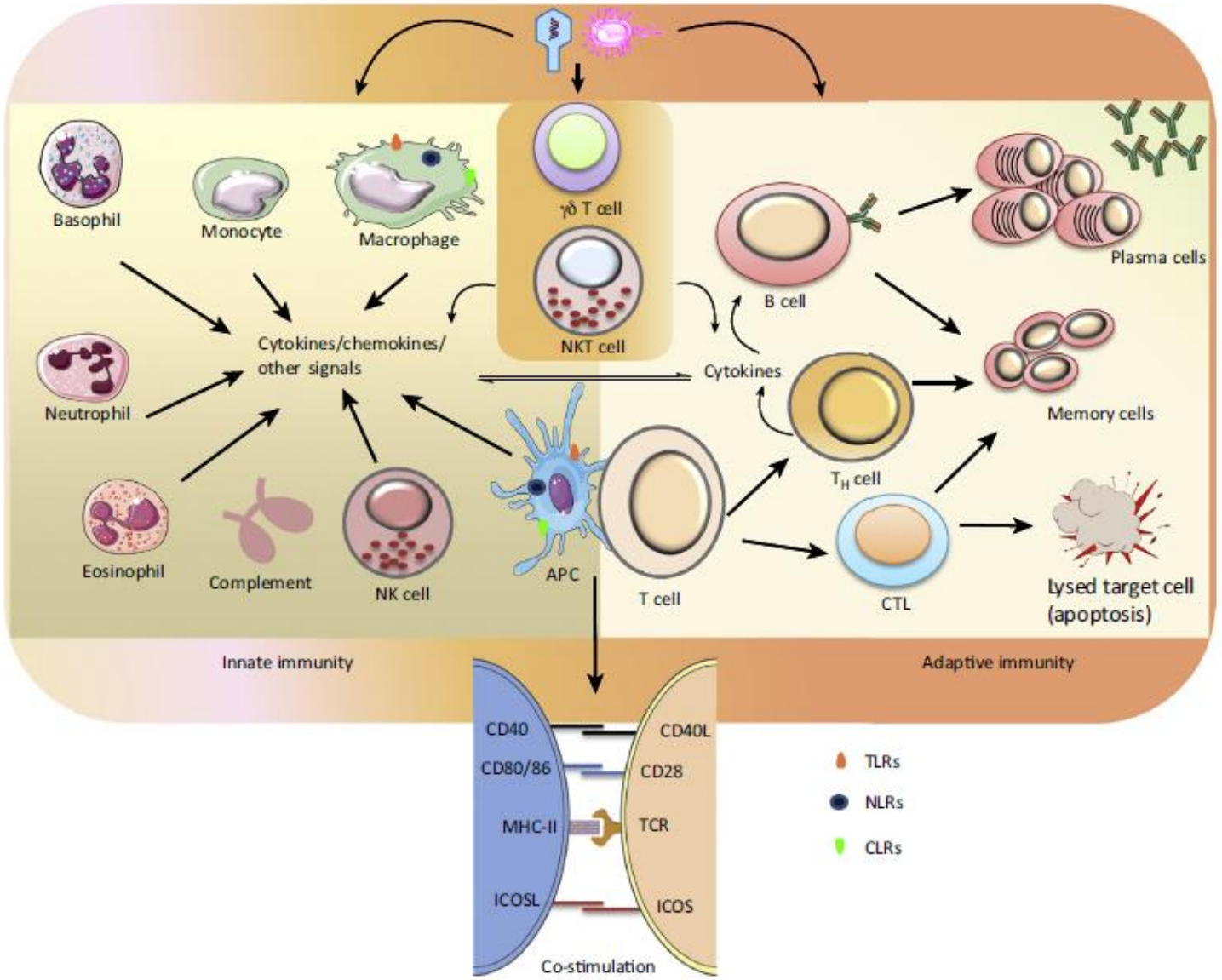
瑞科生物
RECBIO

BFA Adjuvant System

2021.11

Innate and Adaptive Immune Systems



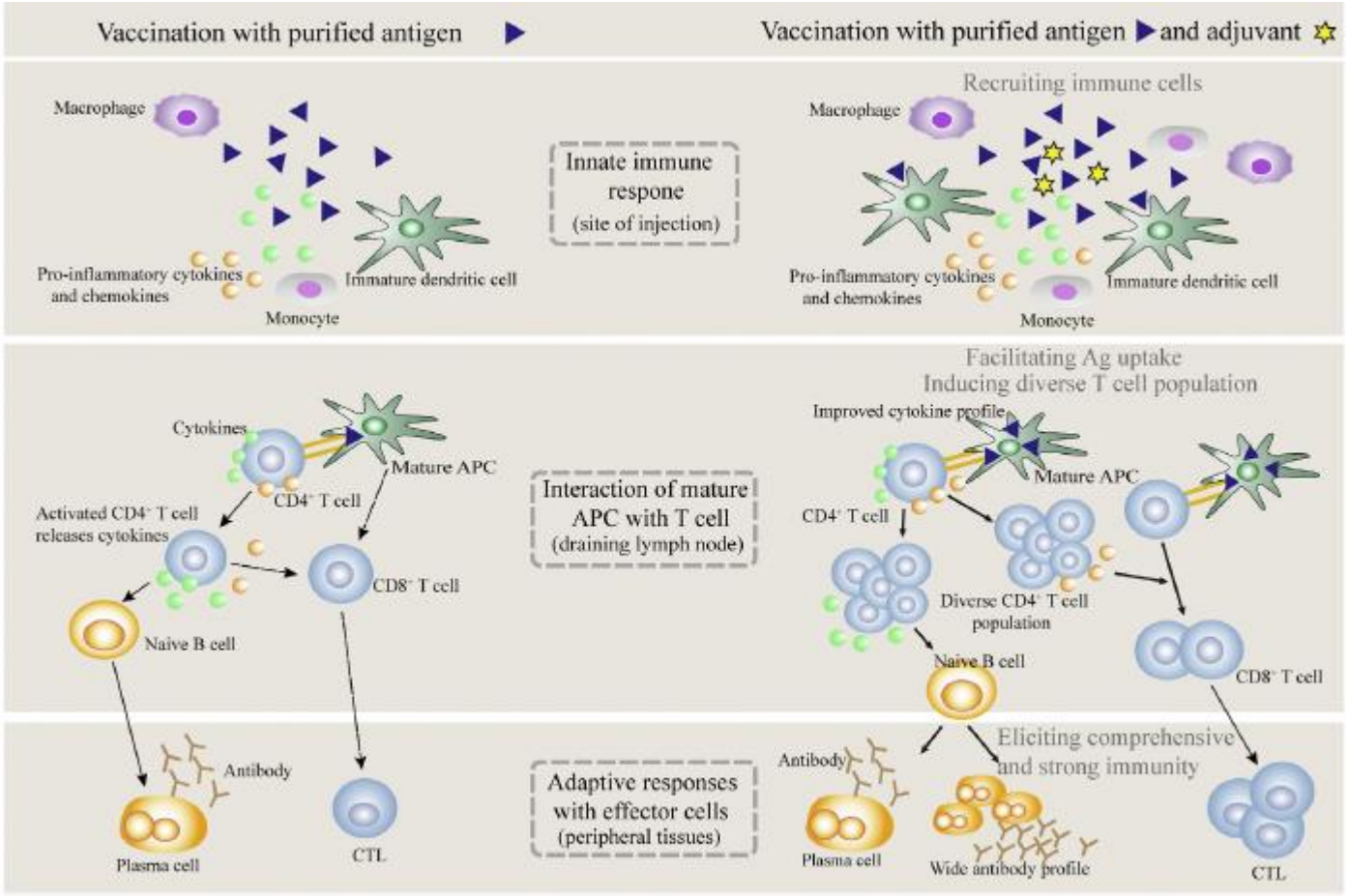
The innate immune system constitutes a front line of defense and provides a nonspecific response against invading pathogens.

