National Institute of Allergy and Infectious Diseases

GVIRF Webinar

Session III: Access to adjuvants

Wolfgang W. Leitner, MSc, PhD
Chief, Innate Immunity Section; Basic Immunology Branch
Division of Allergy, Immunology and Transplantation
National Institute of Allergy and Infectious Diseases/NIH

National Institute of Allergy and Infectious Diseases

Flash Tasks - Agenda

Novel synthetic Th1 and Th17 inducing adjuvants, David Burkhart, Associate Director, the Center for Translational Medicine, University of Montana, US

Advax-CpG adjuvant, Nikolai Petrovsky, Founder and Research Director, Vaxine Pty Ltd., Australia

Alhydroxiquim-II, Sunil A. David, CEO, ViroVax LLC, US

The CAF adjuvant platform: a versatile adjuvant/delivery platform for proteins & peptides, Gabriel Pedersen, Head of Section, Vaccine Adjuvant Research, Staten Serum Institute (SSI), Denmark

ALF adjuvant, Mangala Rao, Chief, Laboratory of Adjuvant & Antigen Research, Walter Reed Army Institute of Research (WRAIR), US

Intranasal vaccine adjuvant for prevention of respiratory and sexually-transmitted infections, Chad Costley, CEO, BlueWillow Biologics Inc, US

dmLT/LTA1 adjuvant, Elizabeth Norton, Associate Professor, Tulane University, US

BECC family of adjuvants, Robert K. Ernst, Professor and Chair, Department of Microbial Pathogenesis, University of Maryland, US

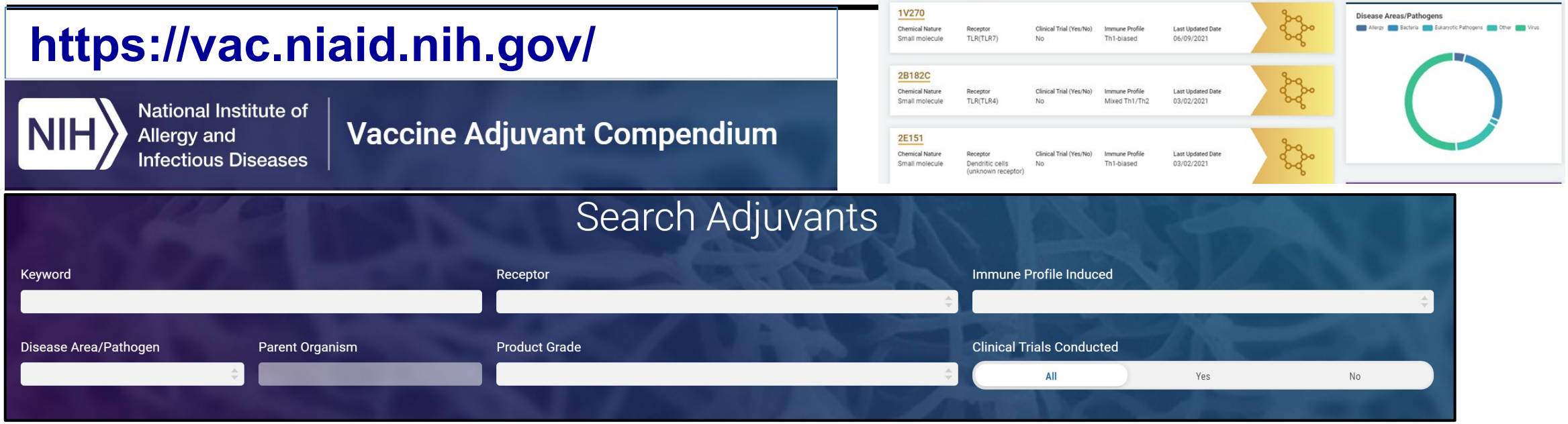
VFI adjuvant portfolio, Celine Lemoine, Head of VFI laboratory in Epalinges, VFI, Switzerland

AAHI adjuvant portfolio, Christopher Fox, SVP, Formulations, AAHI, US

Where to find more information?

NIAID's Vaccine Adjuvant Compendium (VAC)

https://vac.niaid.nih.gov/



- Displays adjuvant characteristics and metadata
- Fosters collaborations beyond NIAID to identify adjuvants tailored to specific vaccine indications

What's the "best" adjuvant, or How do I select an adjuvant?

- **Desirable: Rational adjuvant selection based on adjuvant's characteristics and vaccine's requirements**
  - Currently not possible…
  - Insufficient information available about adjuvant-induced immune profiles, immune correlates of protection for most pathogens, impact of formulation on immune profile of vaccine
- **Alternative: Systematic, side-by-side comparison of adjuvants**
  - NIAID promotes adjuvant comparisons through several programs
    - ACC (Adjuvant Comparison and Characterization)
    - AVAR-T (Advancing Vaccine Adjuvant Research for Mtb)
    - R-CASA (Rational Systematic Characterization and Selection of Adjuvants for HIV Vaccine Candidates)

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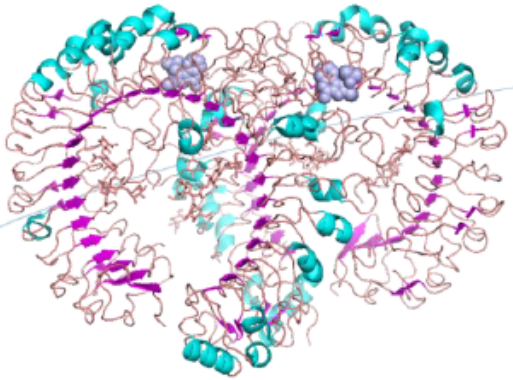


Novel synthetic Th1 and Th17 inducing adjuvants

David Burkhart

Assoc Director, Center for Translational Medicine
Biomedical & Pharmaceutical Sciences
University of Montana
www.umt.edu

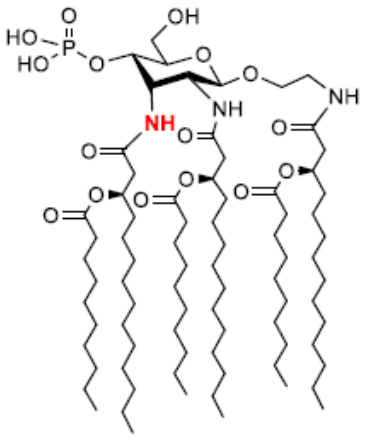
Chief Operations Officer
Inimmune Corporation
Missoula, MT
www.Inimmune.com

A Unique Public/Private Partnership

Proven Success in Immunotherapy

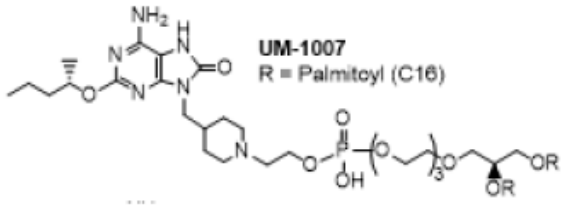
- Strong public/private partnership has grown from 15 to >80 employees (1 team) working on vaccines and immunotherapy research
- Preclinical chemistry, formulation and immunology teams
- Discovery research, IP generation, process development expertise
- Strong and growing pipeline of new candidate drugs and vaccines (new IP)
- Extensive network of academic and industry partners

Late-Stage Synthetic Adjuvant Platforms



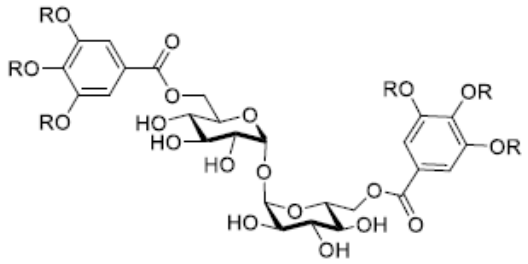
TLR4 Ligands (INI-2002 & INI-2004)

- Patentably distinct new family of synthetic TLR4 ligands (Novel Allose construct)
- Thermostable fully synthetic adjuvant
- Strong safety and efficacy profile (Th1/2) across multiple antigens and animal models (rodents, pigs, NHPs)
- Easily formulated in aqueous, liposome, emulsion or alum adsorbed



TLR7/8 Ligand (INI-4001)

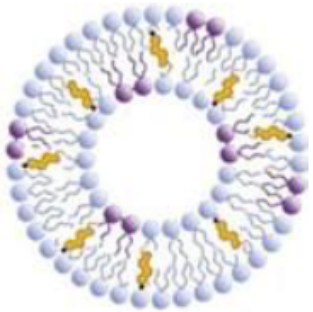
- Synthetic nucleolipid adjuvants
- Lead compound from 7-year $13M NIH Adjuvant Discovery Contract
- Designed for aqueous solubility and efficient incorporation in nanoparticles
- Strong safety and efficacy profile (Th1) across multiple antigens and animal models (rodents, pigs, NHPs)
- Easily formulated in aqueous, liposome, emulsion or alum adsorbed



Mincle Ligands (UM-1098)

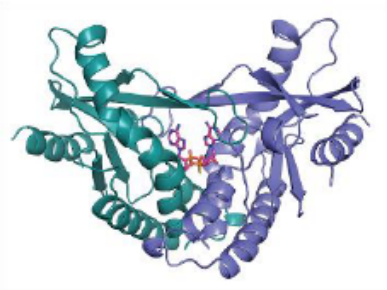
- Novel family of synthetic Mincle ligands
- Strong Th17 immune profile
- Lead compounds from NIH Adjuvant Discovery Contract (ongoing)
- Strong safety and efficacy profile across multiple antigens and animal models (rodents, pigs, NHPs)
- Easily formulated in liposome, emulsion or nanoparticles

Mid and Early-Stage Adjuvant Platforms


Liposome

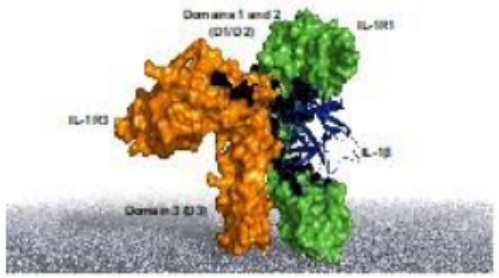
SAS Adjuvant System

- Development of novel synthetic TLR4 + Saponin adjuvant system (fully synthetic "AS01 like" adjuvant)
- Funded by 2 NIAID SBIR Adjuvant Contracts
- Novel thermostable synthetic TLR4 ligand INI-2002
- Portfolio of natural and fully synthetic saponin and isotucaresol adjuvants



STING Agonist based adjuvants

- NIAID Adjuvant Discovery Program (Partnered with OHSU).
- Novel STING agonists developed by SAR
- Human selective agonist
- Novel compounds have strong adjuvant activity



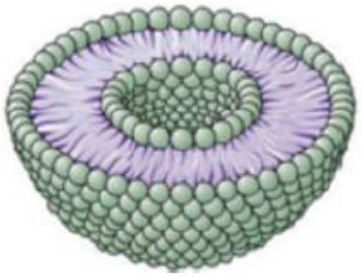
IL-1 Adjuvant System

- NIAID Adjuvant Discovery Program (Partnered with Duke and UM)
- Fully synthetic IL-1 pathway agonists
- Novel synthetic compounds with adjuvant activity identified

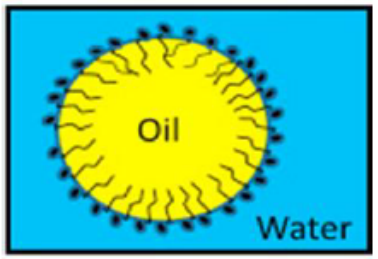
Versatile Agonists: Their Formulations and Development Stage

	INI-2002	INI-2004	INI-4001	TRAC-478	SAS	UM-1098
PRR	TLR4	TLR4	TLR7/8	TLR4+7/8	TLR4 + Saponin	Mincle
API Dev.	cGMP	cGMP	cGMP	cGMP	cGMP	Pre-cGMP
DP Dev.	Pre-cGMP	cGMP	Lip. = cGMP	Pre-cGMP	Pre-cGMP	Pre-cGMP
Formulation	Liposome, Emulsions, Alum	Cationic Liposome	Liposomes, Emulsions, Alum, SNPs	Liposomes, Emulsions, SNPs	AS01-Like liposome	Liposomes, SNPs
Routes	IM, ID, SC	IN	IM, ID, IN	IM, IN	IM, ID	IM, ID
Tox. Stage	Pre-clin	GLP, Ph1	GLP	Pre-Clin	Pre-Clin	Pre-Clin
Animal Models	Murine, Porcine, NHP	Murine, Porcine	Murine, Porcine, NHP	Murine, Porcine	Murine	Murine, Porcine, NHP

