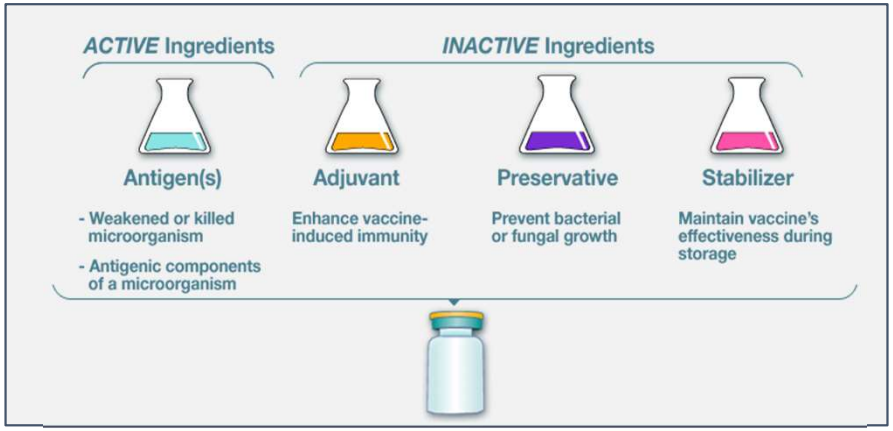
Unclogging the Adjuvant Pipeline:
How the NIAID Adjuvant Program Improves Access and Adjuvant Selection



Wolfgang W. Leitner, MSc, PhD
Chief, Innate Immunity Section
Basic Immunology Branch
DAIT / NIAID / NIH

NIAID Vaccine Adjuvant Compendium

NIH National Institute of Allergy and Infectious Diseases

The Adjuvant Landscape (in licensed vaccines)

Until early 2000's

MF59*

FluAd (flu)

Aluminum salt

Daptacel (DTaP)
Boostrix (Tdap)
Infanrix (DTaP)
Bexero (Meningo)
Kinrix (Dtap/IPV)
Engerix-B (HepB)
IXIARO (JEV)
Gardasil (HPV)
Prevnar (Pneumo)
Trumenba (Meningo)
BioThrax (Antrax)
TENIVAC (Td)
PedvaxHIB (Hib)
and many more…

*Europe (1997)

Current

LNP

Comirnaty (COVID)
mRESVIA (RSV)
SpikeVax (COVID)

MF59

FluAd (flu)
Audenz (panFlu)
Focetria (flu)

Matrix M

Nuvaxovid (COVID)
R21 (malaria)

CTB

Dukoral (cholera, ETEC)

AS04

Cervarix (HPV)

CpG1018 (+/- Alum)

Heplisav (HepB)
VLA2001 (COVID)
Corbevax (COVID)
MVC-COV1901 (COVID)
SCB-2019 (COVID)
Covax-19 (COVID)

Alhydroxiquim-II

Covaxin (COVID)

and a few more…

AS03

Pandemrix (panFlu)
Arepanrix (panFlu)

Advax/CpG

Spikogen (COVID)

AS01B

Shingrix (shingles)
Mosquirix (malaria)
Arexvy (RSV)

MCT/MPL

PollinexQuattro (allergy)

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NIAID Adjuvant Program: *Summary*

Product Development/Research Program stage:	*Solicited Programs:*
Adjuvant Discovery & Combination Adjuvants	• Adjuvant Discovery BAA and SBIR contracts • Molecular mechanisms of combination adjuvants
Adjuvant Development and Pre-Clinical Vaccine Testing	• Adjuvant Development BAA and SBIR contracts • Mimics and biosimilars • Head-to-head comparison and characterization • Down-selection of adjuvants for TB Vaccine • Down-selection of adjuvants for HIV vaccines
Clinical Evaluation	• Opioid vaccine program (HEAL) • Mostly supported by partners/other agencies
Licensure of New/more Efficacious Adjuvanted Vaccines	• 2 licensed products

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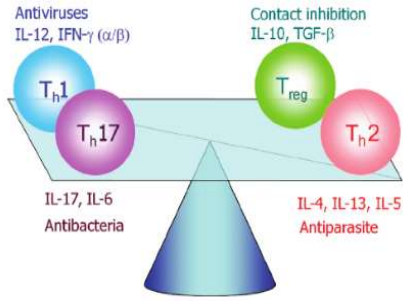
NIAID Adjuvant Programs - *Objectives*

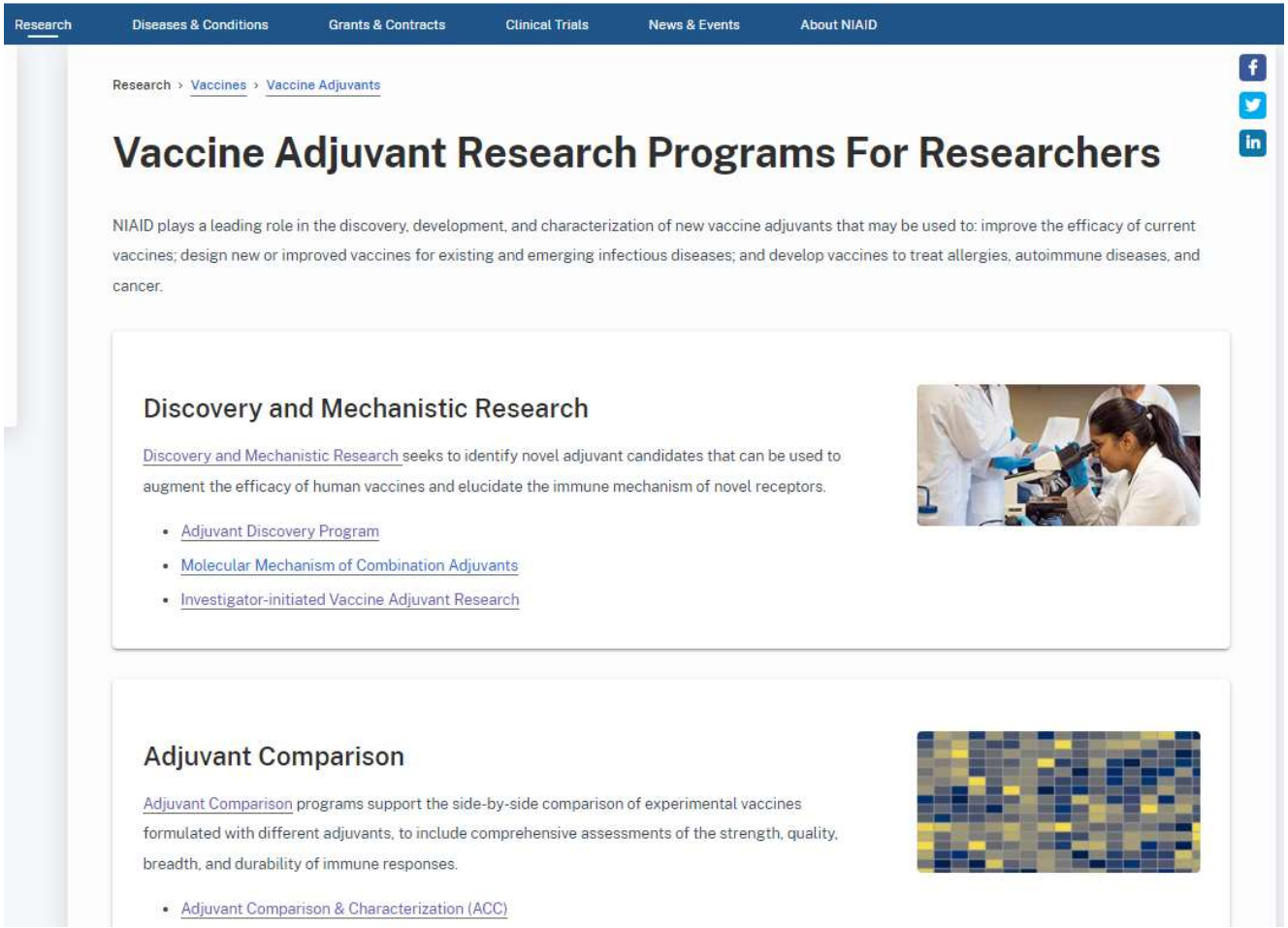
- Continue to prime the vaccine adjuvant pipeline:
  - Adjuvants that drive specific immune profiles
  - Stimulatory AND tolerogenic adjuvants (infectious diseases; immune mediated diseases – allergy, autoimmunity; transplantation)
  - Adjuvants for different populations/adjuvants that work in all populations