This response is mediated by various cells (granulocytes, monocytes, macrophages, dendritic cells, neutrophils, basophils, and natural killer cells, and active molecules as proteins of the complement cascade) through recognition of PAMPs or DAMPs byPRRs.

The innate immune response shapes adaptive immunity resulting in the production of antigen-specific T and B lymphocytes.

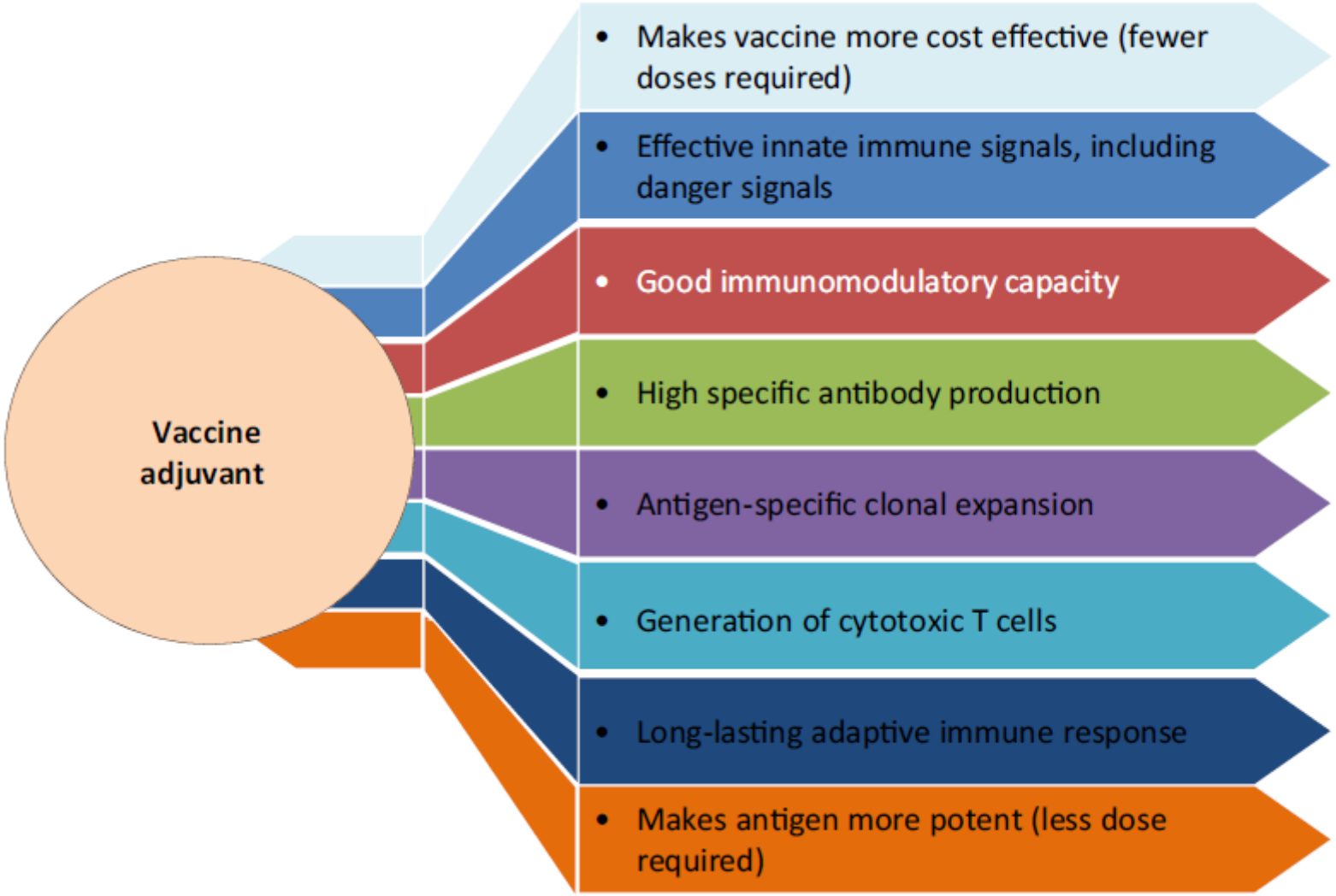
Bonam, S. R., Partidos, C. D., Halmuthur, S. K. M., & Muller, S. (2017). An Overview of Novel Adjuvants Designed for Improving Vaccine Efficacy. Trends Pharmacol Sci, 38(9), 771-793.

The immune responses induced by immunization with vaccines in the presence or absence of an adjuvant



Wang, N., Chen, M., & Wang, T. (2019). Liposomes used as a vaccine adjuvant-delivery system: From basics to clinical immunization. J Control Release, 303, 130-150.

