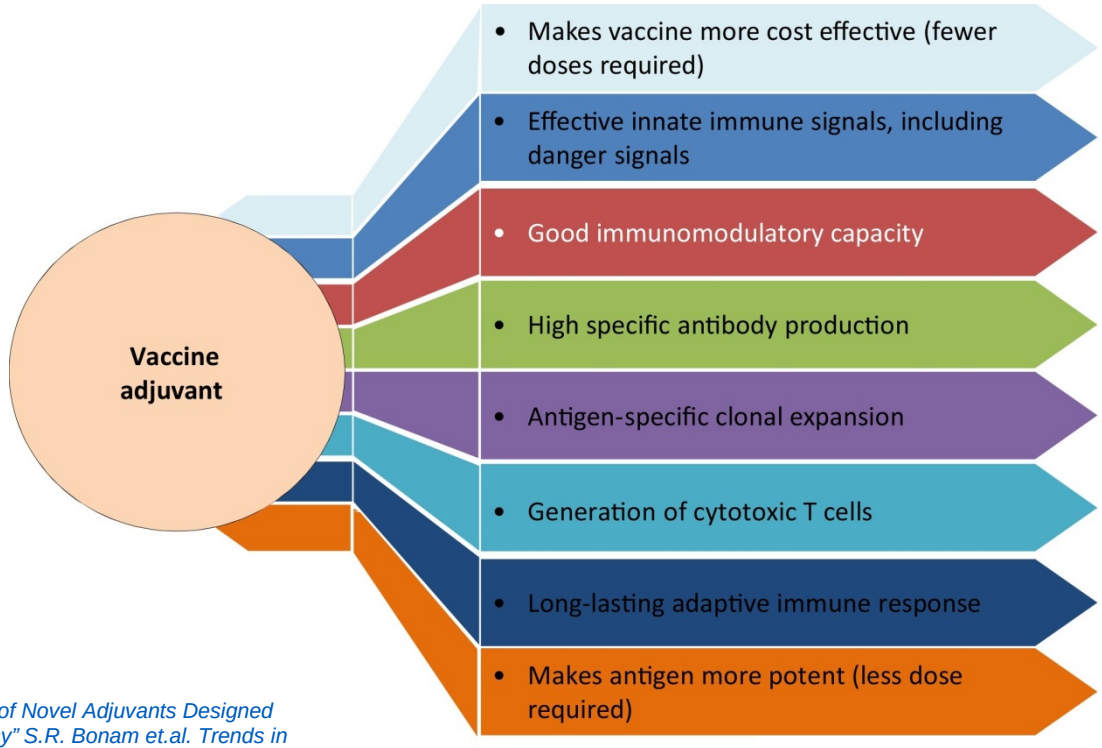
Why do we need adjuvants?

Adjuvants' Role in a Vaccine

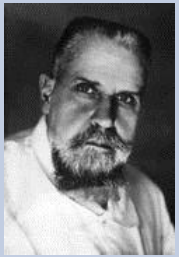


Adapted from: "An Overview of Novel Adjuvants Designed for Improving Vaccine Efficacy" S.R. Bonam et.al. Trends in Pharm. Sci. Volume 38, Issue 9, September 2017, Pages 771-793

Modern Adjuvants Discovery

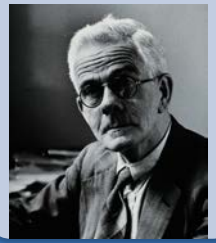
William Coley (1893)

- Killed Bacteria
  - MPL: AS04, AS01
  - CpG



Gaston Ramon (1925)