- Head-to-head comparisons → identify optimal adjuvants for specific indications, establish immune "fingerprints"
- Identify mechanisms of action of existing and new adjuvants
- Support activities to bring new adjuvants to clinical trials
- Make novel adjuvants accessible
  - Adjuvants that can be taken into clinical trials/product development
  - Mimics of successful adjuvants that are not accessible to the community

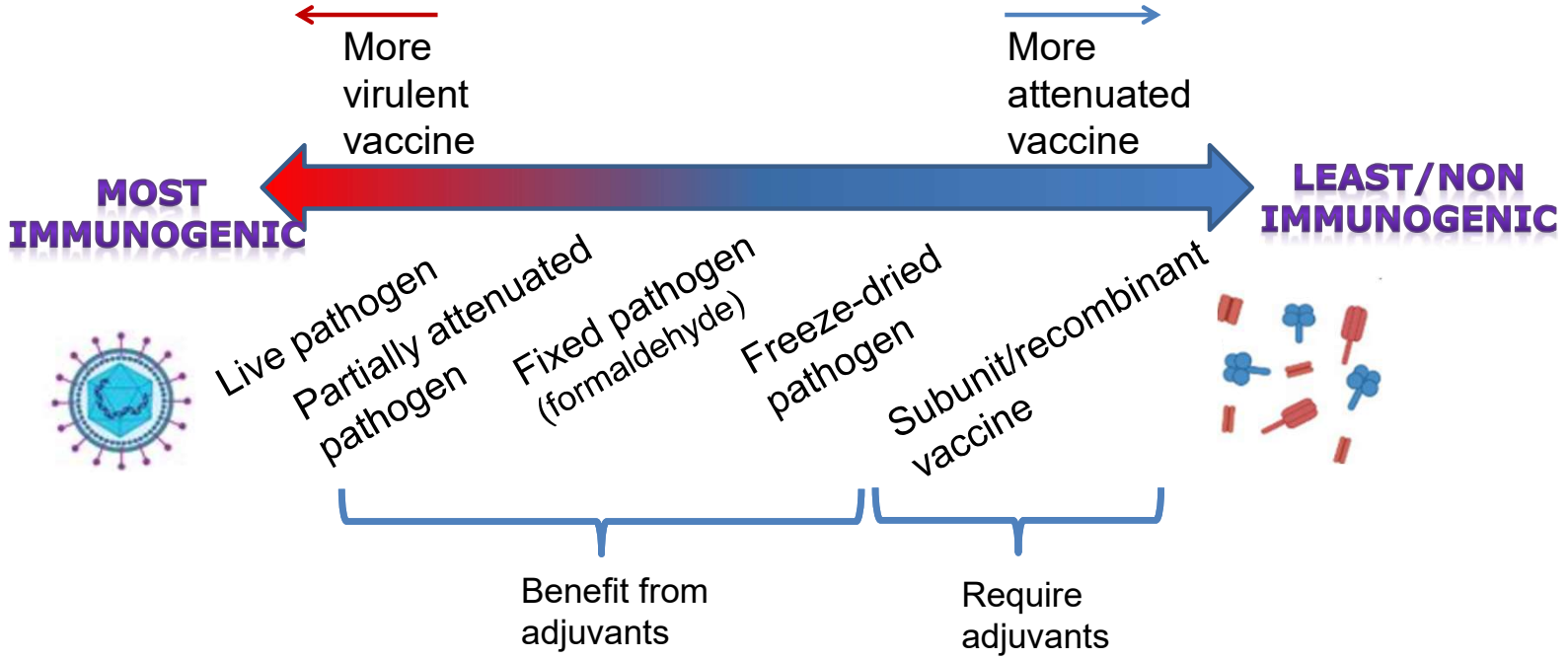
NIAID Adjuvant Programs – More Info at…

https://www.niaid.nih.gov/research/vaccine-adjuvant-research-programs



National Institute of Allergy and Infectious Diseases

Adjuvants – *Which Vaccine Needs One*?

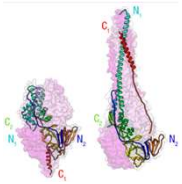


- Pathogen-based (life/attenuated/killed) vaccines already contain immunostimulators → are endogenously adjuvanted
  - LPS/LTA/flagellin (bacteria), RNA (bacteria, viruses), DNA (bacteria)……
  - "Vita-PAMPs" produced only by live pathogen

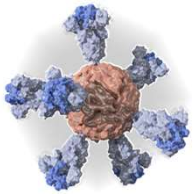
Improving Vaccines - *Options*

Antigen design

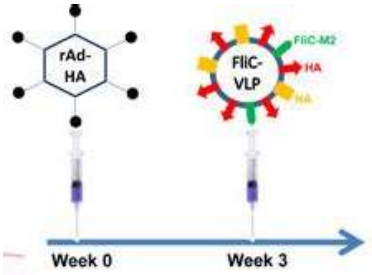
Stabilization



Multimerization

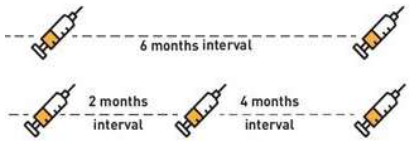


Vaccine platforms



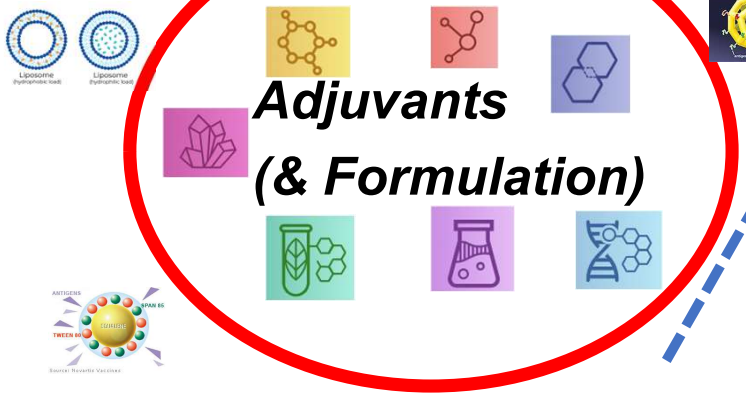
Immunization regimen

Vaccination interval



Vaccination routes

Adjuvants (& Formulation)