Characteristic Properties of Vaccine Adjuvants



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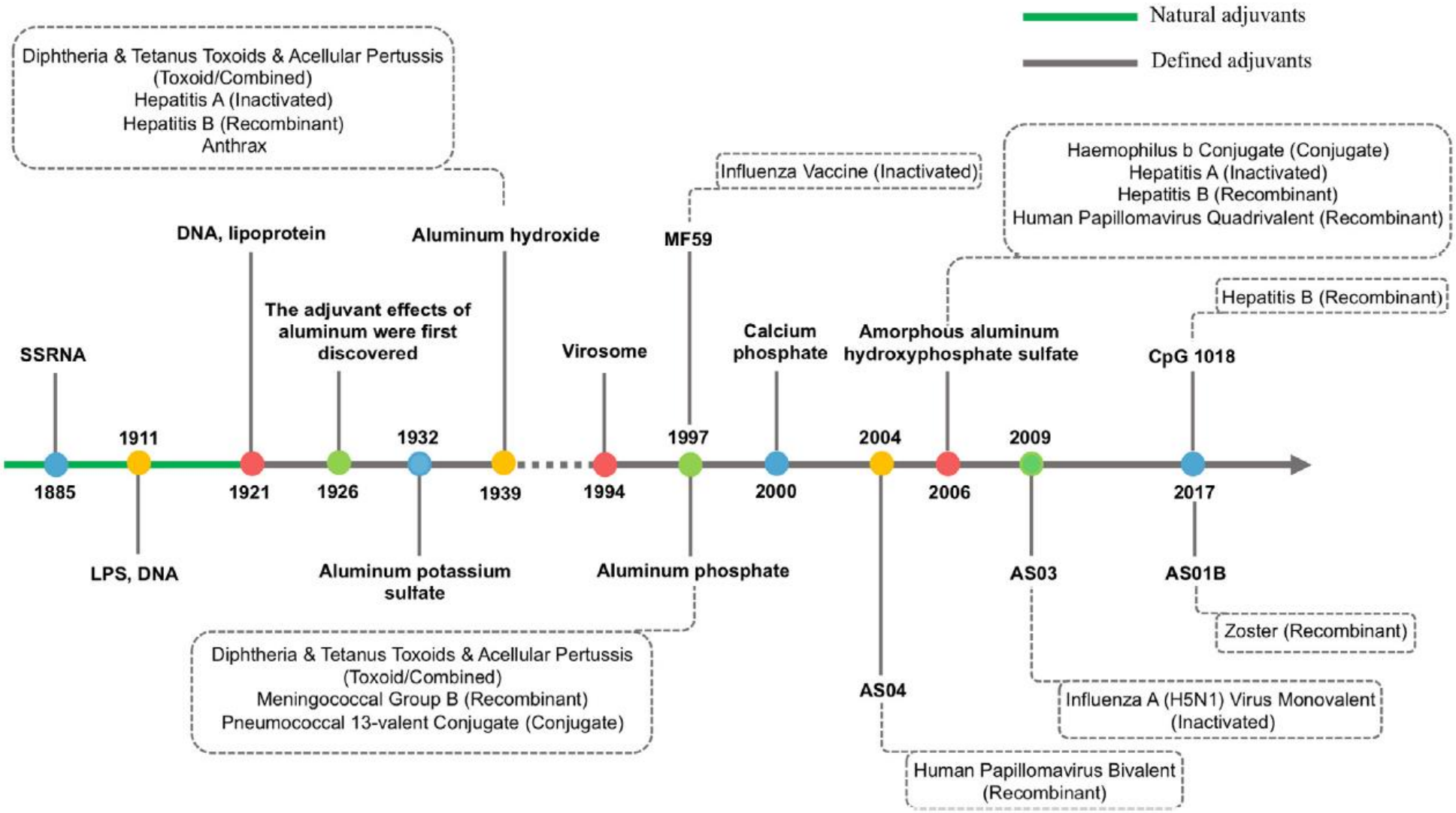
Timelines of major events in vaccine adjuvants development



Shi, S., Zhu, H., Xia, X., Liang, Z., Ma, X., & Sun, B. (2019). Vaccine adjuvants: Understanding the structure and mechanism of adjuvanticity. Vaccine, 37(24), 3167-3178.

GSK's Adjuvant System

Adjuvant System	Composition	Vaccines licensed or in Phase III trials	Vaccines in Phase I or II trials	Development discontinued
AS01	A combination of immunostimulants QS-21 and MPL with liposomes	Malaria vaccine Herpes zoster vaccine	Malaria next generation COPD exacerbations associated with non-typeable Haemophilus influenzae and Moraxella catarrhalis Tuberculosis vaccine HIV vaccine	—
AS02	A combination of immunostimulants QS-21 and MPL with an oil in water emulsion	—		HIV vaccine Tuberculosis vaccine Therapeutic melanoma vaccine Malaria vaccine.
AS03	A combination of an oil in water emulsion with alpha-tocopherol (Vitamin E) as immuno-enhancing component	Pre-pandemic H5N1 vaccine Pandemic H1N1 influenza vaccines (*Arepanrix™*, *Pandemrix™*)	—	
AS04	MPL is adsorbed onto aluminum hydroxide or aluminum phosphate, depending on the vaccine with which it is used	Human papillomavirus vaccine (*Cervarix™*) Hepatitis B for pre- and haemodialysis patients (*Fendrix™*)	—	Herpes simplex vaccine
AS15	A combination of immunostimulants CpG 7909, QS-21 and MPL with liposomes	—	—	MAGE-A3 Cancer Immunotherapeutics: melanoma and non-small-cell lung cancer vaccines

Pulendran, B., P, S. A., & O'Hagan, D. T. (2021). Emerging concepts in the science of vaccine adjuvants. Nat Rev Drug Discov, 20(6), 454-475.

Selected novel delivery systems that act as adjuvants

Adjuvants	Classifications	Components	Mechanisms or Receptors
AS04	Aluminum salt-based combined adjuvant	MPL + Alum	TLR4
Alum + CpG	Aluminum salt-based combined adjuvant		TLR9
MF59	O/W emulsion	Tween 80, span85, squalene	MyD88, ASC
AS02	O/W emulsion	MPL, QS21, AS03	TLR4
AS03	O/W emulsion	Tween 80, α-tocopherol, squalene	IRE1α
AF03	O/W emulsion	Span80, polyoxyethylene cetyl-stearylether, mannitol, squalene	Immune cell recruitment
SE	O/W emulsion	Glycerol, phosphatidylcholine, squalene	Immune cell recruitment
MPL-SE	O/W emulsion	MPL, SE	TLR4
GLA-SE	O/W emulsion	GLA, SE	TLR4
SLA-SE	O/W emulsion	SLA, SE	TLR4
Montanide ISA-720	W/O emulsion	Mannide monooleate, squalene	Depot effect, immune cell recruitment
Montanide ISA-51	W/O emulsion	Mannide monooleate, mineral oil	Depot effect, immune cell recruitment
AS01	liposome	MPL, QS21, DOPC, cholesterol	TLR4, immune cell recruitment
AS015	liposome	CpG, AS01	TLR4, TLR9, immune cell recruitment
Virosome	Microbe-based lipid membrane delivery systems		Promote antigen presentation
Archaeosomes	Microbe-based lipid membrane delivery systems		Promote antigen presentation

Wang, Z. B., & Xu, J. (2020). Better Adjuvants for Better Vaccines: Progress in Adjuvant Delivery Systems, Modifications, and Adjuvant-Antigen Codelivery. Vaccines (Basel), 8(1).