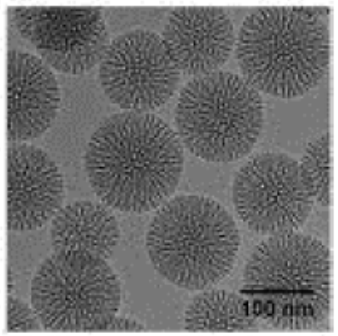
IP: Patents in place to allow use of these with any antigens chosen



Liposomes



Emulsions



Silica NPs

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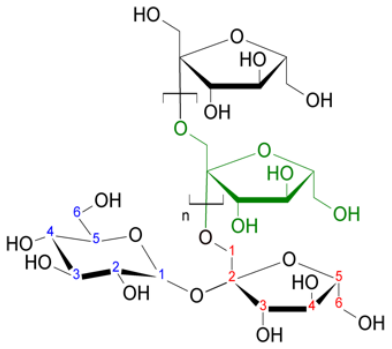
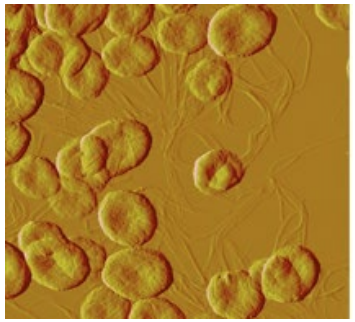
Advax-CpG adjuvant

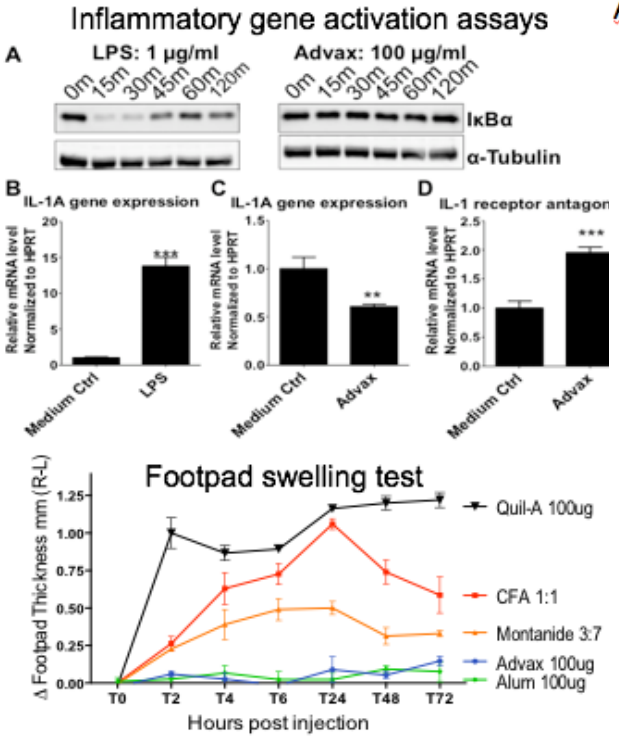
Prof. Nikolai Petrovsky
Chairman and Research Director, Vaxine Pty Ltd

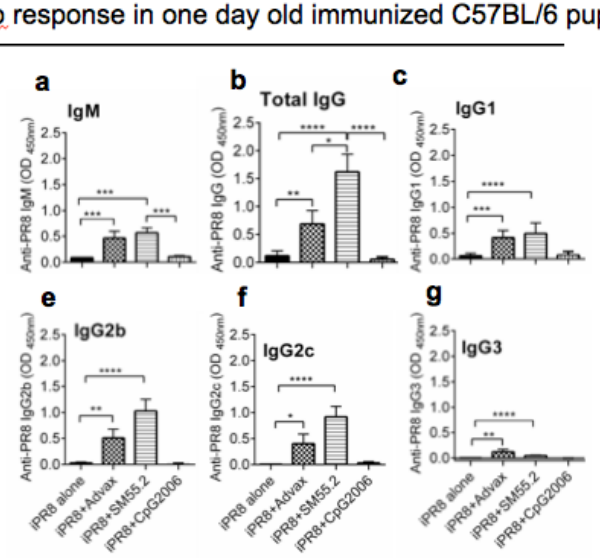
Advax™(delta inulin) breaks inflammatory paradigm

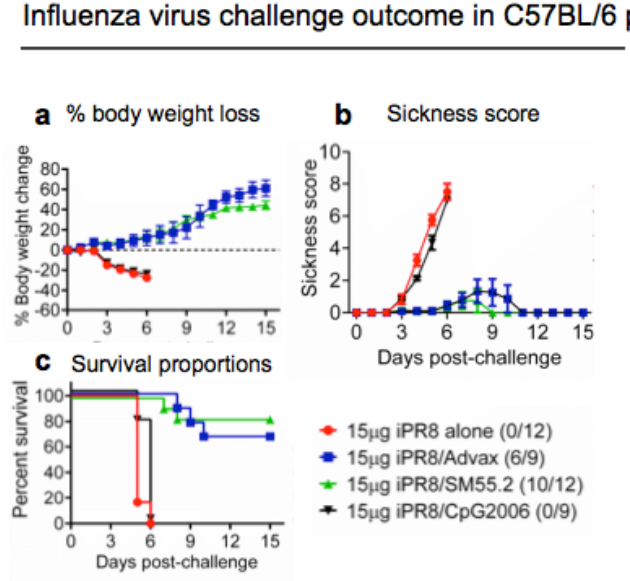
β-D-(2→1) polyfructofuranosyl α-D-glucose (inulin)



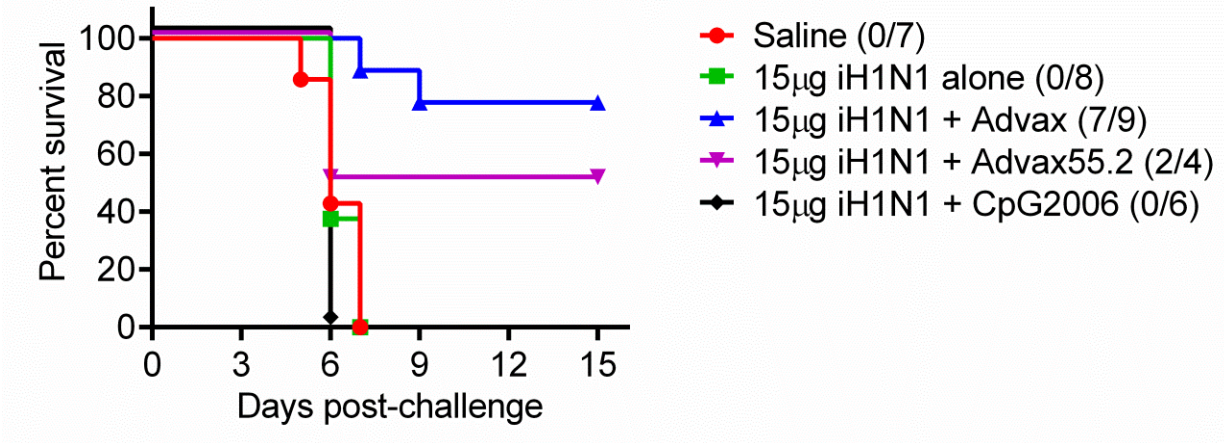






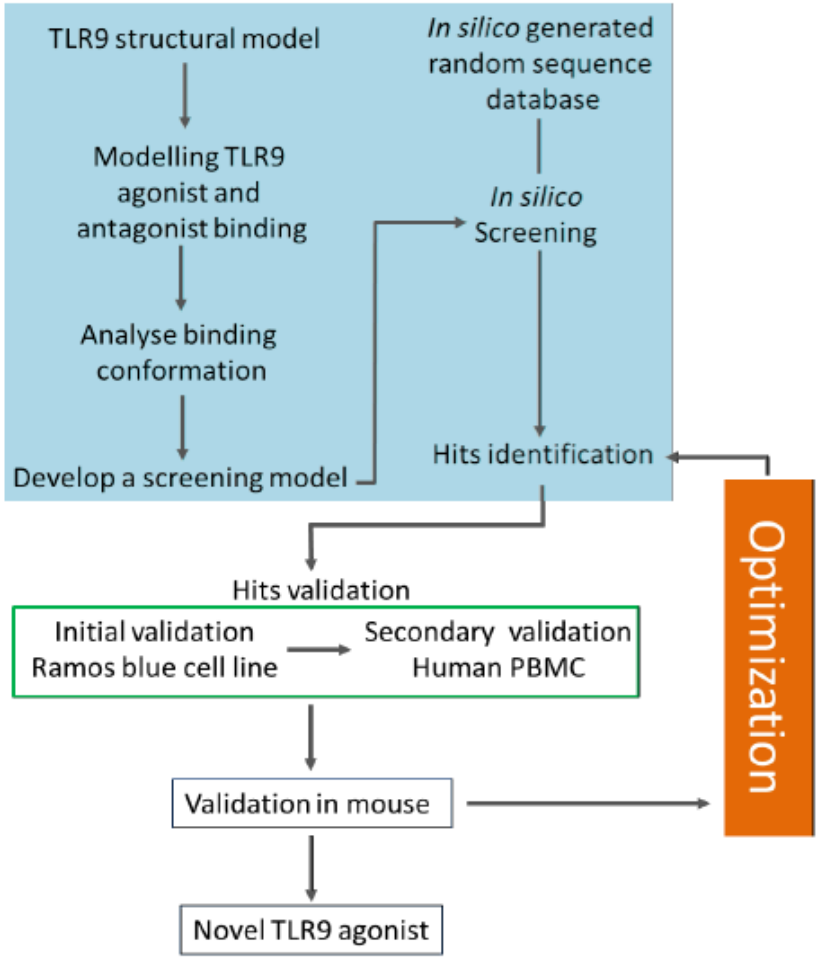


Survival of 1-day-old immunized pups challenged 6 months later



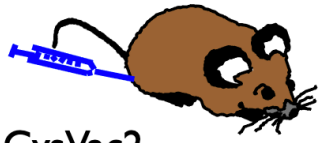
Vaxine's unique CpG (TLR9) adjuvants

Use of AI to identify potent TLR9 agonists

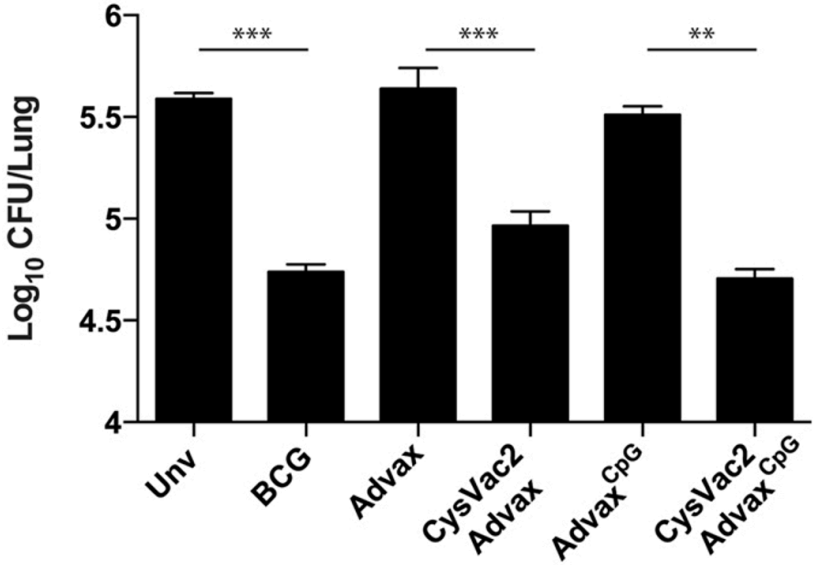


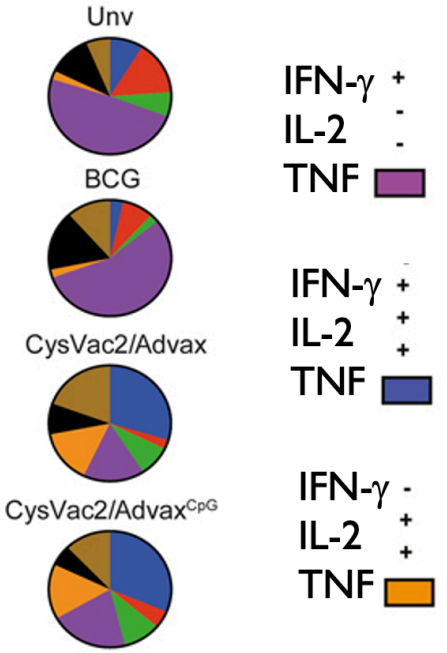
CpG55.2 top hit (also 246.1 and others)