Route & method of vaccine delivery

IM

ID

SQ

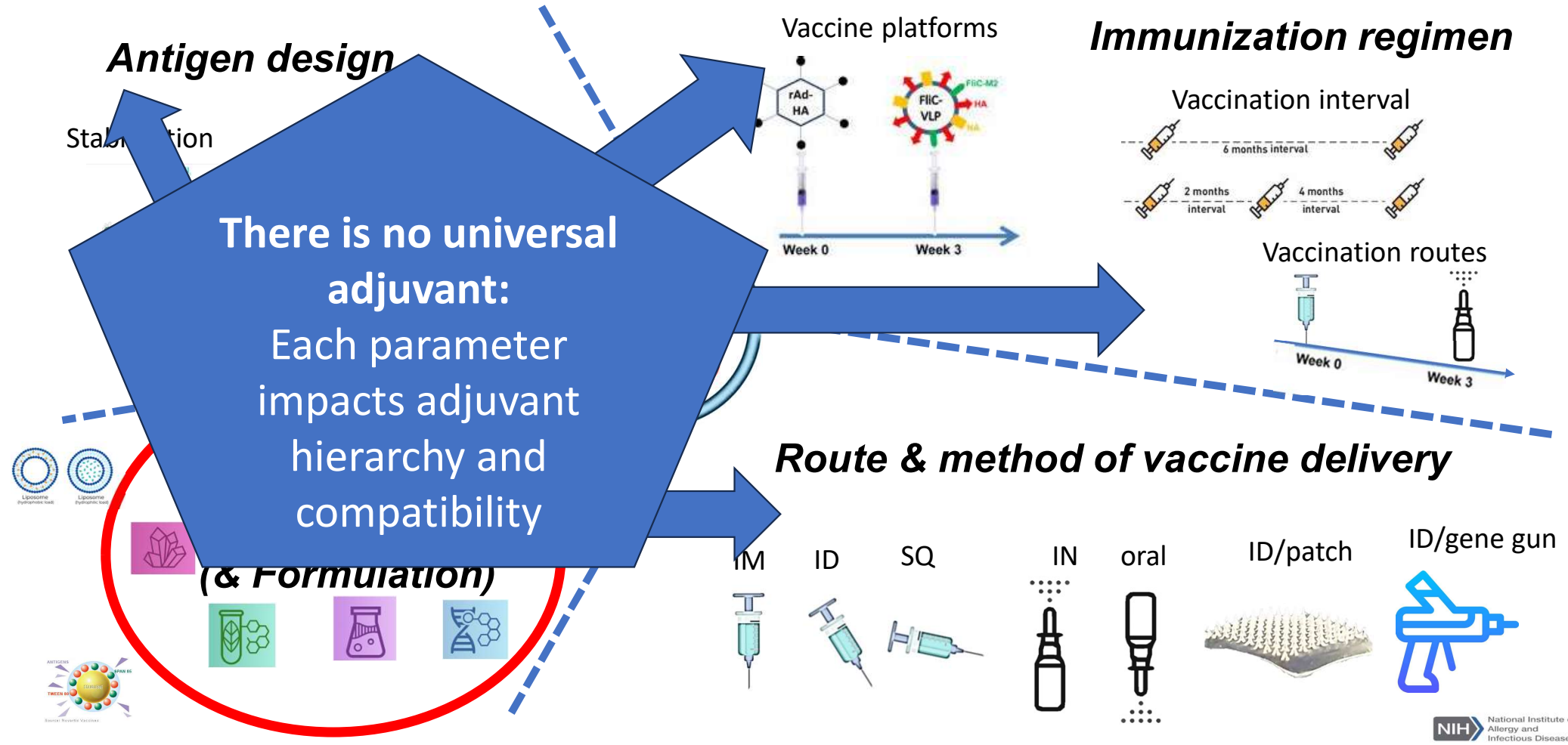
IN

oral

ID/patch

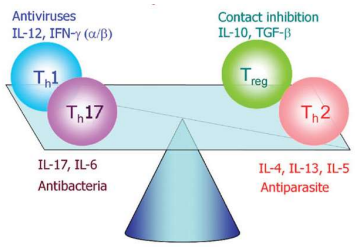
ID/gene gun

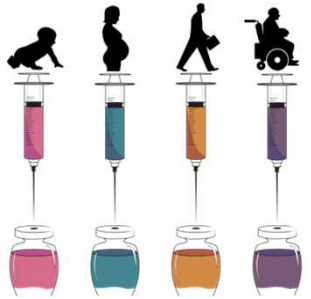
Improving Vaccines - *Options*



Considerations When Selecting Adjuvants*

- Induces the desired immune profile
  - *Caveat*: Correlates of protection not known for most pathogens
- Access/ability to move into clinical trials
  - Otherwise, waste of time/money/resources
- Age (immune status) of target population
  - *Caveat*: Adjuvant hierarchy is different dependent on age (incl. which combination adjuvant is synergistic/antagonistic)





Solution: "Unbiased" adjuvant comparison

- Formal side-by-side comparison to identify most suitable candidate
- *Caveat*: Hierarchy of adjuvants may be different in humans and selected animal model

Corresponding NIAID Programs

- Adjuvant Comparison and Characterization (**ACC**): *incl. Flu, COVID*
- Advancing Vaccine Adjuvant Research for Tuberculosis (**AVAR-T**): *focus on Tb*

*in a perfect world….