Adjuvants in FDA-approved human vaccines

	Product Name	Trade Name	Type	Adjuvant	Administration
1	Anthrax Vaccine Adsorbed	Biothrax	N/A	Aluminium hydroxide	Intramuscular/ Subcutaneous
2	Diphtheria & Tetanus Toxoids Adsorbed	N/A	Toxoid	Aluminum phosphate	Intramuscular
3	Diphtheria & Tetanus Toxoids & Acellular Pertussis Vaccine Adsorbed	Infanrix	Toxoid	Aluminum hydroxide	Intramuscular
4	Diphtheria & Tetanus Toxoids & Acellular Pertussis Vaccine Adsorbed	DAPTACEL	Toxoid	Aluminum phosphate	Intramuscular
5	Diphtheria & Tetanus Toxoids & Acellular Pertussis Vaccine Adsorbed, Hepatitis B (recombinant) and Inactivated Poliovirus Vaccine Combined	Pediarix	Combined (Toxoid, Recombined, Inactivated)	Aluminum hydroxide & Aluminum phosphate	Intramuscular
6	Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine	KINRIX	Combined (Toxoid, Inactivated)	Aluminum hydroxide	Intramuscular
7	Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed and Inactivated Poliovirus Vaccine	Quadracel	Combined (Toxoid, Inactivated)	Aluminum phosphate	Intramuscular
8	Diphtheria and Tetanus Toxoids and Acellular Pertussis Adsorbed, Inactivated Poliovirus and Haemophilus b Conjugate (Tetanus Toxoid Conjugate) Vaccine	Pentacel	Combined (Toxoid, Inactivated, Conjugate)	Aluminum phosphate	Intramuscular
9	Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)	PedvaxHIB	Conjugate	Amorphous aluminum hydroxyphosphate sulfate	Intramuscular
10	Hepatitis A Vaccine, Inactivated	Havrix	Inactivated	Aluminum hydroxide	Intramuscular
11	Hepatitis A Vaccine, Inactivated	VAQTA	Inactivated	Amorphous aluminum hydroxyphosphate sulfate	Intramuscular
12	Hepatitis A Inactivated and Hepatitis B (Recombinant) Vaccine	Twinrix	Recombinant (Inactivated)	Aluminum hydroxide & Aluminum phosphate	Intramuscular
13	Hepatitis B Vaccine (Recombinant)	Recombivax HB	Recombinant (subunit)	Amorphous aluminum hydroxyphosphate sulfate	Intramuscular
14	Hepatitis B Vaccine (Recombinant)	Engerix-B	Recombinant	Aluminum hydroxide	Intramuscular
15	Hepatitis B Vaccine (Recombinant), Adjuvanted	HEPLISAV-B	Recombinant	CpG 1018	Intramuscular
16	Human Papillomavirus Quadrivalent (Types 6, 11, 16, 18) Vaccine, Recombinant	Gardasil	Recombinant	Amorphous aluminum hydroxyphosphate sulfate	Intramuscular
17	Human Papillomavirus 9-valent Vaccine, Recombinant	Gardasil 9	Recombinant	Amorphous aluminum hydroxyphosphate sulfate	Intramuscular
18	Human Papillomavirus Bivalent (Types 16, 18) Vaccine, Recombinant	Cervarix	Recombinant	AS04	Intramuscular
19	Influenza A (H5N1) Virus Monovalent Vaccine, Adjuvanted	N/A	Inactivated	AS03	Intramuscular
20	Influenza Vaccine, Adjuvanted	FLUAD	Inactivated	MF59	Intramuscular
21	Japanese Encephalitis Virus Vaccine, Inactivated, Adsorbed	IXIARO	Inactivated	Aluminum hydroxide	Intramuscular
22	Menactra Meningococcal Group B Vaccine	BEXSERO	Recombinant	Aluminum hydroxide	Intramuscular
23	Meningococcal Group B Vaccine	TRUMENBA	Recombinant	Aluminum phosphate	Intramuscular
24	Pneumococcal 13-valent Conjugate Vaccine (Diphtheria CRM197 Protein)	Prevnar 13	Conjugate	Aluminum phosphate	Intramuscular
25	Tetanus & Diphtheria Toxoids, Adsorbed	TDVAX	Toxoid	Aluminum phosphate	Intramuscular
26	Tetanus & Diphtheria Toxoids Adsorbed for Adult Use	TENIVAC	Toxoid	Aluminum phosphate	Intramuscular
27	Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed	Adacel	Toxoid and inactivated toxin	Aluminum phosphate	Intramuscular
28	Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed	Boostrix	Toxoid and inactivated toxin	Aluminium hydroxide	Intramuscular
29	Zoster Vaccine Recombinant, Adjuvanted	SHINGRIX	Recombinant	AS01B	Intramuscular

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Adjuvants used in licensed vaccines