CysVac2/Advax$^{CpG55.2}$ protects against mTB



CysVac2 — 3x 2 wks; 6 wks → aerosol M. tb — 4 weeks → Bacterial load





Counoupas et al, Sci Rep. 2017

TB CRE

Disease models used in Advax adjuvant testing

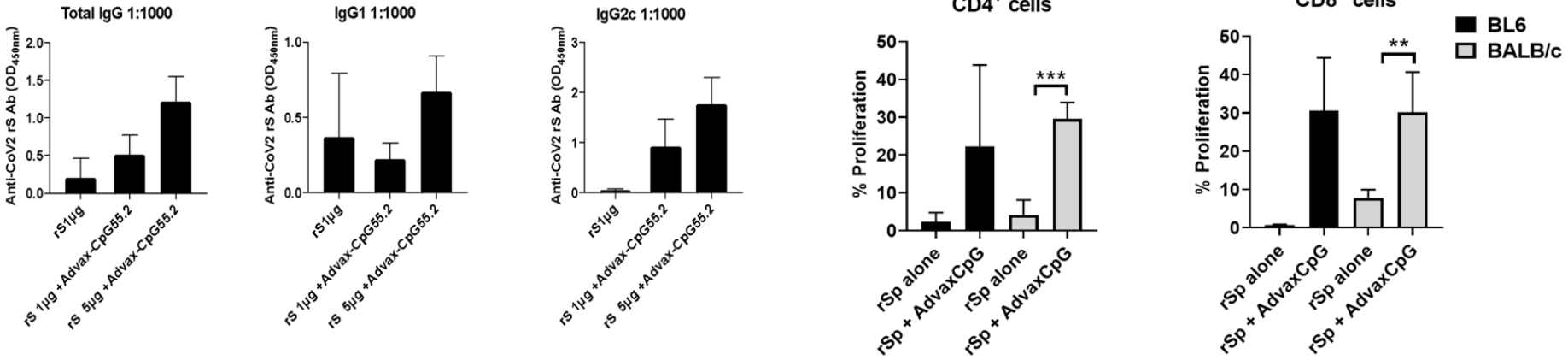
- COVID-19
- Influenza
- Tuberculosis
- RSV
- Shigella
- Hepatitis B
- SARS
- MERS
- Anthrax
- Japanese encephalitis
- West Nile virus
- Rabies
- Ricin toxin
- Ebola/Marburg
- HIV

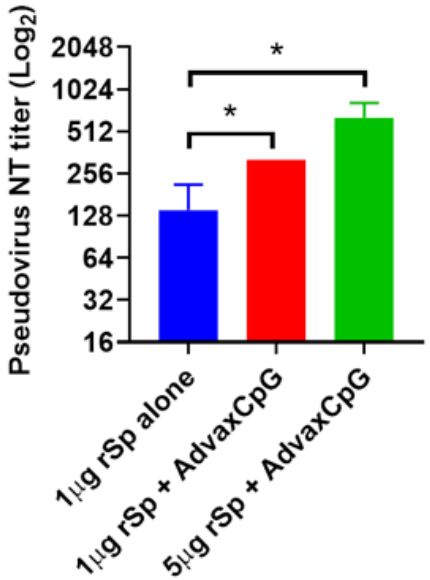
- African Horse sickness
- Peste de petit ruminants
- Glanders
- Onchocerciasis
- Typhoid
- Malaria
- CMV
- Listeria
- Hantaan hemorrhagic fever

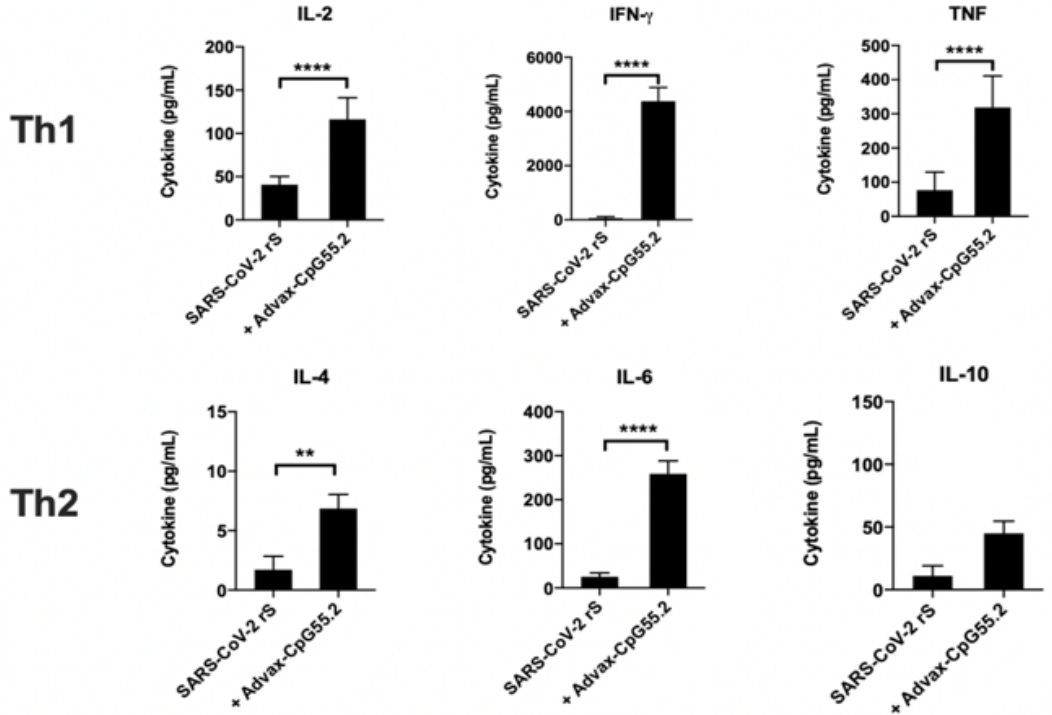
- Cancer
- Allergy
- Alzheimer's disease
- Opioid addiction

vaxine

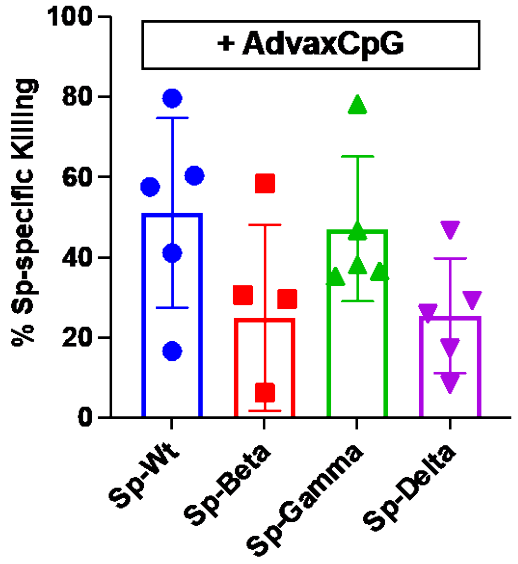
Advax-CpG55.2 combination enhances CD4 and CD8 T cell immunity including CTL activity







In vivo CTL assay



Yoshikazu-Honda et al, Vaccine, 2021

Advax adjuvant applications

Contents lists available at ScienceDirect

Vaccine

journal homepage: www elsevier com/locate/vaccine

Short communication

Maternal immunization with adjuvanted RSV prefusion F protein effectively protects offspring from RSV challenge and alters innate and T cell immunity

Katherine M. Eichinger [a,b,c,d], Jessica L. Kosanovich [a], Madeline A. Lipp [a], Timothy N. Perkins [e], Nikolai Petrovsky [f,g], Christopher Marshall [h], Mark A. Yondola [h], Kerry M. Empey [a,b,d,i,]

JOURNAL OF GENERAL VIROLOGY

RESEARCH ARTICLE

Menon *et al.*, *Journal of General Virology* 2017;98:2143–2155

DOI 10.1099/jgv.0.000863

DNA prime/protein boost vaccination elicits robust humoral response in rhesus macaques using oligomeric simian immunodeficiency virus envelope and Advax delta inulin adjuvant

Veena Menon,[1] Victor I. Ayala,[1] Sneha P. Rangaswamy,[2] Irene Kalisz,[1] Stephen Whitney,[1] Lindsey Galmin,[1] Asma Ashraf,[1] Celia LaBranche,[3] David Montefiori,[3] Nikolai Petrovsky,[4] Vaniambadi S. Kalyanaraman[1] and Ranajit Pal[1,*]

AMERICAN SOCIETY FOR MICROBIOLOGY | mBio®

RESEARCH ARTICLE

Combination Adjuvants Enhance Recombinant Protein Vaccine Protection against Fungal Infection

Marcel Wüthrich,[a] Hannah E. Dobson,[a] Cleison Ledesma Taira,[a] Uju Joy Okaa,[a] Lucas dos Santos Dias,[a] Marcos Isidoro-Ayza,[a] Nikolai Petrovsky,[d,e] Bruce S. Klein[a,b,c]

Contents lists available at ScienceDirect

Clinical Microbiology and Infection

journal homepage: www.clinicalmicrobiologyandinfection.com

Original article

Evaluating the efficacy and safety of SpikoGen®, an Advax-CpG55.2—adjuvanted severe acute respiratory syndrome coronavirus 2 spike protein vaccine: a phase 3 randomized placebo-controlled trial

Payam Tabarsi [1], Nassim Anjidani [2], Ramin Shahpari [2], Masoud Mardani [3], Araz Sabzvari [2], Babak Yazdani [2], Hamidreza Kafi [2], Newsha Fallah [2], Ali Ebrahimi [2], Ali Taheri [2], Nikolai Petrovsky [4], Saghar Barati [2,*]

PLOS | NEGLECTED TROPICAL DISEASES

RESEARCH ARTICLE

The Immunomodulatory Role of Adjuvants in Vaccines Formulated with the Recombinant Antigens *Ov*-103 and *Ov*-RAL-2 against *Onchocerca volvulus* in Mice

Jessica A. Hess[1], Bin Zhan[2,3], April R. Torigian[1], John B. Patton[1], Nikolai Petrovsky[4,5], Tingting Zhan[6], Maria Elena Bottazzi[2,3], Peter J. Hotez[2,3], Thomas R. Klei[7], Sara Lustigman[8], David Abraham[1]*

MucosalImmunology

www.nature.com/mi

ARTICLE OPEN

Intrapulmonary vaccination with delta-inulin adjuvant stimulates non-polarised chemotactic signalling and diverse cellular interaction

Kia C. Ferrell[1,2], Erica L. Stewart[1,2,3], Claudio Counoupas[1,2], Thomas M. Ashhurst[4,5], Warwick J. Britton[1,2,6], Nikolai Petrovsky[3] and James A. Triccas[1,2,5]