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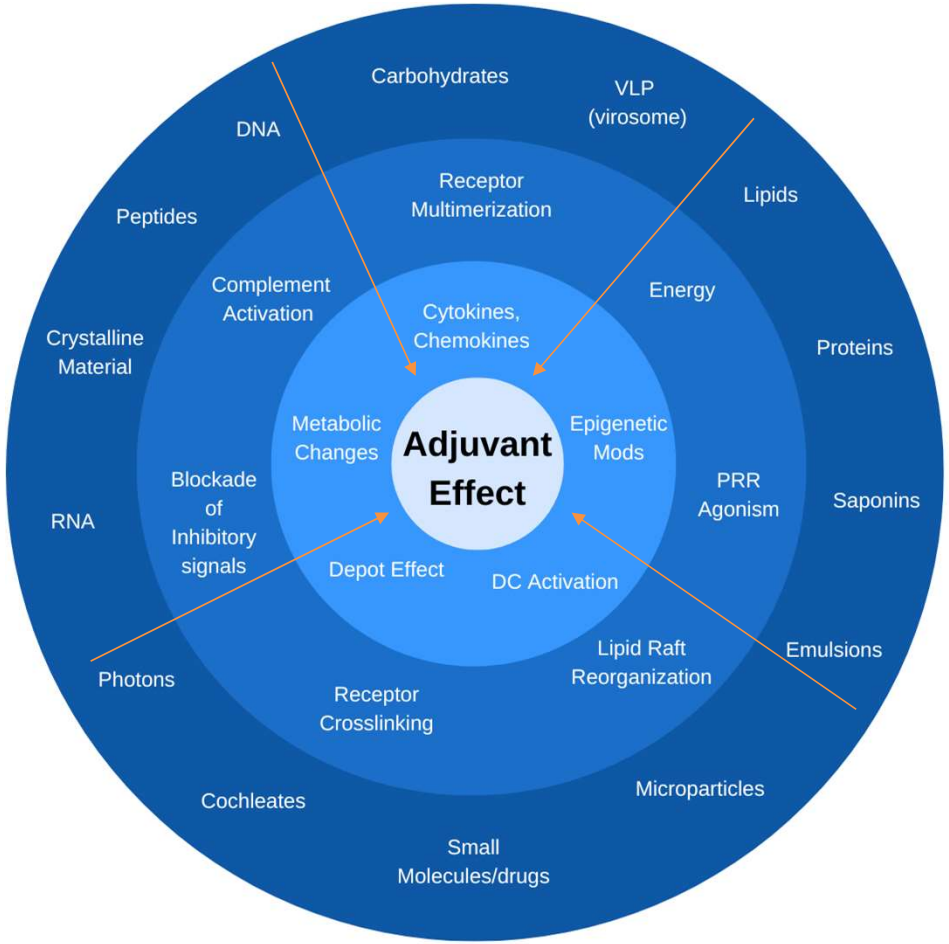
What Is An Adjuvant?

- Defined by a biological effect, not the type of inducer or MOA
  - Definition also used by the FDA
- Traditionally, vaccine adjuvants are natural products:
  - Immune stimulators from pathogens
  - Derivatives of naturally occurring adjuvants
  - Plant-derived molecules
- Anything that stimulates the innate immune system could be used as an adjuvant
  - Molecules that bind to immune receptors
  - Anything that causes cell death
  - Mechanical, chemical insults to tissue
  - Energy (*e.g.*, laser light)



How Do Adjuvants Work?

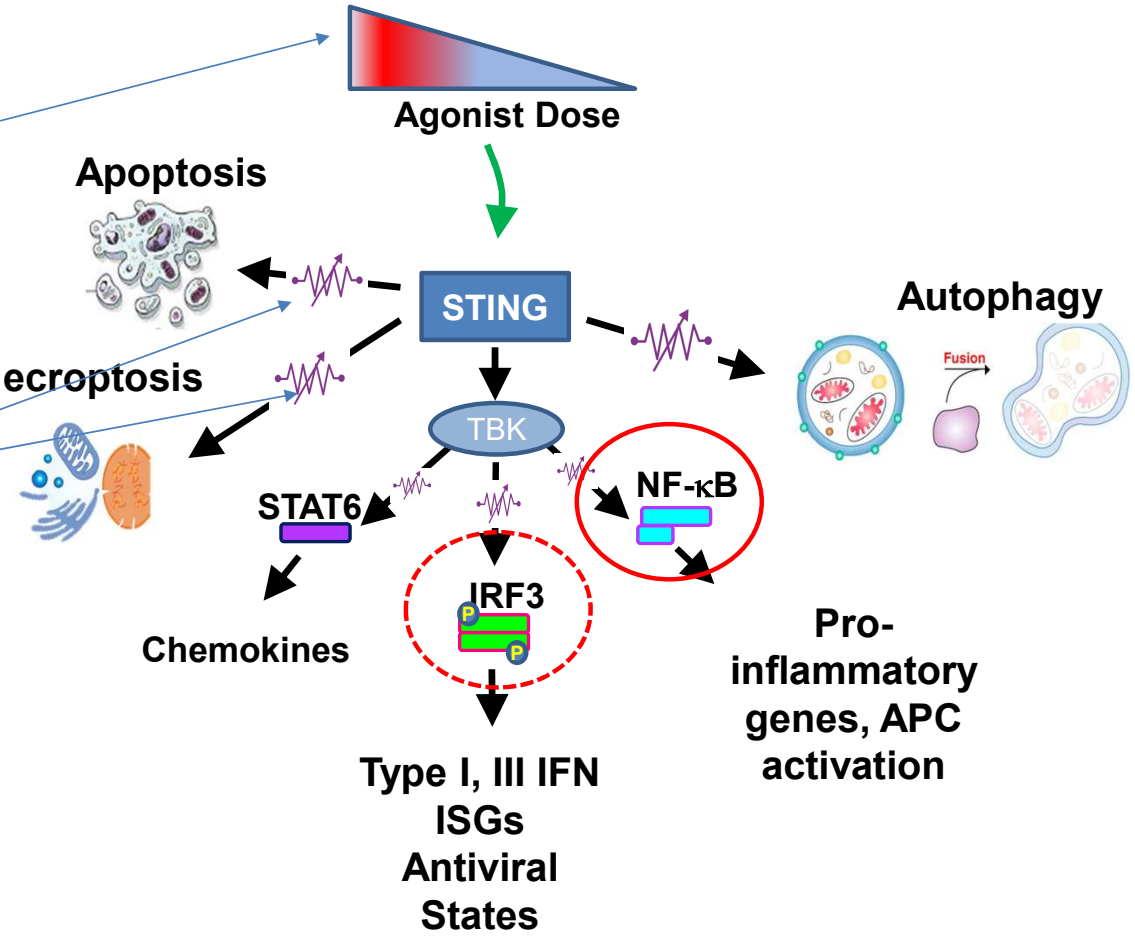
- Innate immune receptors are NOT switches that only have an ON or OFF position

Innate Immune Receptors as Rheostats

- Adjuvants trigger a variety of signals/outcomes
- Signal is tunable:

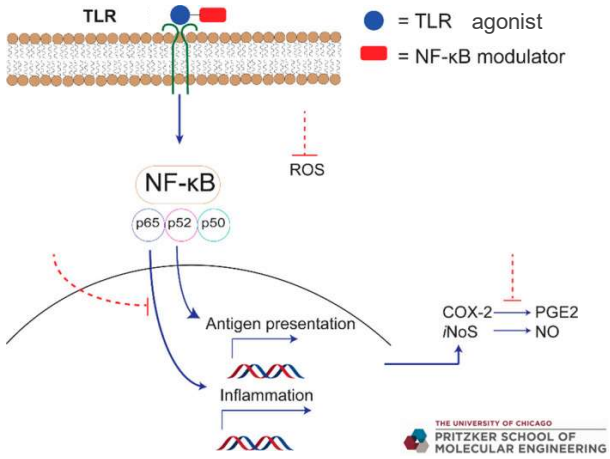
1) Signal **strength** – controlled by adjuvant dose, agonist structure, formulation