Alum

Aluminium hydroxide

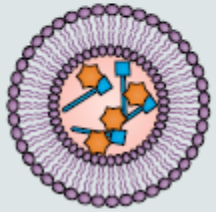
Aluminium phosphate

AS01

MPL

QS-21

Liposomes



CpG 1018

22-mer single-stranded DNA

AS04

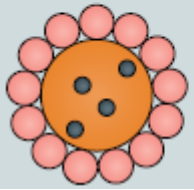
Alum

MPL

AS03

Squalence and α-tocopherol

Tween (polysorbate) 80

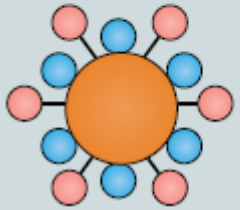


MF59

Squalene

Tween (polysorbate) 80

Span 85



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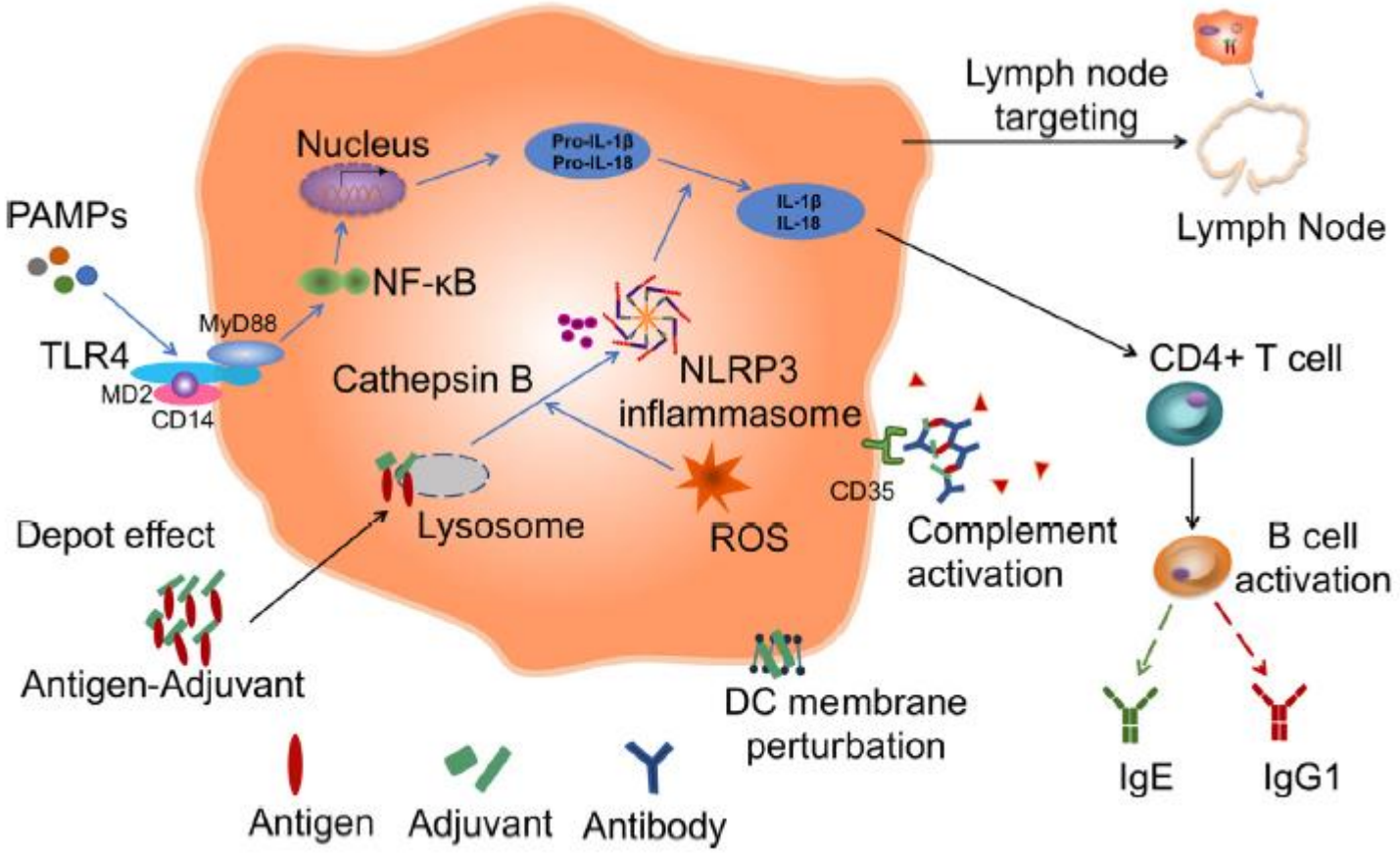
Acting mechanisms of aluminum salt-based adjuvants



Substantial amounts of mechanistic studies demonstrate that the aluminum salt-based adjuvants stimulate the Th2 immune responses though

(1) depot effect;
(2) enhanced antigen uptake by antigen presenting cells;
(3) the NLRP3 inflammasome activation;
(4) stimulation and differentiation of CD4+ T cells;
(5) perturbation of dendritic cell membrane;
(6) complement activation.

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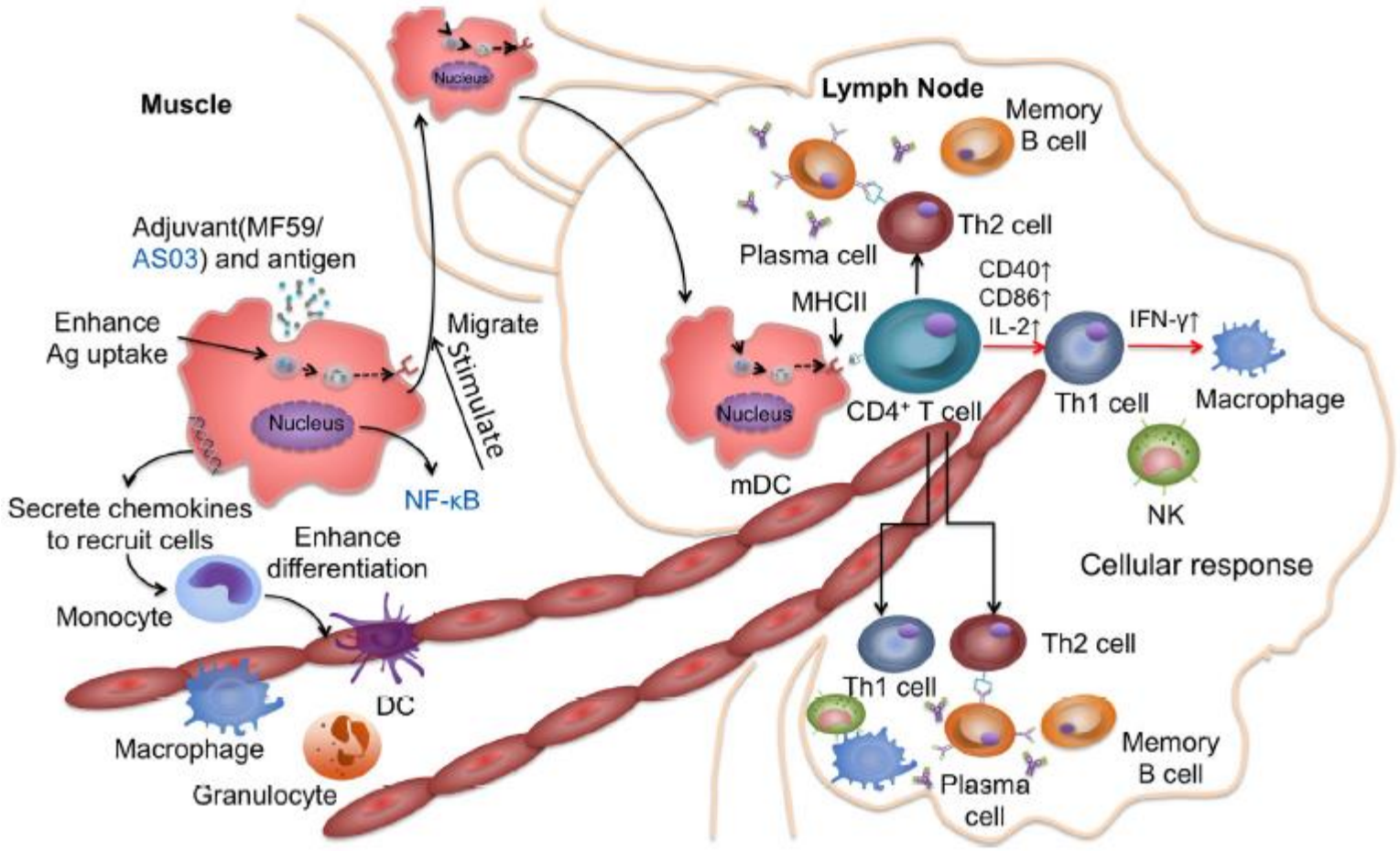
Models for the activation mechanism of MF59 and AS03