Vaxine's Advax and CpG55.2 adjuvants

Easy to manufacture, high yield, easy licensing, low cost

Low reactogenicity, high immunogenicity incl. CD8 T cell

Translatable from mice to humans

Easy formulation/room temperature stability

Eight million human doses of Advax-CpG55.2 safely delivered

CpG55.2 amenable to other formats, e.g. Alum-CpG55.2

Additional adjuvants in pipeline: TLR2, TLR4, TLR7, NOD2

vaxine

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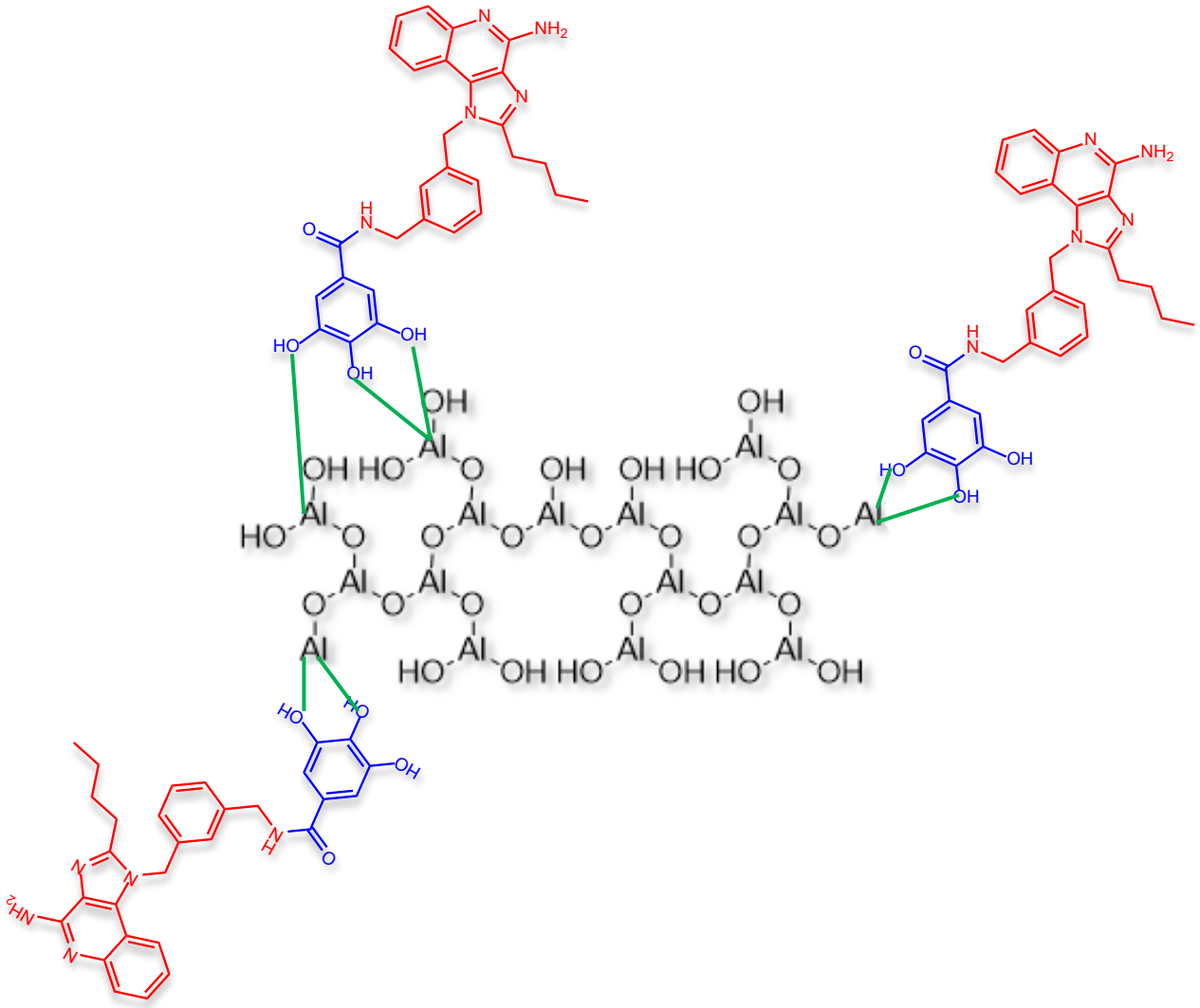
Alhydroxiquim-II

Aluminum **hydroxi**de-**Im**idazo**qui**noline

GVIRF Webinar

Vaccine Adjuvants for Global Health

September 13, 2023



N-(3-((4-amino-2-butyl-1*H*-imidazo[4,5-*c*]quinolin-1-yl)methyl)benzyl)-3,4,5-trihydroxybenzamide

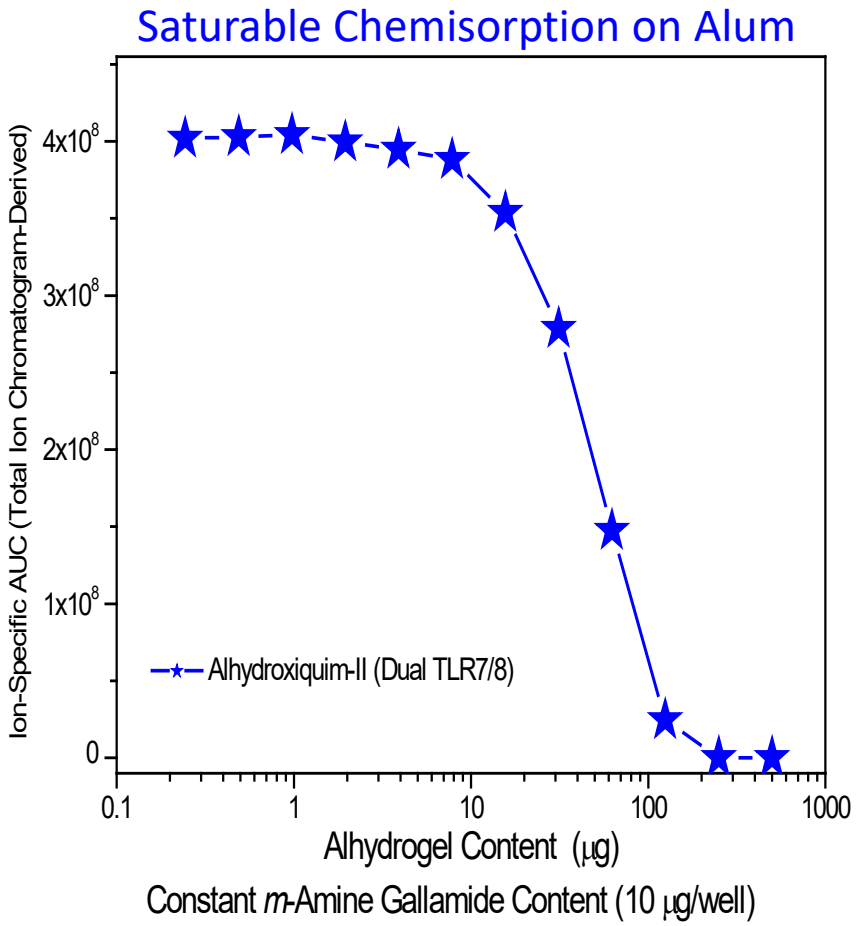
Chemisorbed on:

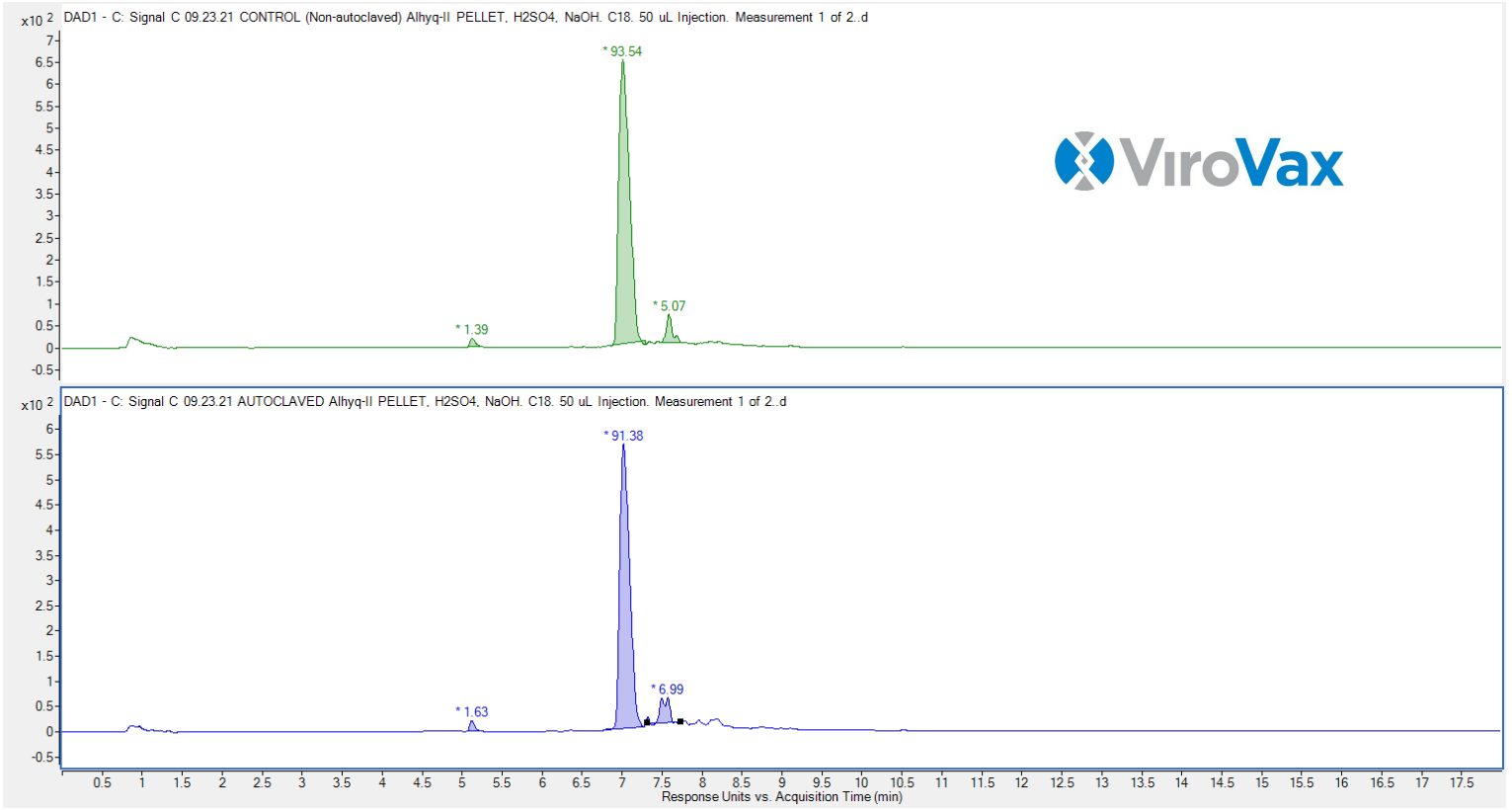
Alumimum hydroxide

Sunil A. David

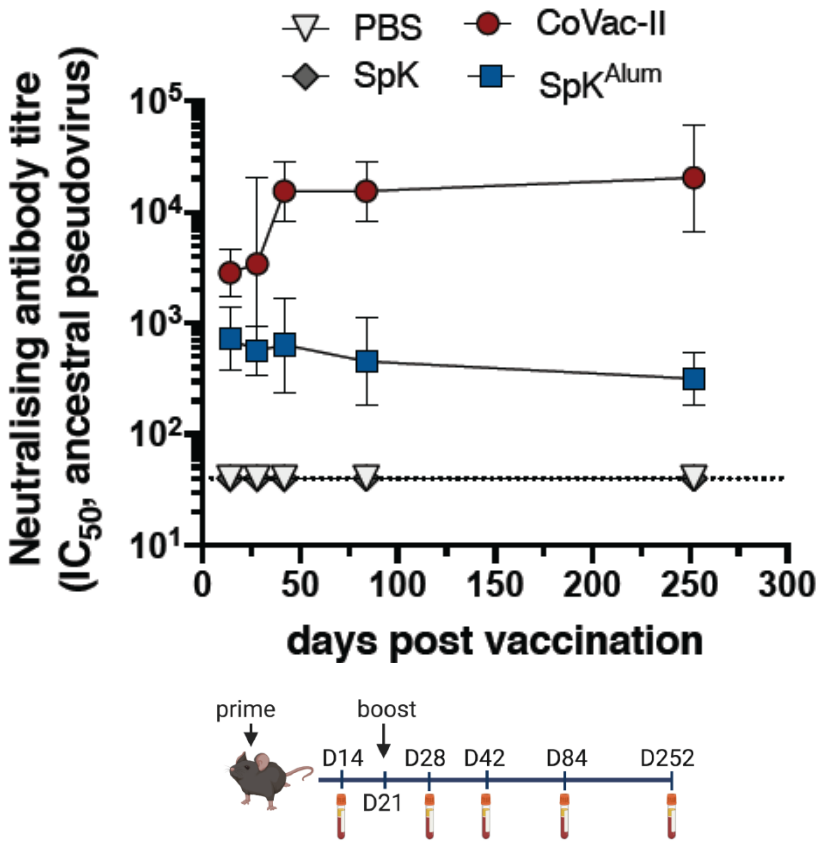
ViroVax

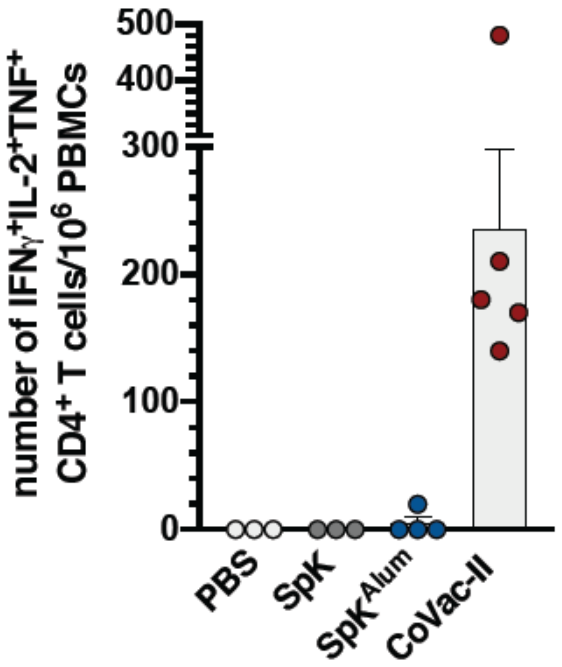
Stability of Alhydroxiquim-II: Terminal Sterilization by Autoclaving