2) Signal **quality** – determined by combination of downstream signals



NFκB-Inhibitors as Co-Adjuvant

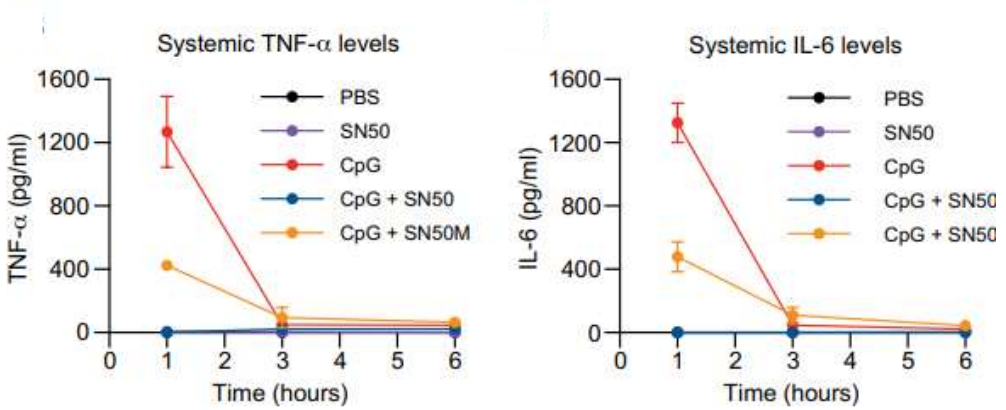
- Co-delivery of partial NF-κB inhibitor with a TLR-agonist
- Objectives
  - Block pro-inflammatory signals: reduce/eliminate reactogenicity (adverse events)
  - Improve immunogenicity of vaccine



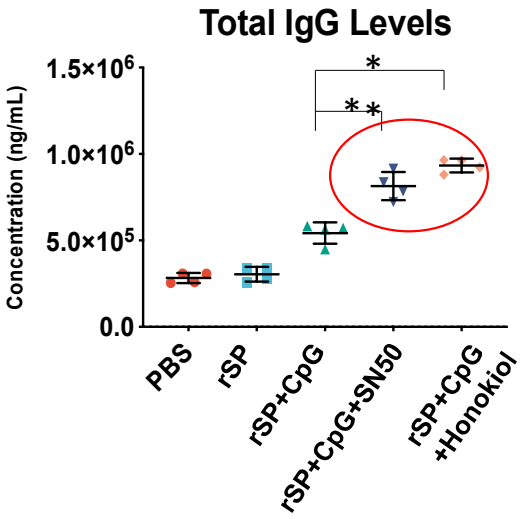
Are inflammation and immunogenicity linked or can they be uncoupled?

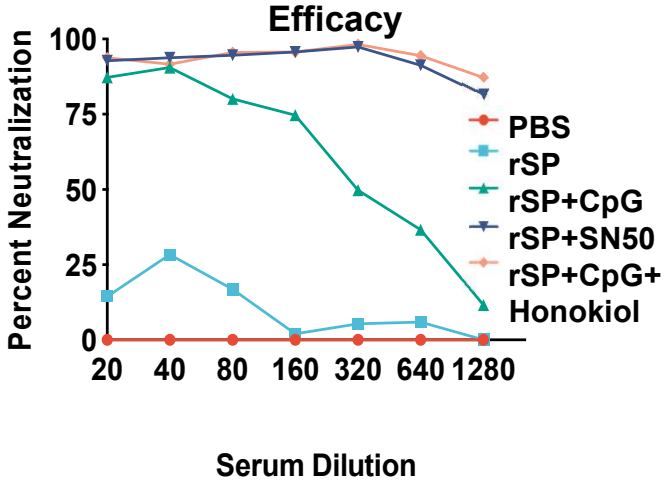
NFκB-Inhibitors as Co-Adjuvant

- Peptide-based inhibitor eliminates inflammatory response induced by CpG adjuvant



- Peptide and small-molecule-based inhibitors improve vaccine immunogenicity and efficacy



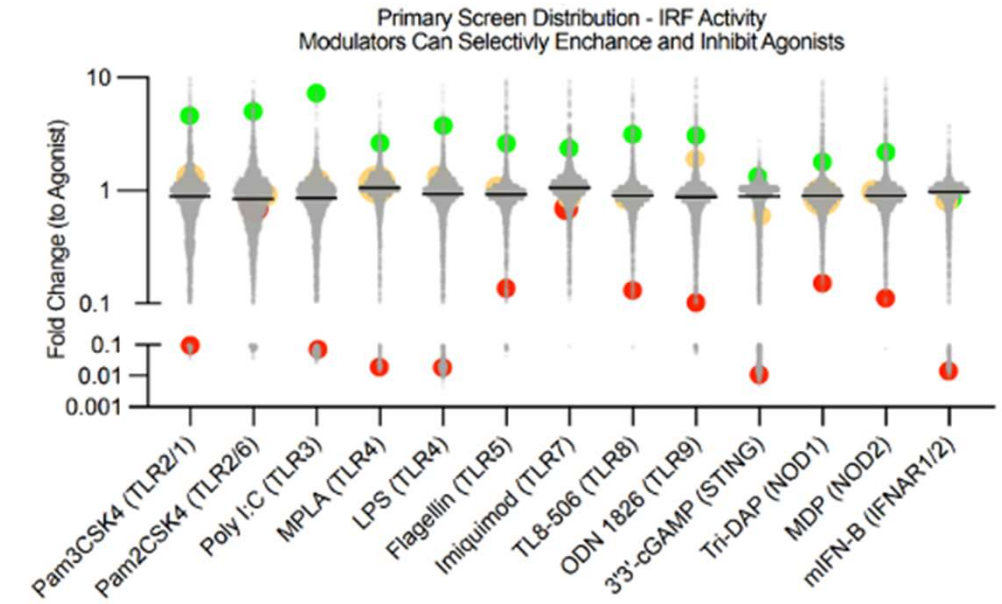


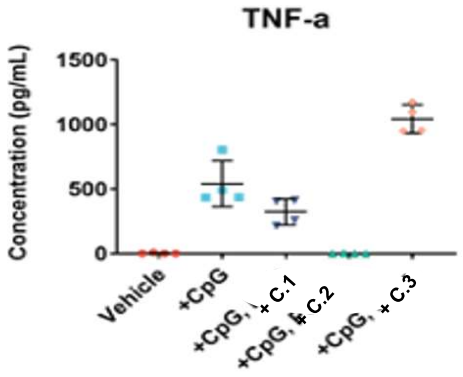
Data provided by Dr. A. Esser-Kahn, U. Chicago

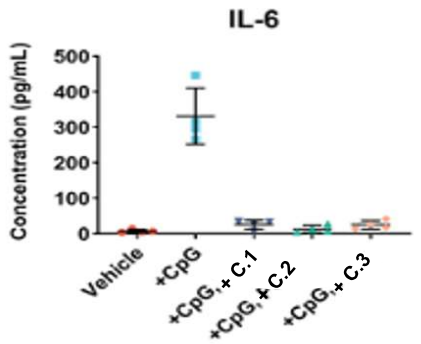
Adjuvant Signal Modulators: *What's Next?*

- HTS for SM-signal modifiers
  - Readout: ↑ or ↓ of NFkB or IRF signal induced by PRR agonists
  - Modifier should have no adjuvant activity by itself

- Different modifiers have differential effects on immune profile
  - Potential to fine-tune vaccine-induced immune responses





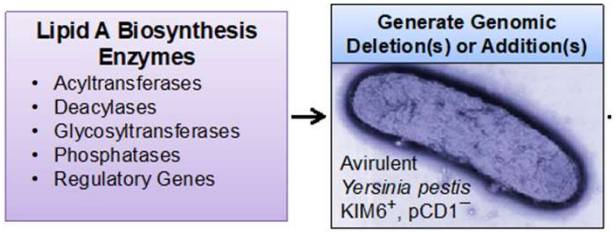


Data provided by Dr. A. Esser-Kahn, U. Chicago

Adjuvants in the Pipeline – an Overview

Directions

- **Synthetic derivatives of PAMPs**
  - INI-2002/2004
  - PHAD
  - BECC
  - CpG ODNs (*e.g.* 55.2), ...