Both MF59 and AS03 create a transient and local immunocompetent environment following injection.

They promote cytokine and chemokine productions, and recruitment of cells to injection site.

The activated antigen-loaded APCs migrate to draining lymph nodes where APCs could prime naive CD4+ T cells.

The chemokine-driven immune cell recruitment is the key characteristic of the mechanism for both MF59 and AS03.

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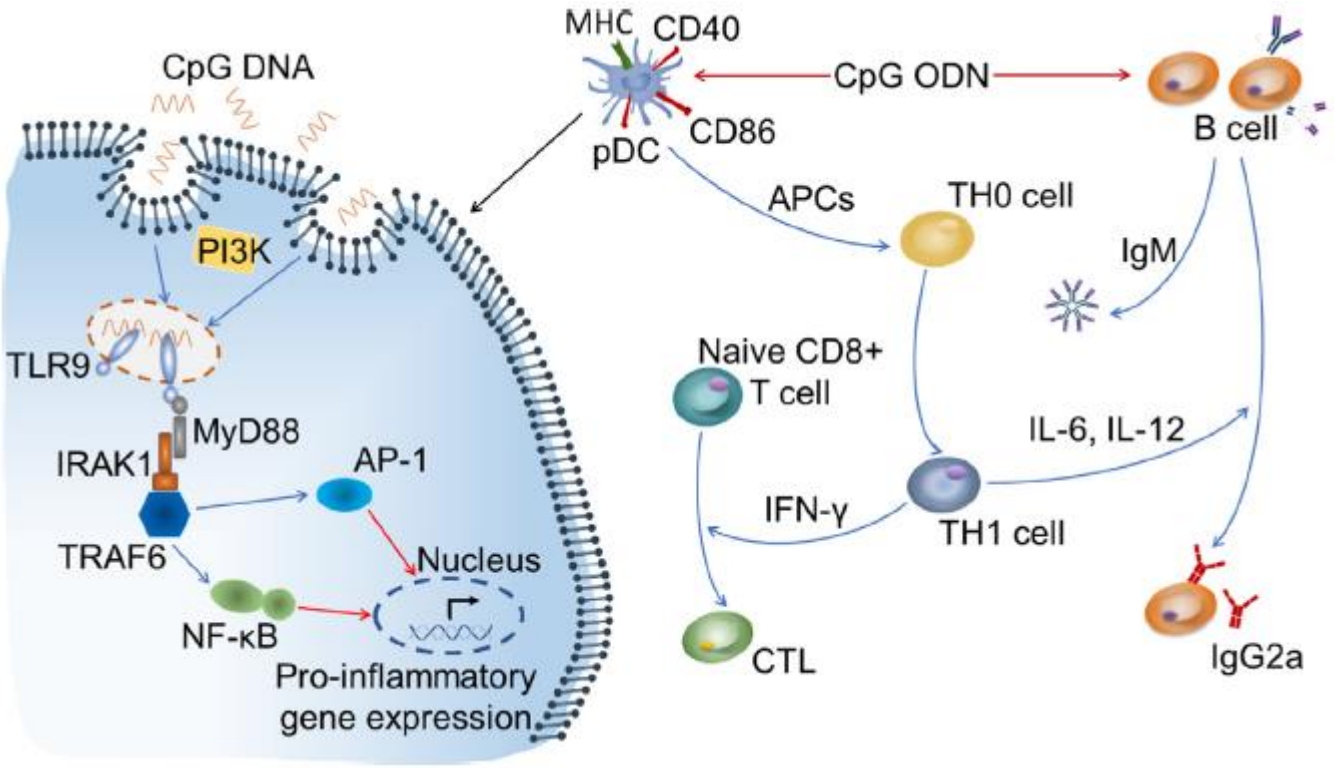
Acting mechanisms of CpG ODNs



As a new type of adjuvant, synthetic oligodeoxynucleotides (ODNs) that contain immune stimulatory CpG motifs is in favor of Th1 cell responses.

After initial CpG ODN uptake inside of the antigen presenting cells, the Pl3K facilitates the tranlocation into endosomal vesicles containing TLR9.

The interaction between TLR9 and CpG ODN transduces the cytoplasmic activation signal.

CpG ODNs directly activate B cells and plasmacytoid dendritic cells, producing proinflammatory- and T helper 1 (Th1) cytokine-rich environment.

CpG ODNs could facilitate the pDCs maturation and enhance antigen processing and presentation.

CpG ODN induces T cells to promote development of CTL via IFN-c, and increases production of IL-6, IL-12 to support secretion of IgG2a antibodies.