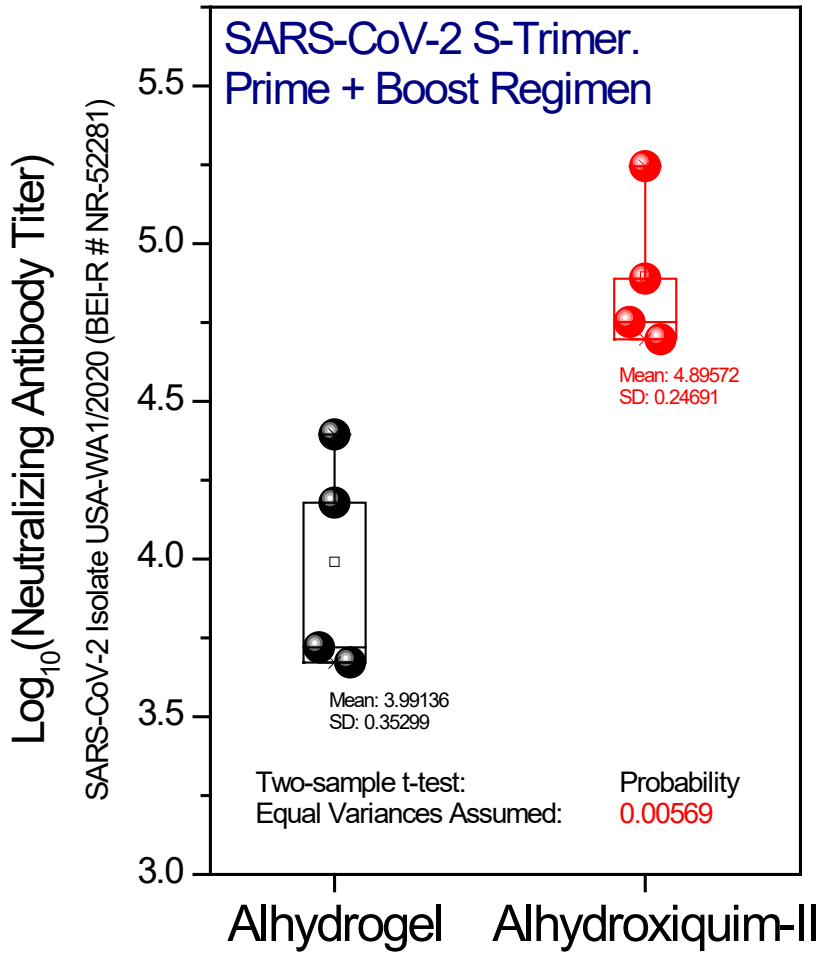
Th1-biased T Cell Immunity (Mice)





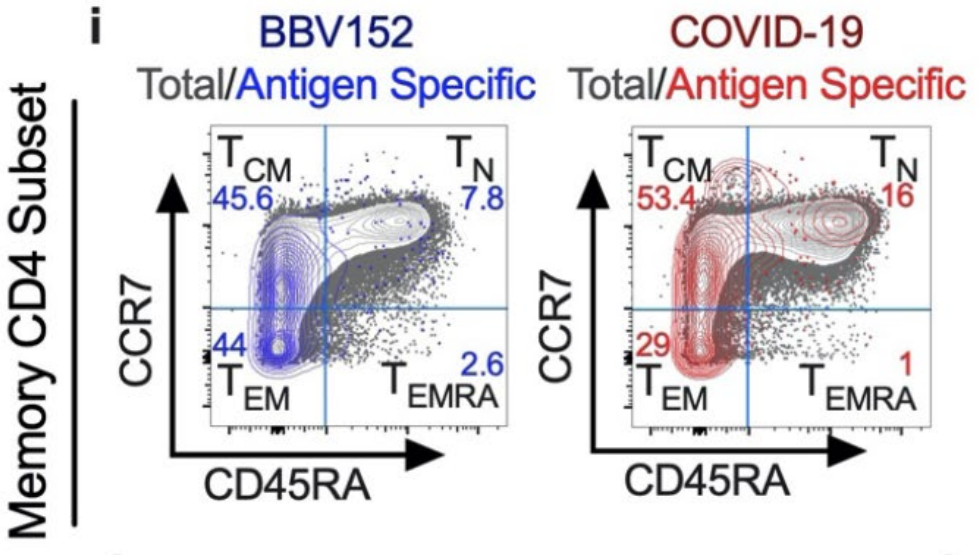
CoVac-II: S-trimer + Alhydroxiquim-II

nAb Titers (Horse)



Neutralising antibodies against the SARS-CoV-2 Delta variant induced by Alhydroxiquim-II-adjuvanted trimeric spike antigens. C. Counoupas *et al.*, doi.org/10.1101/2021.08.18.456891

T Cell Immunity in Humans

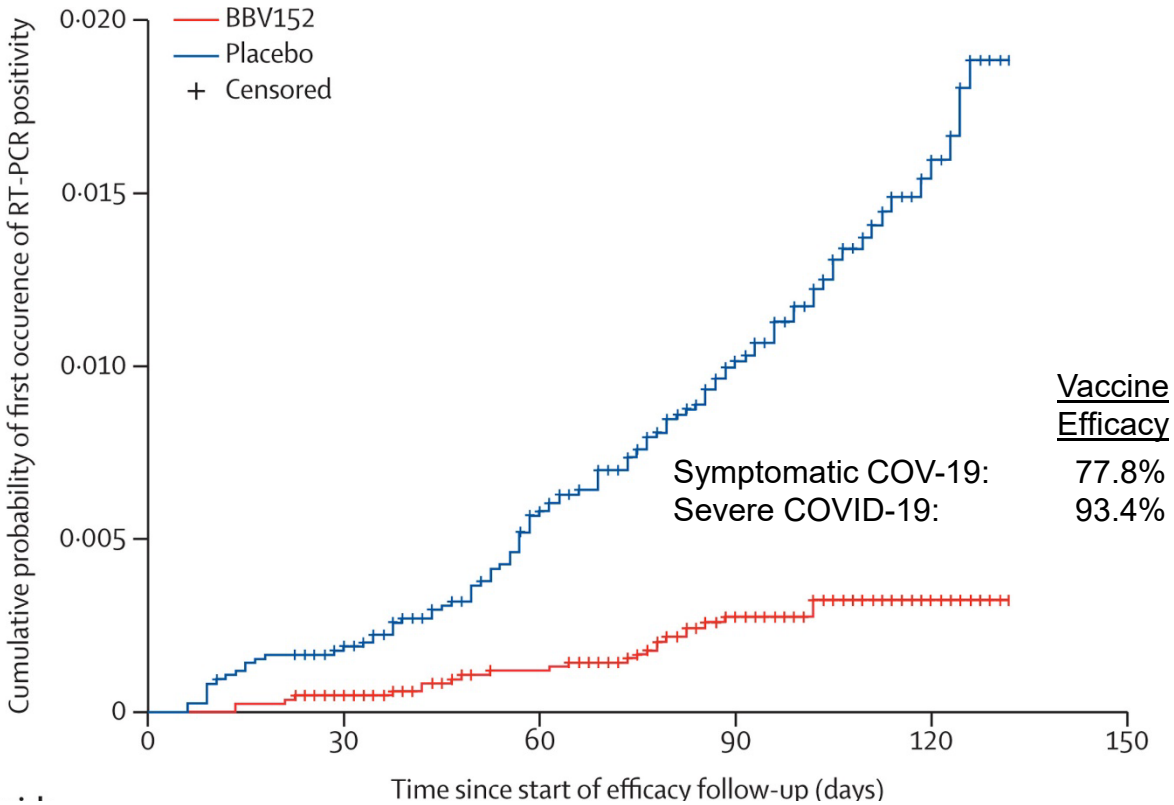


T_N: Naïve CD4⁺cells
T_{CM}: Central Memory T cells
T_{EM}: Effector Memory T cells
T_{EMRA}: Terminally differentiated effector memory cells re-expressing CD45RA

Vikkurthi R, et al., *Nat Microbiol*. 2022; 7: 974-985.

Alhydroxiquim-II is the Adjuvant in Covaxin®

>300 million doses administered



Ella R *et al*., *Lancet*, November 11, 2021. DOI: https://doi.org/10.1016/S0140-6736(21)02000-6

Novel synthetic Th1 and Th17 inducing adjuvants, David Burkhart, Associate Director, the Center for Translational Medicine, University of Montana, US

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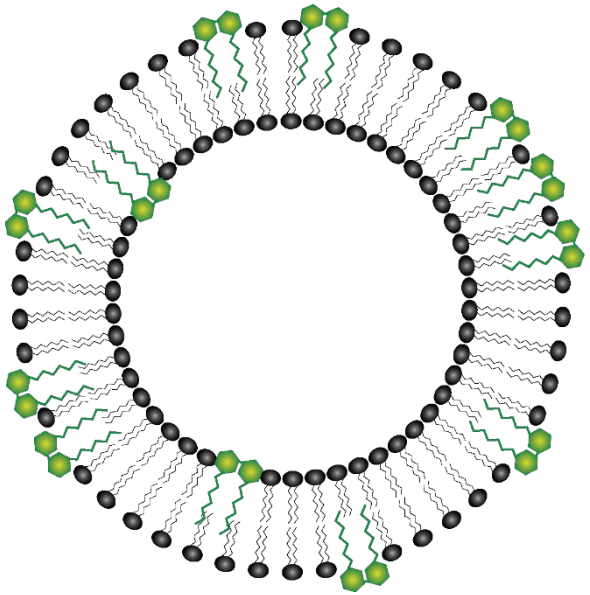
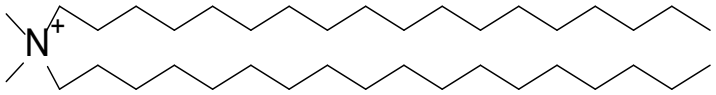
VFI adjuvant portfolio, Celine Lemoine, Head of VFI laboratory in Epalinges, VFI, Switzerland

AAHI adjuvant portfolio, Christopher Fox, SVP, Formulations, AAHI, US

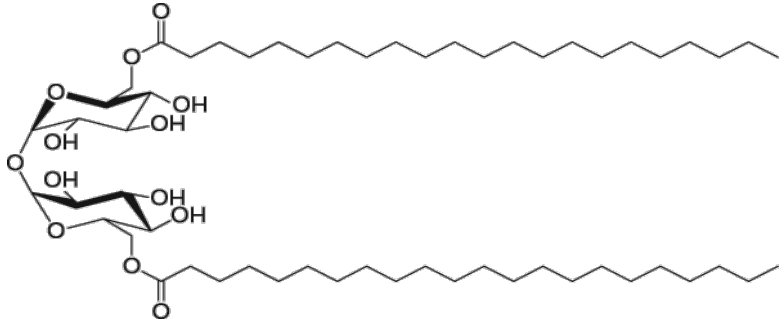
The CAF® Adjuvant platform

- Cationic adjuvant formulation (CAF)
- Dimethyldioctadecylammonium (DDA)
  - Delivery system (GMP quality)
- MINCLE agonist (TDB or MMG)
  - Immunomodulator (GMP quality)
- Stable well-characterized liposomes
  - >3 years shelf-life at 2-8 °C
  - Can be sterile-filtered
  - Produced by an **up-scaleable GMP** manufacturing process