(R.Ernst, U. Maryland)

Starting point:
Known PAMP/ PAMP structure

- **Small-molecule PRR agonists**
  - Fos47
  - 3M-052
  - PVP-037
  - INI-4001…..

Starting point:
'Random' compound library → unbiased screen

- **Adjuvant mimics**
  - EVAX-S
  - LMQ
  - ALFQ
  - LiT4q, …..

Starting point:
Known/well-established adjuvant (≠ biosimilar)

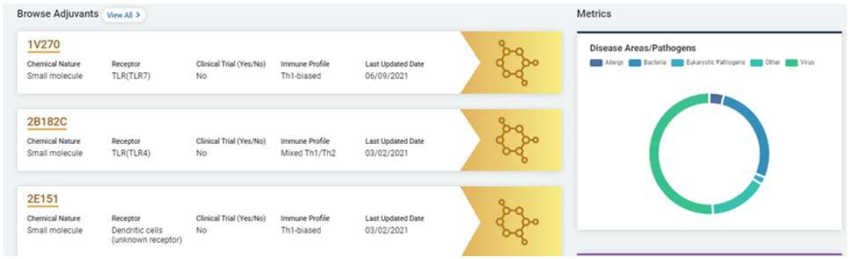
- **Combination adjuvants**
  - Advax-CpG
  - Alhydroxiquim-II
  - GLA-SE
  - LMQ
  - TRAC478, …

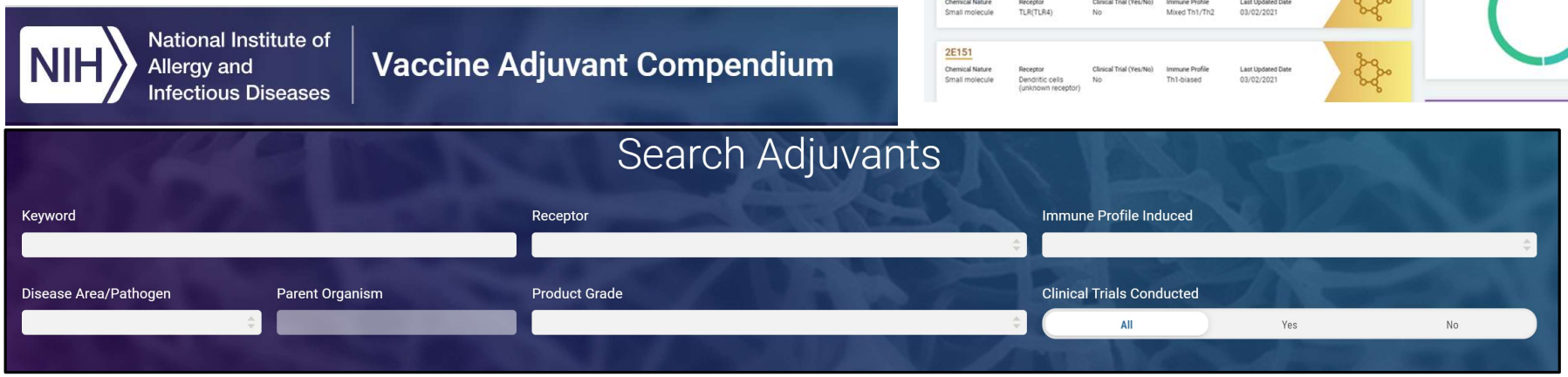
- **Response modifiers**
  - Kinase inhibitors
  - SOCS1 inhibitors
  - NFkB inhibitors, …

Starting point:
'Random' compound library or known modulators of innate signaling pathways

Access to Novel Adjuvants: NIAID's *Vaccine Adjuvant Compendium* (VAC)

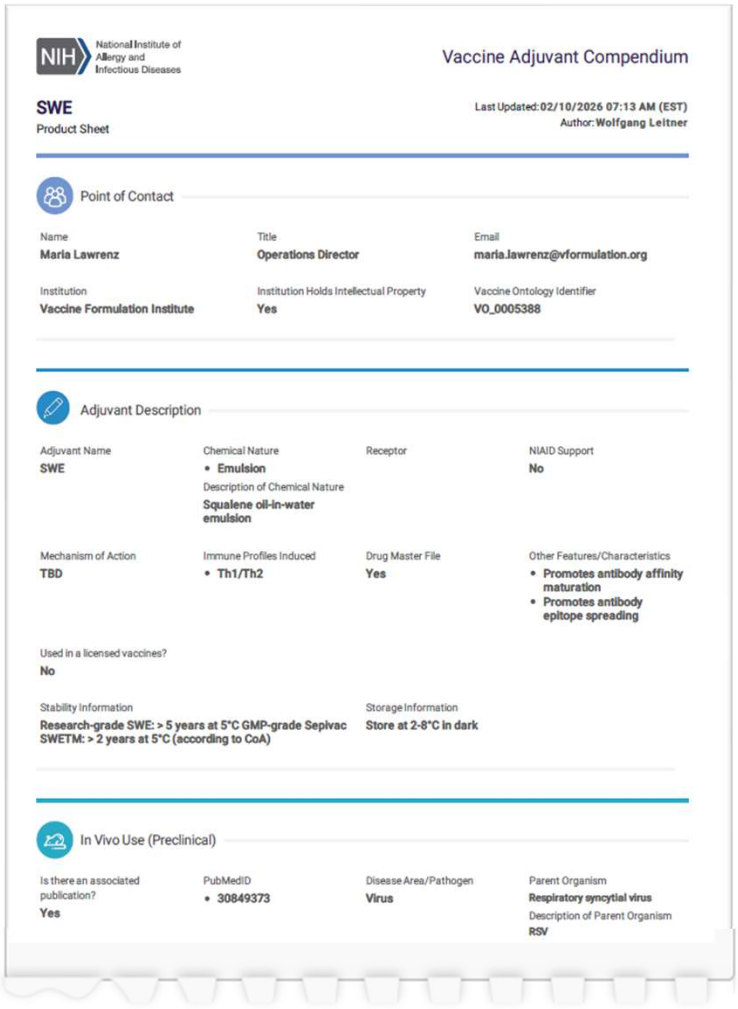
https://vac.niaid.nih.gov





- NIAID online database of **accessible** adjuvants
- Displays adjuvant characteristics and metadata
- *Objective*: connect adjuvant developers with vaccine developers