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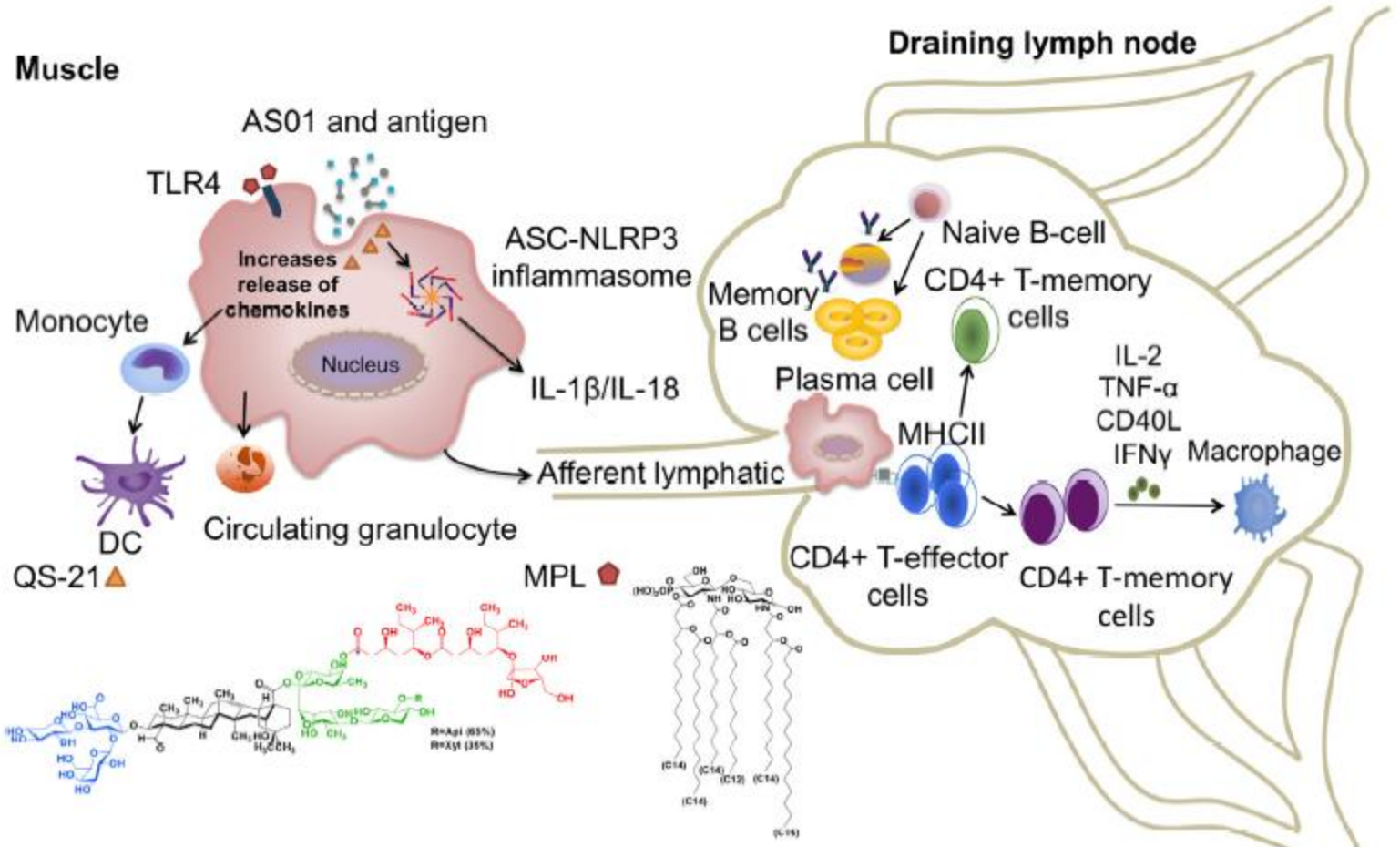
Acting mechanisms of AS01B



Adjuvant AS01B and antigen are injected into the muscle and taken up by APCs.

MPL activates APCs through TLR4. QS-21 activates the NLRP3 inflammasome, resulting in the release of IL-1b and IL-18.

MPL and QS-21 act synergistically to increase the release of chemokines, circulat granulocyte and enhance the recruitment of monocytes and dendritic cells.

In draining lymph nodes, highly activated dendritic cells efficiently induce naive CD4+ T-cell differentiation into CD4+ T memory cells and CD4+ T-effector cells.

Cytokines secreted by CD4 + T-effector cells such as IL-2, TNF-a, CD40L and IFN-c could stimulate naive B-cell division into plasma cells and memory B cells.

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Adjuvants under clinical investigation

Type of adjuvant	Adjuvant name	Conditions	Clinical phase
Lipids	GLA-SE (Lipid A analogue, oil-in-water emulsion)	Malaria	Phase 1
		Influenza	Phase 2
	GLA-AF (Lipid A analogue)	Influenza	Phase 1
		HIV	Phase 1
	MPL	Hepatitis B	Phase 2
	CCS/C	Influenza	Phase 2
Emulsions	Montanide ISA 51	Malaria	Phase 1
		Influenza	Phase 2
	Montanide ISA 720	Malaria	Phase 2
Saponins	Matrix M™	Malaria	Phase 1
		Respiratory Syncytial Virus F-protein	Phase 3
		Melanoma	Phase 2
	Matrix-M1	Malaria	Phase 1
Nucleotide	CpG 7909	Malaria	Phase 1
	dsRNA	Influenza	Phase 1
	IL-12 DNA	HIV	Phase 1
	Interleukin-2/Immunoglobulin (IL-2/Ig) DNA	HIV	Phase 1
		HIV	Phase 1
	Poly-ICLC	HIV	Phase 1
Cytokines	GM-CSF	Hepatitis B	Phase 2
		HIV	Phase 2
	IL-12	HIV	Phase 1
	IL-15	HIV	Phase 1
Others	Advax™ delta inulin adjuvant	Seasonal influenza	Phase 1
	ViscoGel	Haemophilus influenzae type b	Phase 1/2a
	Flagellin	Pseudomonas aeruginosa	Phase 3
	AS01B	Malaria	Phase 2
	AS02 (MPL, QS21, oil-in-water emulsion)	Malaria	Phase 2
	Virosomes	Falciparum Malaria	Phase 1
		Chronic Hepatitis C	Phase 1
		Hepatitis A	Licensed
	Alum + TLR7 agonist	Anthrax	Phage 1

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Vaccine adjuvants in COVID-19 vaccines in limited use or in advanced clinical trials

Adjuvant	Vaccine	Manufacturers	Status
Alum	Inactivated SARS-CoV-2 virus vaccines	Sinopharm Sinovac	Approved for limited or emergency use in certain countries
Matrix-M	Recombinant SARS-CoV-2 spike (S) protein	Novavax	Phase III
AS03	Recombinant SARS-CoV-2 spike (S) protein as a soluble protein or on virus-like particles	GSK (AS03) Sanofi (antigen) Medicago (antigen)	Phase I/II Phase III
CpG 1018	Recombinant SARS-CoV-2 spike (S) protein on virus-like particles	Dynavax (CpG 1018) Medicago (antigen)	Phase I/II
TLR7/TLR8 ligand adsorbed in alum	Inactivated SARS-CoV-2 vaccines	Bharath Biotech	Phase III/emergency use in India

COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TLR, Toll-like receptor.