DDA



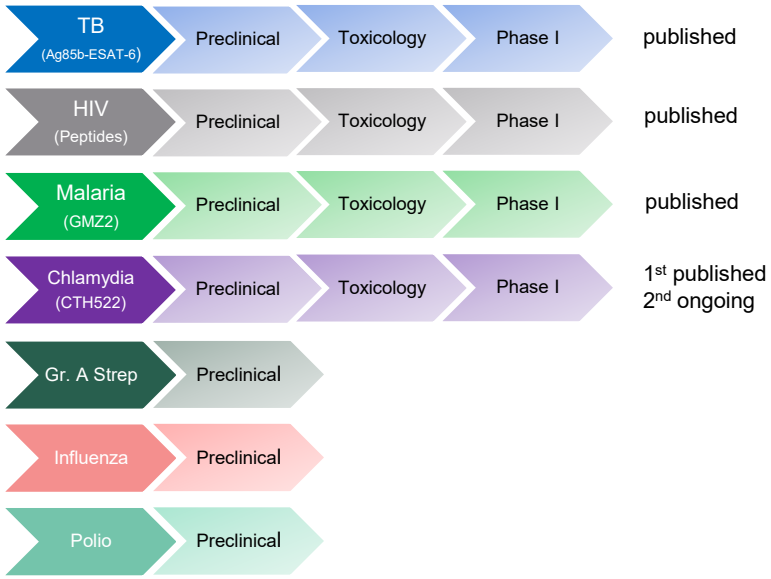
TDB/MMG

CAF® Adjuvants in clinical trials

STATENS SERUM INSTITUT

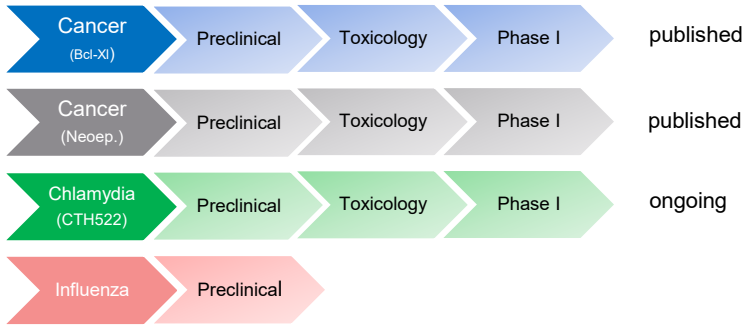
CAF®01

- 5 finalized + 1 ongoing phase 1 CT
- 4 different antigens
- Strong **Th1/Th17** and antibody responses



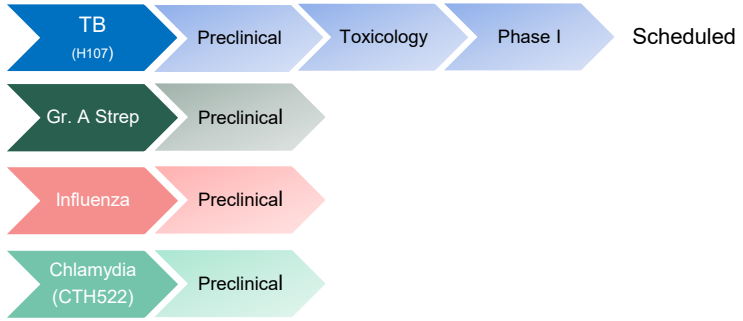
CAF®09b

- 2 finalized phase 1 CT
- Cancer trials: TAA and neoepitopes
- Strong **CTL** induction



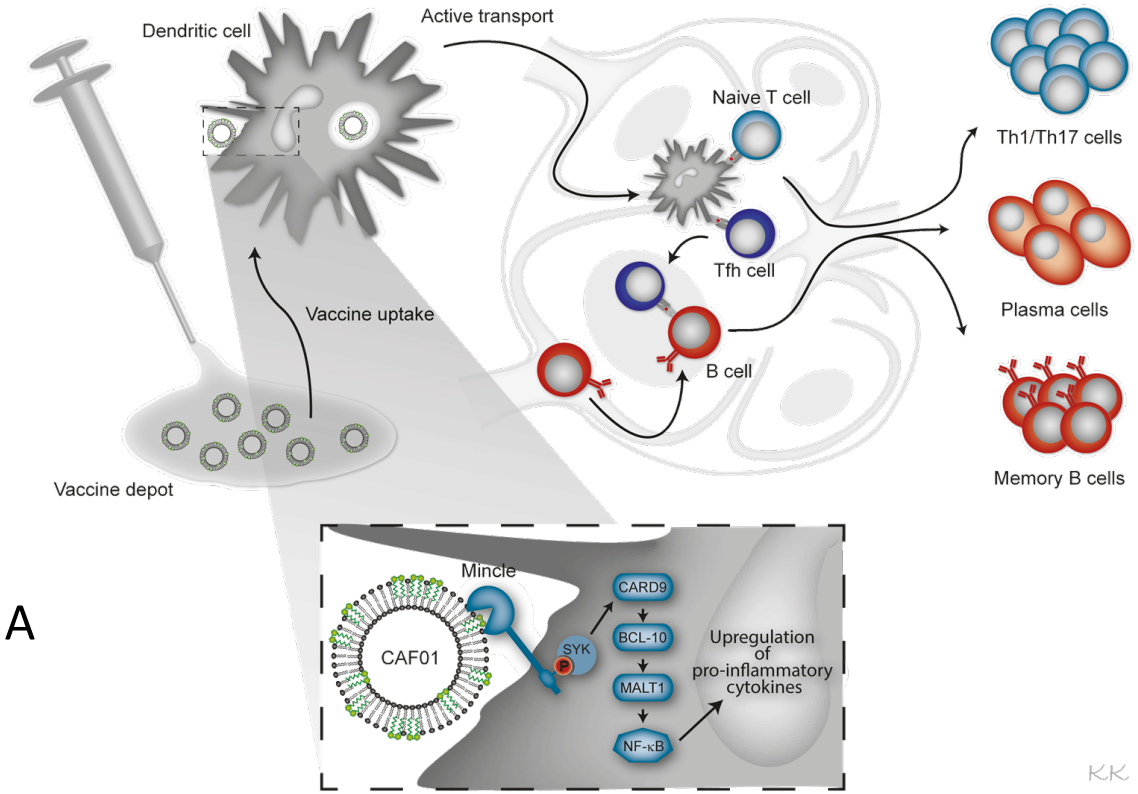
CAF®10b

- CAF® + TLR9 agonist
- 1 scheduled phase 1 CT
- Increased **Th1/Th17** and antibody responses (NHPs)



CAF® Adjuvants – Safe Formulations

- Safe in toxicology studies
- Established MoA
- Simple mixing of antigen with adjuvant
  - Antigen adsorption onto CAF®
  - Proteins, peptides, inactivated vira, split virus, mRNA
- Adjuvants available for collaboration
  - Non-GMP material available for preclinical testing
  - GMP material available for clinical phase 1 testing
  - Collaboration with CRODA for large scale production - tech-transfer ongoing



Contact: GAKP@ssi.dk

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Walter Reed Army Institute of Research (WRAIR)

Defense Health • Global Health

Army Liposome Formulation (ALF) Adjuvant

Mangala Rao, Ph.D.
Chief, Laboratory of Adjuvant and Antigen Research
MHRP, Walter Reed Army Institute of Research
mrao@hivresearch.org

Vaccine Adjuvants for Global Health
GVIRF Webinar
13 September 2023

WRAIR
Walter Reed Army Institute of Research

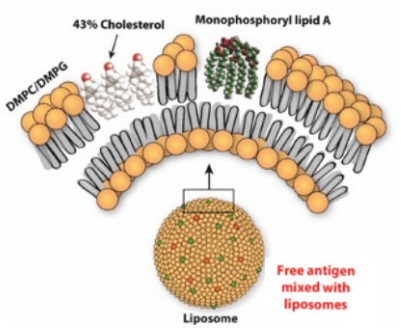
Army Liposome Formulations (ALF)

1970 — Basic Liposome Research at WRAIR

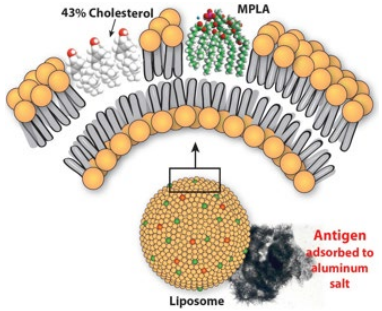
2015 — Pre-Clinical & Clinical Research

2019 — Research & Development of Army Liposome Formulation

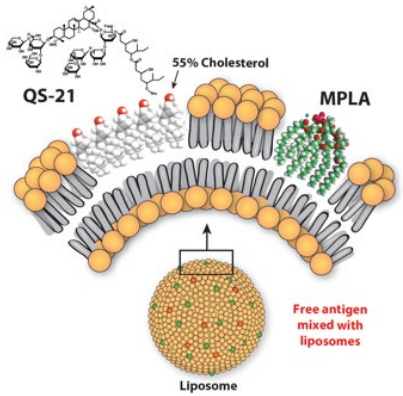
2020 ..... **2023** — Phase 1 Studies with ALFA, ALFQ, and ALFQA



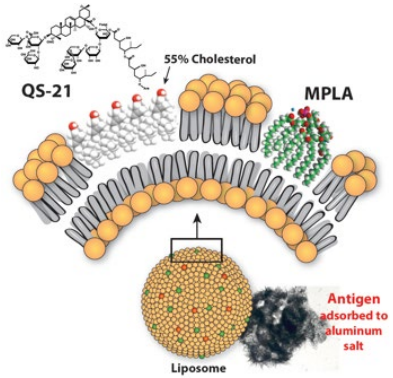
ALF: Liposomes (43 mole% cholesterol) with monophosphoryl lipid A



ALFA : ALF + aluminum salt

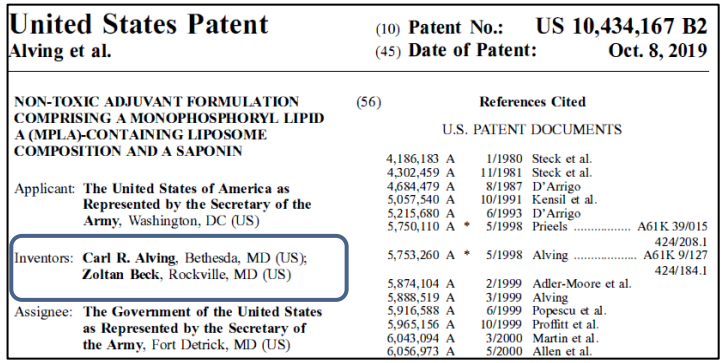


ALFQ : ALF + QS21 (55 mole% cholesterol)



ALFQA : ALFQ + aluminum salt

Carl Alving, Kristina Peachman, Gary Matyas, Mangala Rao and Zoltan Beck (2020). Army Liposome Formulation (ALF) family of vaccine adjuvants. Expert Review of Vaccines.



United States Patent
Alving et al.

(10) **Patent No.: US 10,434,167 B2**
(45) **Date of Patent: Oct. 8, 2019**

NON-TOXIC ADJUVANT FORMULATION COMPRISING A MONOPHOSPHORYL LIPID A (MPLA)-CONTAINING LIPOSOME COMPOSITION AND A SAPONIN

Applicant: **The United States of America as Represented by the Secretary of the Army**, Washington, DC (US)

Inventors: **Carl R. Alving**, Bethesda, MD (US); **Zoltan Beck**, Rockville, MD (US)

Assignee: **The Government of the United States as Represented by the Secretary of the Army**, Fort Detrick, MD (US)

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,186,183	A	1/1980	Steck et al.	
4,302,459	A	11/1981	Steck et al.	
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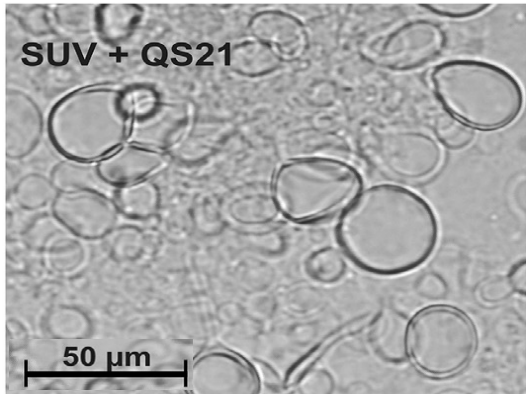
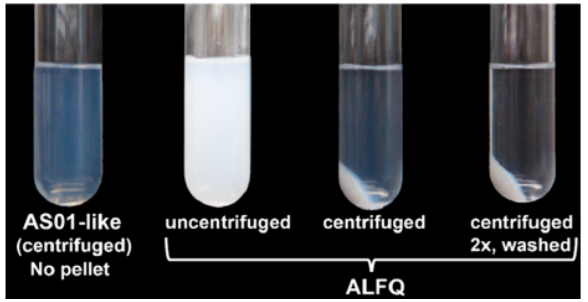
6,043,094	A	3/2000	Martin et al.	
6,056,973	A	5/2000	Allen et al.	