Access to Novel Adjuvants: VAC



National Institute of Allergy and Infectious Diseases

Vaccine Adjuvant Compendium

SWE
Product Sheet

Last Updated: 02/10/2026 07:13 AM (EST)
Author: Wolfgang Leitner

Point of Contact

Name	Title	Email
Maria Lawrenz	Operations Director	maria.lawrenz@vformulation.org

Institution	Institution Holds Intellectual Property	Vaccine Ontology Identifier
Vaccine Formulation Institute	Yes	VO_0005388

Adjuvant Description

Adjuvant Name	Chemical Nature	Receptor	NIAID Support
SWE	• Emulsion Description of Chemical Nature: Squalene oil-in-water emulsion		No

Mechanism of Action	Immune Profiles Induced	Drug Master File	Other Features/Characteristics
TBD	• Th1/Th2	Yes	• Promotes antibody affinity maturation • Promotes antibody epitope spreading

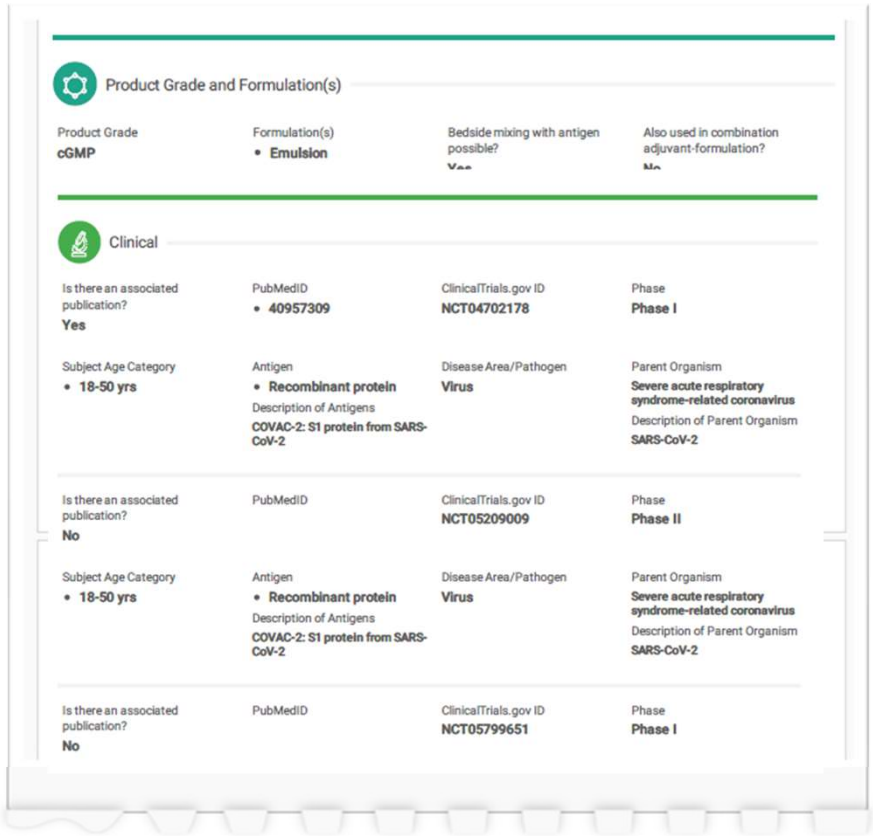
Used in a licensed vaccines?
No

Stability Information	Storage Information
Research-grade SWE: > 5 years at 5°C GMP-grade Sepivac SWETM: > 2 years at 5°C (according to CoA)	Store at 2-8°C in dark

In Vivo Use (Preclinical)

Is there an associated publication?	PubMedID	Disease Area/Pathogen	Parent Organism
Yes	• 30849373	Virus	Respiratory syncytial virus Description of Parent Organism: RSV

Sample adjuvant datasheet in VAC



Product Grade and Formulation(s)

Product Grade	Formulation(s)	Bedside mixing with antigen possible?	Also used in combination adjuvant-formulation?
cGMP	• Emulsion	Yes	No

Clinical

Is there an associated publication?	PubMedID	ClinicalTrials.gov ID	Phase
Yes	• 40957309	NCT04702178	Phase I

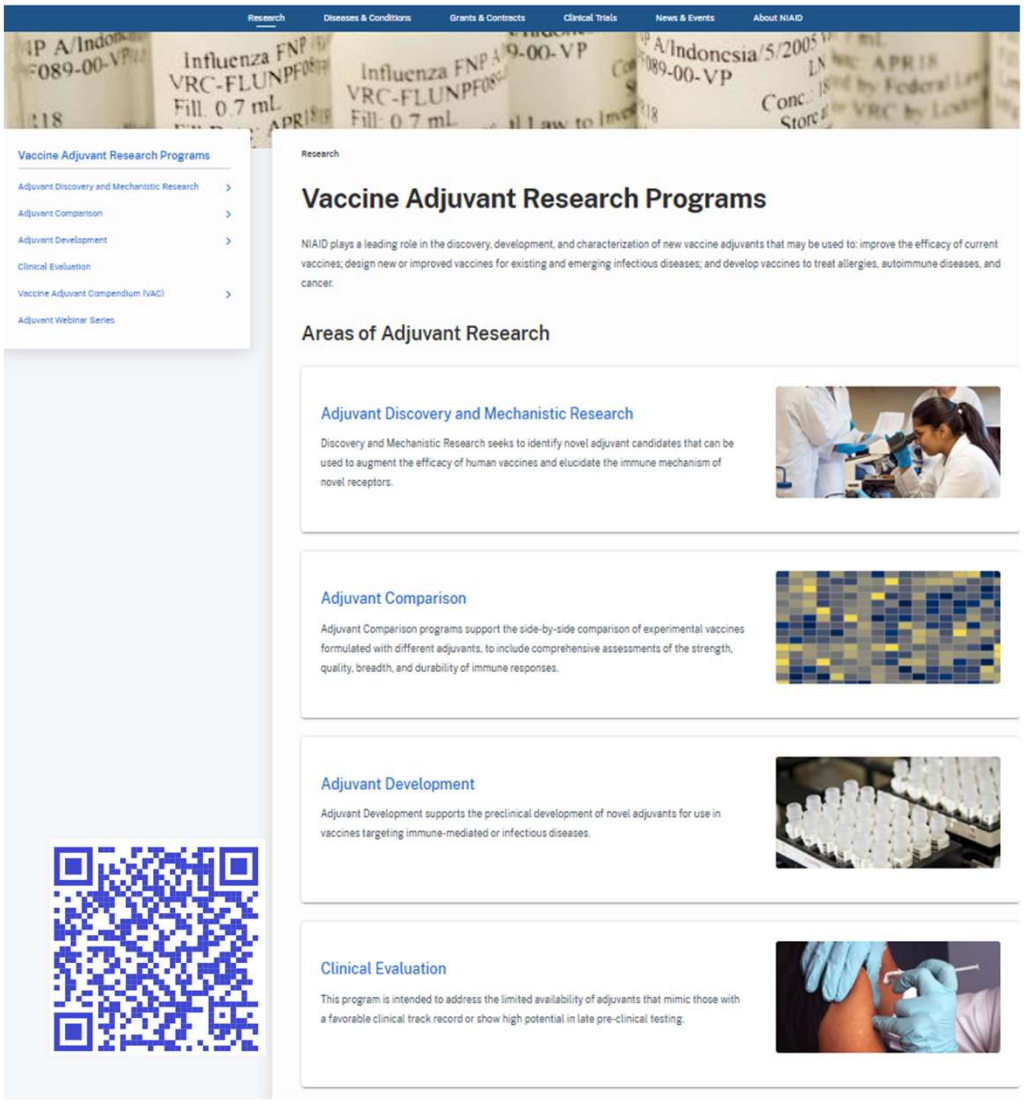
Subject Age Category	Antigen	Disease Area/Pathogen	Parent Organism
• 18-50 yrs	• Recombinant protein Description of Antigens: COVAC-2: S1 protein from SARS-CoV-2	Virus	Severe acute respiratory syndrome-related coronavirus Description of Parent Organism: SARS-CoV-2