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BFA Adjuvant System

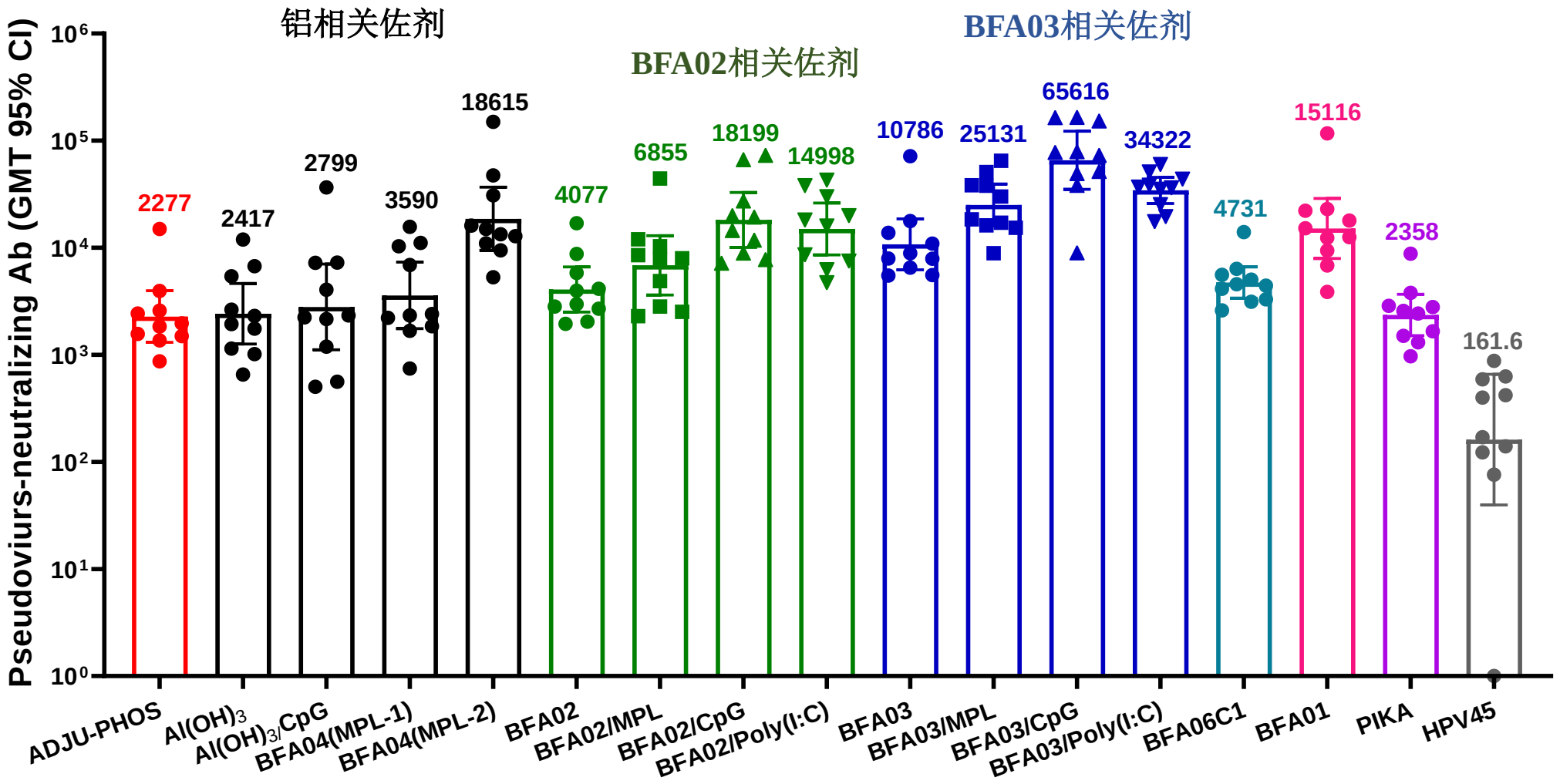
BFA Adjuvant System	Composition	Application?项目名称或代码?
Alum	—	
CpG	—	
BFA01	Benchmarking AS01	
BFA02	Benchmarking MF59	
BFA03	Benchmarking AS03	
BFA04	Benchmarking AS03	
BFA05	Based on emulsion and TLR4 agonist	
BFA06C1	Based on cationic liposome and TLR4 agonist	
BFA06C2	Based on emulsion and TLR9 agonist	
BFA06C3	Based on emulsion and TLR3 agonist	
BFA06C4	Based on emulsion and TLR4 agonist	
BFA06C5	Based on emulsion and TLR9 agonist	
BFA06C6	Based on emulsion and TLR3 agonist	
BFA03-D1	Based on emulsion and cationic lipid	
BFA07	Based on semi-synthesis saponin	
BFA09	Based on liposome and semi-synthesis and TLR4 agonist	
……		

BFA Adjuvant Design:

- Based on liposome, emulsion, Alum, other nanoparticles, etc
- Combining the various molecules(TLR agonists， NLR agonist， PRR agonist， etc)

For the future:

- Cell death adjuvants, metabolic adjuvants, epigenetic adjuvants
- From natural products to synthetic molecules
- System vaccinology
- etc


铝相关佐剂
BFA02相关佐剂
BFA03相关佐剂
Pseudoviurs-neutralizing Ab (GMT 95% CI)
10⁶
10⁵
10⁴
10³
10²
10¹
10⁰
2277
2417
2799
3590
18615
4077
6855
18199
14998
10786
25131
65616
34322
4731
15116
2358
161.6
ADJU-PHOS
Al(OH)3
Al(OH)3/CpG
BFA04(MPL-1)
BFA04(MPL-2)
BFA02
BFA02/MPL
BFA02/CpG
BFA02/Poly(I:C)
BFA03
BFA03/MPL
BFA03/CpG
BFA03/Poly(I:C)
BFA06C1
BFA01
PIKA
HPV45

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THANKS!