Characteristics	AS01B	ALFQ
Size	Monodisperse small unilamellar vesicles **(SUV)**	Polydisperse mixture of small and large unilamellar vesicles **(SUV-GUV)**
Phospholipid content concentration origin	**Unsaturated**, DOPC 1.272 mM N/A	**Saturated**, DMPC DMPG 11.45 mM Synthetic
Cholesterol conc mol% origin	0.64 mM **33.7** N/A	14 mM **55** Synthetic (plant derived)
MPLA dose origin	50 µg MPL®	200 µg Synthetic 3D-PHAD®
QS-21	50 µg	100 µg
MPLA to Phospholipid ratio	1:39	1:88
Vaccine formulation	Antigen mixed with AS01B	Antigen mixed with ALFQ
Form	Aqueous (wet)	Aqueous (wet)
Storage temperature	4°C	4°C



Polydisperse, Small unilamelar vesicles (SUV)-Giant unilamelar vesicles (GUV) 50 nm - 30,000 nm



pharmaceutics 2023, 15, 2212 MDPI

Article

QS21-Initiated Fusion of Liposomal Small Unilamellar Vesicles to Form ALFQ Results in Concentration of Most of the Monophosphoryl Lipid A, QS21, and the Cholesterol in Giant Unilamellar Vesicles

Erwin G.Abucayon, Mangala Rao, Gary R. Matyas, and Carl R. Alving

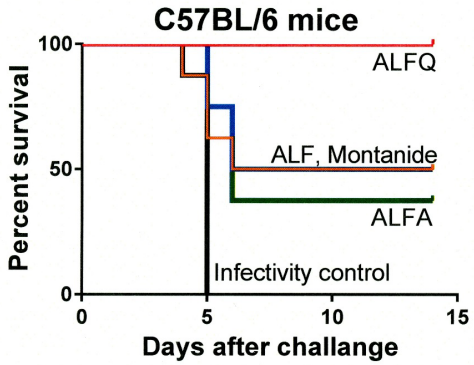
Sample of Preclinical and Clinical Studies

Malaria (Mice)

Liposomes containing monophosphoryl lipid A and QS-21 serve as an effective adjuvant for soluble circumsporozoite protein malaria vaccine FMP013

Christopher J. Genito [a], Zoltan Beck [b], Timothy W. Phares [a], Fanta Kalle [a], Keith J. Limbach [c,d], Maureen E. Stefaniak [c,d], Noelle B. Patterson [c,d], Elke S. Bergmann-Leitner [e], Norman C. Waters Gary R. Matyas [b], Carl R. Alving [b], Sheetij Dutta [a,*]

Vaccine 35: 3865-3874 (2017)



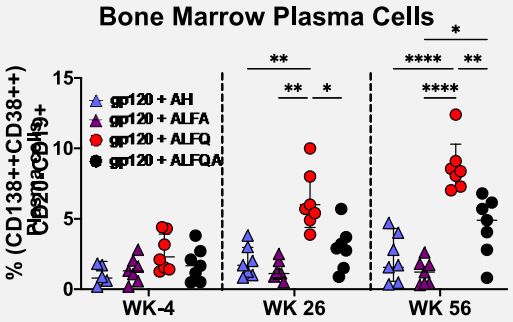
Campy (NHP)

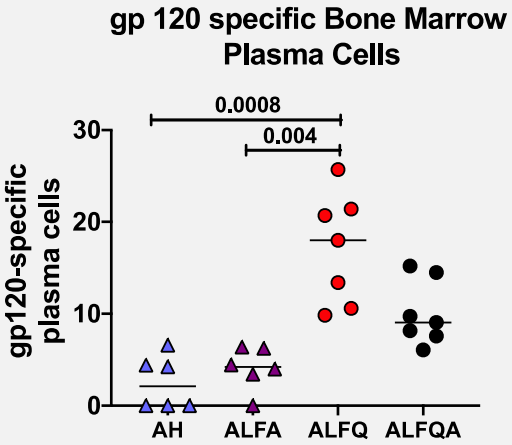
Protective efficacy CPS-CRM conjugate in Aoetus nancymaae NHPs

Adjuvanted group	No. of animals	Diarrhea attack rate, *n* (%)	Protective efficacy against diarrhea (%)[a]	*P*[b]
CPS-CRM + alum	10	5 (50)	29	0.43
CPS-CRM + ALF	17	4 (24)	66	0.008
CPS-CRM + ALFQ	10	1 (10)	86	0.005
PBS	20	14 (70)		

Ramakrishnan A., et al.. mSphere2019 Jun 26:4(3):e00440-19

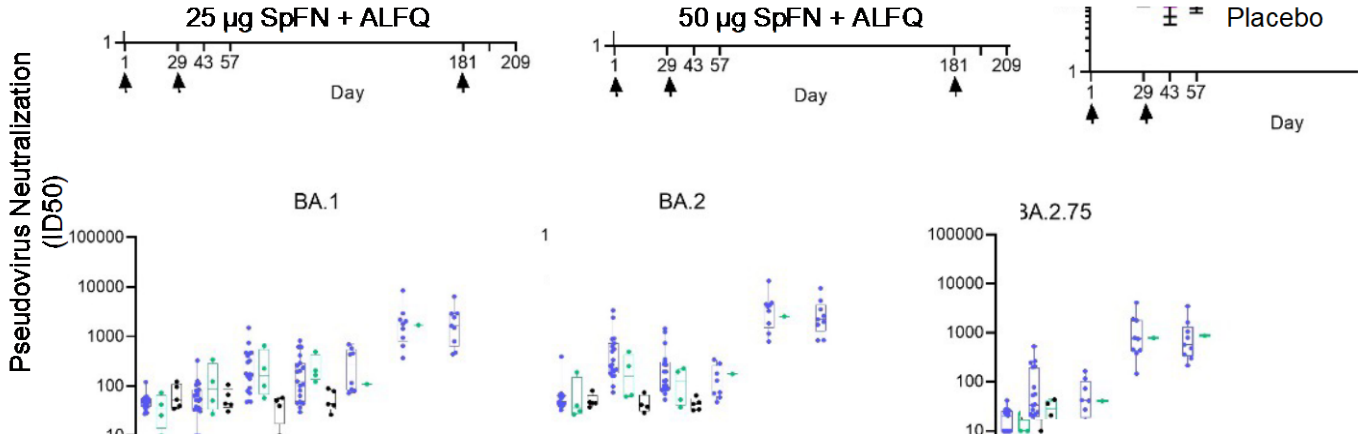
HIV-1 Env Protein (NHP)





Rao et al., unpublished

SARS-CoV-2 (Phase 1 Study)



A randomized double-blind placebo-controlled first-in-human clinical trial of a SARS-CoV-2 recombinant spike ferritin nanoparticle vaccine adjuvanted with Army Liposome Formulation containing monophosphoryl lipid A and QS-21 Brittany L. Ober Shepherd et al (under revision)

ALF in Clinical Trials

Vaccine	Trial	Adjuvant	Study Site	Status
Malaria	FMP013 (part A and part B: Challenge)	ALFQ	WRAIR CTC	Completed
Malaria	FMP014 (part A)	ALFQ	WRAIR CTC	Completed
SARS-CoV-2 (SpFN)	EID030	ALFQ	WRAIR CTC	Completed
HIV	A244, FLSC (RV546)	ALFQ	Thailand	Ongoing
HIV	gp120 A244/B63521 (RV 575)	ALFQA	WRAIR CTC	Ongoing
HIV	Env-C Plasmid DNA, gp145 (RV460)	AH, ALFA, dmLT	Kenya	Ongoing
Campylobacter (Diarrhea)	NMRC/NIAID	ALFQ	U.S.A	Ongoing
HIV	Rapid dose escalation (Ad26 and CH505 Trimer) RV591	ALFQ	Uganda	2023
HIV	Ad26 prime gp120 boost (RV576)	ALFQ	Thailand	2024
HIV	bNAbs, therapeutic vaccination (RV582)	ALFQ	Thailand	2024
Influenza	Synthetic Peptides	ALFQ	U.S.A.	2024
HIV	ALVAC, Delta V1 gp120 (C.L.E.A.R)	ALFQA	U.S.A	2025

Vaccine	Total # Vaccinated to Date	Total # of doses Administered
Malaria and SARS-CoV-2	49	124
RV575	57	148
RV546	37	37
Total	143	309
RV460 (ALF)	93	375

- Vaccine formulations containing ALF and ALFQ were found to be safe and well-tolerated
- No deaths or serious adverse events to date
- Mild to moderate reactogenicity

Advantages of Army Liposome Formulations

- Allows the Army to develop ALF family of adjuvants particularly ALFQ for vaccines
- Tech transfer of Army-owned IP of potent ALFQ adjuvant
- Readily combined with vaccines for multiple existing and emerging infectious diseases
- Ability to incorporate ALFQ adjuvants into early clinical trials
- Successfully cGMP manufactured 7.5 liters of ALF55
- ALFQ is non pyrogenic; currently stable for 6.5 years, on a stability program
- ALFQ has been used in 3 rabbit pharmacology-toxicology studies with a good safety profile and no adverse reactions

Learn more about ALFQ on NIH's Vaccine Adjuvant Compendium (VAC)

Laboratory of Adjuvant and Antigen Research (LAAR) Staff

(Past and Present)

Learn more about ALFQ on NIH's Vaccine Adjuvant Compendium (VAC)

Acknowledgements

MHRP Laboratory of Adjuvant and Antigen Research

Gary R. Matyas
Zoltan Beck
Kristina Peachman
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Elaine Morrison
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Zuzana Villar
Arsene Noe
Lorean Rosado
MAJ Joshua Carmen
Alexander Anderson
Akshaya Ganesh
Camille Lange
Reisha Maharaj
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COL Jason Regules

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Laura Polakowski
Christopher Hamlin

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Jason Koontz
ORA staff

WRAIR PBF

Stasya Zarling
PBF staff

This work was supported by a cooperative agreement (W81XWH-11-2-0174) between the Henry M. Jackson Foundation for the Advancement of Military Medicine (HJF) and the U.S. Army Medical Research and Development Command

Research was conducted under an IACUC-approved animal use protocol in an AAALAC International - accredited facility with a Public Health Services Animal Welfare Assurance and in compliance with the Animal Welfare Act and other federal statutes and regulations relating to laboratory animals.

The investigators have adhered to the policies for protection of human subjects as prescribed in AR 70–25.

Thank you to the clinical trial participants and volunteers!

Walter Reed Army Institute of Research

Accelerating countermeasure development to preserve and ensure operational readiness and improve global health

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AAHI adjuvant portfolio, Christopher Fox, SVP, Formulations, AAHI, US

BlueWillow Biologics

NE01 Clinical-Stage, Intranasal Vaccine Adjuvant Platform

Presented to

The National Institutes of Allergy & Infectious Disease

September 2023

Novel intranasal adjuvant platform differentiated by nature of immune response, human safety and flexibility

Immune Response

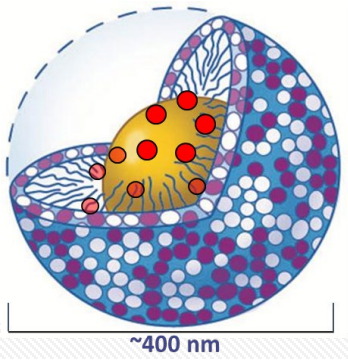
- Mucosal, systemic and cell-mediated immunity
- Decreased viral carriage and shedding
- Biased Th1/Th17 over Th2
- B- and T-cell homing to mucosa for long-term memory

Human Safety & Toxicology

- Demonstrated human safety (303 subjects dosed to date)
- Extensive preclinical tox work completed including 3 successful IND tox studies
- Particle size designed to preclude CNS penetration
- No olfactory bulb or other CNS toxicity seen in any preclinical or clinical studies

Platform Flexibility

- Compatible with multiple antigen types
- Needle-free
- Low Cost
- Thermostable
- Established CMC and GMP
- Rapid response enabling