Is there an associated publication?	PubMedID	ClinicalTrials.gov ID	Phase
No		NCT05209009	Phase II

Subject Age Category	Antigen	Disease Area/Pathogen	Parent Organism
• 18-50 yrs	• Recombinant protein Description of Antigens: COVAC-2: S1 protein from SARS-CoV-2	Virus	Severe acute respiratory syndrome-related coronavirus Description of Parent Organism: SARS-CoV-2

Is there an associated publication?	PubMedID	ClinicalTrials.gov ID	Phase
No		NCT05799651	Phase I

https://vac.niaid.nih.gov



wleitner@niaid.nih.gov

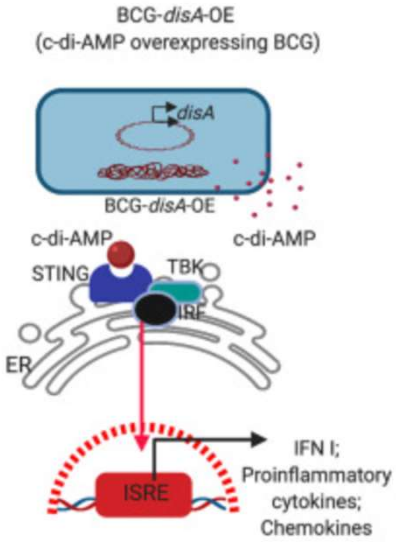
https://www.niaid.nih.gov/research/vaccine-adjuvant-research-programs

“Endogenous” Adjuvantation

Issue: exogenous adjuvants a) may interfere with vaccine stain’s ability to infect host cells, and b) complicate manufacturing/increases cost of vaccines designed for developing countries

Example 1: BCG overproducing cyclic di-AMP (STING agonist)

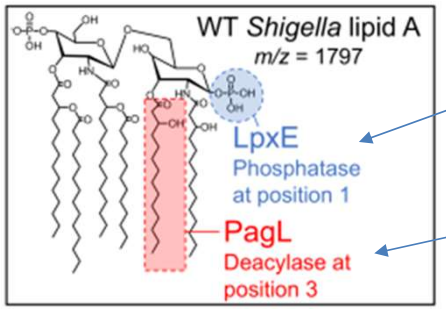
- BCG strain engineered to overexpress diadenylate cyclase gene
- Significantly improved vaccine immunogenicity and efficacy
- Also improved trained immunity induction (and efficacy of BCG against cancer)



Singh, Nat Comm 2022

Example 2: Shigella producing modified LPS (TLR4 agonist)

- Live-attenuated vaccines are highly immunogenic, but too reactogenic (pathogenic Lipid A structure)
- Transgenic strain expresses lipid A-modifying enzymes (using bacterial enzymatic combinatorial chemistry (BECC))



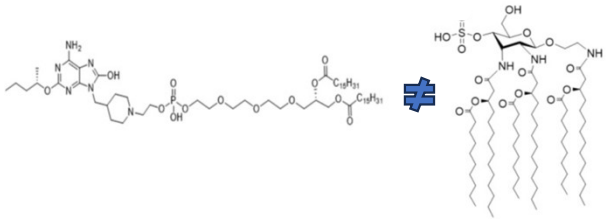
Blunted endotoxemia, no negative impact on immunogenicity

No benefit

Sherman, Res Sq 2024

Conclusions, Outlook

- Adjuvant selection *should* be rational, but we aren't there yet
  - Not enough is known re: "required" vaccine-induced immune profile for most diseases
  - Need to compare different adjuvants side-by-side (ideally also in NHP/human trials)

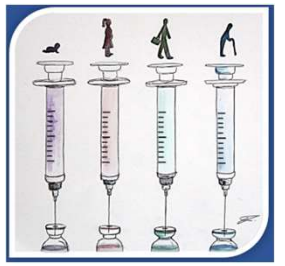


- Many adjuvants are available (and accessible) for vaccine developers
  - COVID pandemic significantly accelerated adjuvant research
  - There is no justification to 'default' to alum when developing a new vaccine
  - Even established vaccines could benefit from the replacement of alum
  - Both alum and emulsion-based adjuvants can be enhanced with TLR agonists

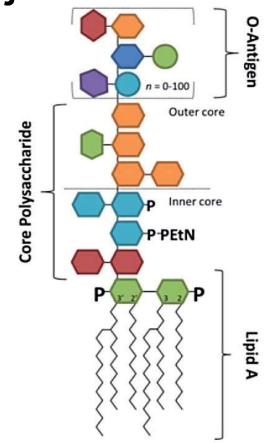
NIAID vaccine adjuvant compendium

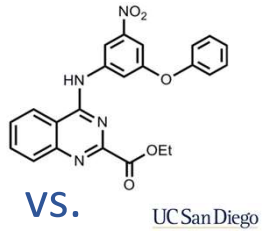
Conclusions, Outlook

- Keep target population in mind
  - Target PRR may not be expressed/functional
  - Example of adjuvants for the elderly: IL12 for mRNA, Alum/CpG for subunit (COVID)



- Small molecules can replace large, complex PAMP-based adjuvants
  - Are easier to produce (cheaper), clean, easier to modify
  - Formulation is essential (preventing systemic availability)

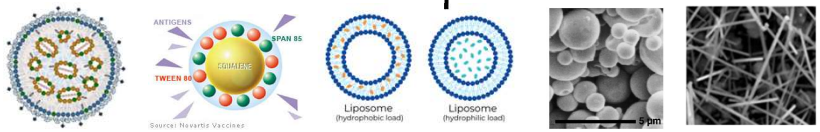




VS.

UC San Diego

- Formulation can make or break a vaccine *(a topic for another talk)*
  - Formulations change immune profiles induced by PRR agonists
  - Formulations need to be compatible with the vaccine antigen (often empirical)



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