- Oils
  - MF59, AS03
- Plant Extracts
  - QS21, AS01

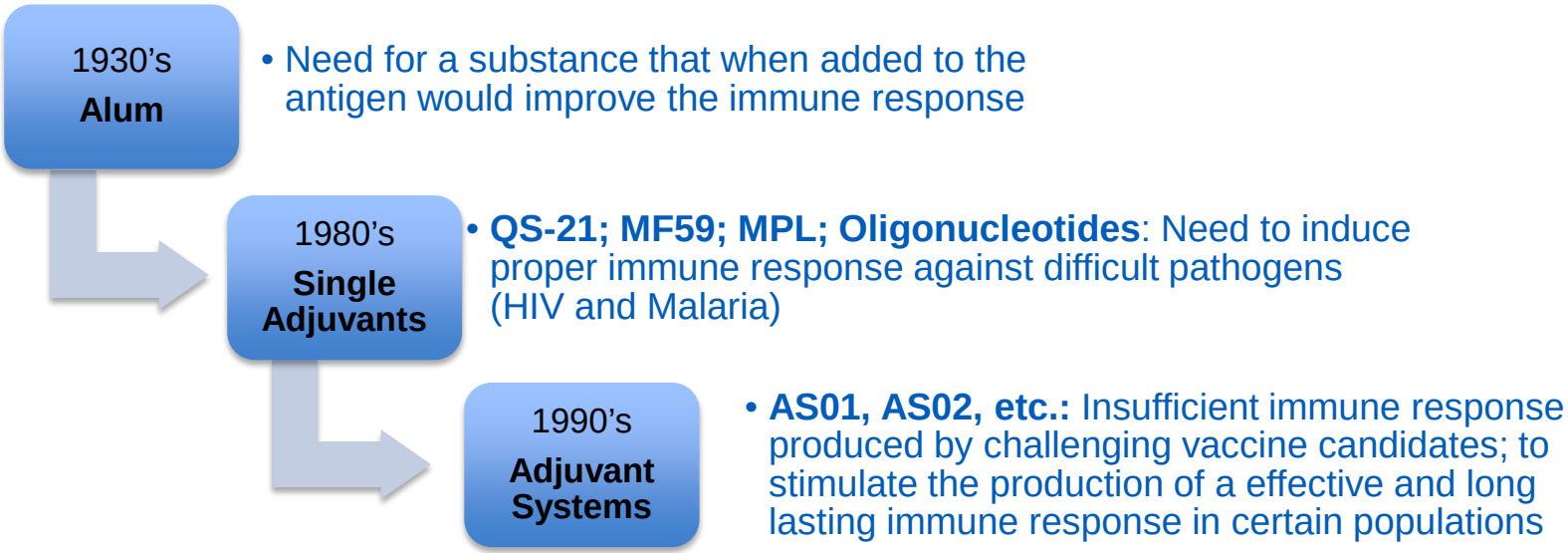


Alexander Glenny (1926)

- Aluminum Salts

Adapted from: "M. Friede, Adjuvants for Vaccines, a Pragmatic Approach", ADVAC, 2016

Adjuvant Experimentation in Vaccines Timeline



Different Types of Adjuvants Have Distinct Effects on the Immune System

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

Adapted from: "Old and New Adjuvants" A.S. McKee et. al. Current Op. in Immunol. Volume 47, August 2017, Pages 44-51

Type of Adjuvants Tested in Vaccines Worldwide

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

Adapted from: "Old and New Adjuvants" A.S. McKee et. al. Current Op. in Immunol. Volume 47, August 2017, Pages 44-51

Adjuvants in Clinical Development/Licensed Worldwide

Adjuvant	Description	Vaccine
Licensed		
Aluminum salts (Alum)	Insoluble particulates of hydroxide, phosphate or hydroxyphosphate sulfate salts	Included in licensed products for routine childhood vaccines and many others
Oil-in-water emulsions (MF59, AS03)	Oil dispersed nanoemulsions (mainly squalene) stabilized with non-ionic surfactants	Included in licensed products for seasonal influenza vaccine (MF59) or pandemic influenza vaccines (MF59, AS03)
Virosomes	Dispersed lipid vesicles including viral membrane (influenza) proteins	In licensed products for influenza vaccine (*Inflexal*) and HAV vaccine (*Epaxal*)
AS04	Natural product TLR4 ligand (MPL) adsorbed on to alum	Licensed products for HBV vaccine (*Fendrix*) and HPV vaccine (*Cervarix*)
MPL	Natural product TLR4 ligand	Approved products for tree pollen and grass pollen allergies on a *named patient* basis in Europe (*Pollinex*)
RC-529	Synthetic TLR4 ligand adsorbed to aluminum hydroxide	Was a licensed product in Argentina for HBV (*Supervax*)
Phase III		
Liposomes (AS01)	Dispersed lipid vesicles containing TLR4 ligand (MPL) and saponin QS-21	Phase III, submitted for licensure for malaria vaccine (RTS,S) and for approval for herpes zoster vaccine (HZ/su)
CpG ODN (1018 ISS)	Soluble TLR9 ligand (oligonucleotide) co-administered with HBV vaccine	Submitted for licensure for HBV vaccine
Topical cream with TLR7 ligand	Topical ointment of TLR7 ligand (imiquimod) applied in conjunction with intradermal vaccination	Influenza vaccine
Phase II		
EGVac system	Bacterial polysaccharide/bacterial DNA	Therapeutic HPV vaccine
Saponin complexes (ISCOM, Matrix-M)	Lipid, purified saponins and cholesterol cage-like nanocomplexes	Influenza vaccine
GLA-SE	Oil-in-water nanoemulsion with synthetic TLR4 ligand (GLA)	Tuberculosis vaccine, RSV vaccine, and Leishmania vaccine
IC31	Cationic peptide complexed with TLR9 ligand (oligonucleotide)	Tuberculosis vaccine
Oil-in-water emulsion (ISA51)	Oil dispersed nanoemulsion (mainly squalene) stabilized with non-ionic surfactant	Included in licensed seasonal influenza vaccine
AS02	Oil-in-water nanoemulsion with TLR4 ligand (MPL) and saponin, QS-21	Malaria and HIV vaccines (withdrawn after Phase II)
VAX2012Q, VAX125	TLR5 ligand protein (flagellin) linked to antigen	Influenza vaccine
Poly I:C (Ampligen, rintatolimod) **PIKA**	Double-stranded RNA polymer analogue and TLR3 ligand	Influenza vaccine Rabies vaccine
VCL-HB01 (Vaxfectin)	Cationic liposome	Genital herpes vaccine based)

Adapted from: "Towards an evidence based approach for the development of adjuvanted vaccines" D. T. O'Hagan et. al. Current Op. in Immunol. Volume 47, August 2017, Pages 93-102

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**

VACCINE INNOVATION: VACCINE ADJUVANTS

- **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