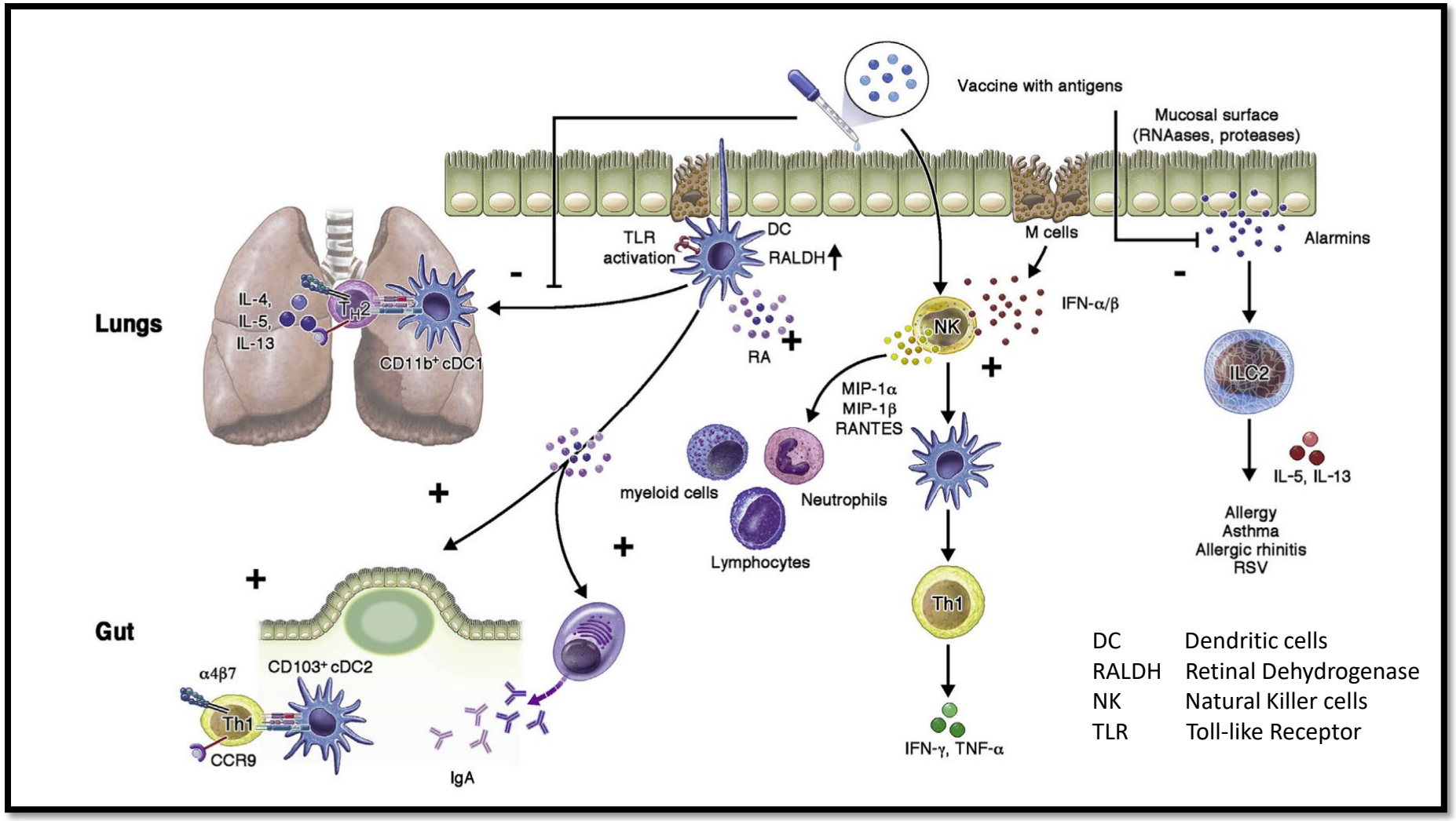
- Oil-in-water emulsion with antigens incorporated in oil or water phase depending on antigen hydrophilicity
- All components GRAS except cationic surfactant CPC (toothpaste and mouthwash ingredient)

BlueWillow Biologics

NE01 adjuvant elicits mucosal, systemic, and cell-mediated immunity

Mechanism of Action

- Efficient engagement, uptake, processing and presentation of antigen by DC cells
- Upregulation of DC TLR 2 & TLR4, RALDH
- Suppression of Th2 cytokines, ILC2 and alarmin production
- Activation of Th1 cells and cytokines
- Production of sIgA and Th17



Ref: Baker, James R Jr et al. "The unfulfilled potential of mucosal immunization." *The Journal of allergy and clinical immunology* vol. 150,1 (2022): 1-11.

BlueWillow Biologics

Compatibility and POC data across a broad range of viral and bacterial pathogens

	Pathogen	Antigen Type						Preclinical Model	Outcomes			Immune Response	
		SP * (mono)	SP * (bivalent)	Whole Virus	Pre-Fusion F	Post-Fusion F	Polysaccharide Conjugate		Safety	Protection	Reduction in Carriage/Shedding	Systemic	Mucosal
Viral	Influenza	√						Mouse	√	√	√	√	√
								Ferret	√	√	√	√	√
								Rabbit	√	*NP*	*NP*	√	√
				√				Pig	√	√	√	*NP*	*NP*
								Mouse	√	√	*NP*	√	√
	HSV-2		√					Guinea Pig	√	√	√	√	√
	SARS-CoV-2	√						Mouse	√	*NP*	*NP*	√	√
								Hamster	√	√	√	√	√
	RSV				√			Cotton Rat	√	√	√	√	√
								Rat	√	*NP*	*NP*	√	√
				√				NHP	√	√	√	√	√
								Cotton Rat	√	√	√	√	√
						√		Mouse	√	*NP*	*NP*	√	√
	MERS-CoV	√						Mouse	√	*NP*	*NP*	√	√
	HIV	√						Mouse	√	√	√	√	√
	HBV	√						Mouse	√	*NP*	*NP*	√	√
Bacterial	Anthrax	√						Mouse	√	√	*NP*	√	√
								Rabbit	√	√	√	√	√
								Guinea Pig	√	√	*NP*	√	√
	Tuberculosis		√					Mouse	√	√	√	√	√
	Pneumonia	√						Mouse	√	*NP*	*NP*	√	√
	Chalmydia						√	Mouse	√	√	√	√	√

BlueWillow Biologics

* SP = Subunit Protein(s)

* *NP – Not performed*

NE01 Uniquely Positioned as Clinical-stage, Safe, Intranasal Adjuvant

- Pre-clinical efficacy data from animal models targeting large range of pathogens provides strong support for likeliness of success in humans.
- First-in-human clinical trials targeting influenza and anthrax were designed to establish safety of the novel NE01 adjuvant for intranasal delivery. **No SAEs attributable to vaccine have been observed in >300 humans dosed.**
- NE01-adjuvanted intranasal vaccines induce **mucosal immunity** with secretory antibodies and Th17.
- Secondary and exploratory immunogenicity endpoints encouraging that **Th1 dominant immune response** seen repeatedly in animal models also occurs in humans.
- Opportunities remain to optimize antigen dose ranging, nasal delivery method, mucosal sampling and assay development in future clinical trials. Significant learnings have occurred from BlueWillow's clinical experience with the adjuvant.

Novel synthetic Th1 and Th17 inducing adjuvants, David Burkhart, Associate Director, the Center for Translational Medicine, University of Montana, US

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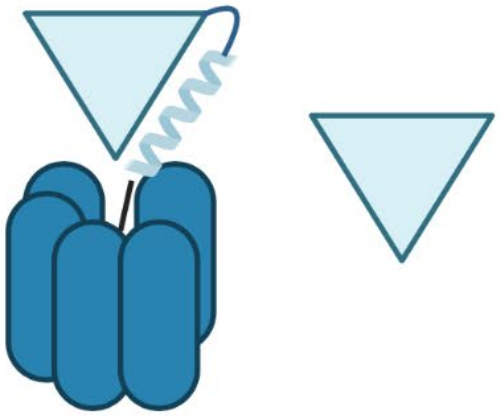
AAHI adjuvant portfolio, Christopher Fox, SVP, Formulations, AAHI, US

dmLT and LTA1 Adjuvants

Elizabeth B. Norton, MPH, PhD
Associate Professor, Dept. of Microbiology & Immunology
Tulane University
enorton@tulane.edu

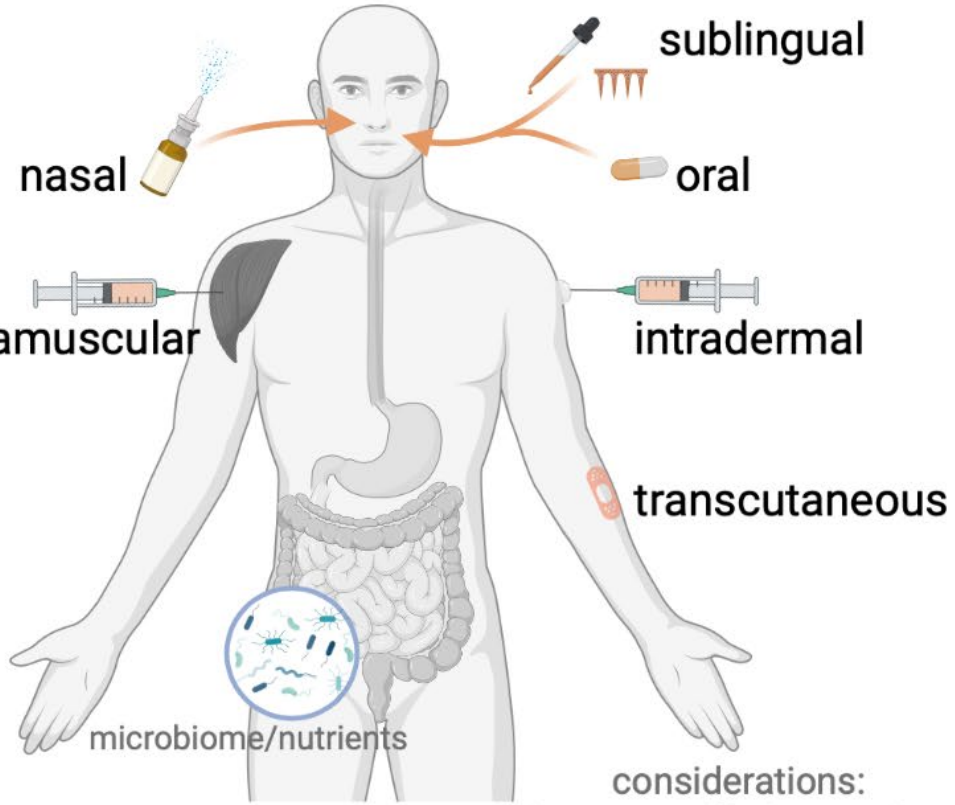
adjuvant selection

dmLT, LTA1



+

delivery route



considerations:
tissue specific interactions

+

antigen form

live attenuated or killed

protein polysaccharide

protein-conjugate

genetic (DNA, RNA)

Enterotoxin-based adjuvants derived from heat-labile toxin of *E. coli*

dmLT:
(LT-R192G/L211A)

Routes: **oral,** sublingual,
intradermal, intramuscular,
transcutaneous

Clinical Trials:
Yes (>10 studies, Phase I, II)
ETEC, polio, *(HIV, Shigella)*
No SAE infants – adults

LTA1:
(A1 domain of LT)

Routes: **intranasal,**
intrapulmonary,
intradermal, intramuscular,

Clinical Trials:
No
(Phase I planned for ~2026 Klebsiella pneumoniae)

(1) Delivered to mucosal tissue to promote local and systemic immunity
(2) Delivered by injection to promote systemic immunity and may also direct immunity to mucosal tissue
(3) Simple admixing with antigen, and Th1/Th2/Th17 and IgG/IgA multifaceted response
(4) Good vial stability, easy manufacturing through *E. coli* expression systems for large quantities

Recent Clinical Trial Results: dmLT

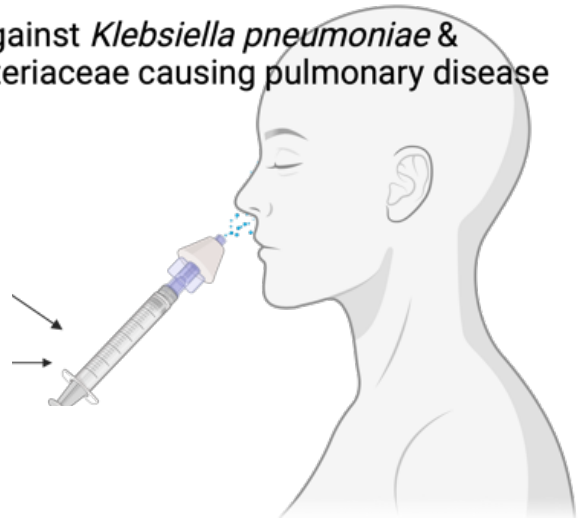
Pathogen/ Antigen(s)	Route	Study Population	Trial	Major Immunologic findings
ETEC: live attenuated (ACE527)	oral	Adults USA	Phase I/II (**NCT01739231**)	dmLT reduced shedding, increased plasma antibody responses (ns), and **increased protective efficacy from 23.1% (ACE527 alone) to 65.9%** following challenge
ETEC: whole-killed (ETVAX)	oral	Adults, Kids, Infants, Bangladesh	Phase I/II (**NCT02531802**)	increased plasma antibody response to O78 LPS and protein CFs present in the lowest amounts (CS5, CS6); enhanced antigenic breadth of plasma antibody responses; enhanced and broadened mucosal immune responses to protein antigens and 078 LPS in youngest age group (6-11 month infants); supports dose reduction
ETEC: Subunit (CssBA)	Injected (i.m.)	Adults USA	Phase I (**NCT03404674**)	dose-dependent enhancement of systemic immune responses (serum IgG, IgA, and antigen-specific B cells); induced robust anti-LT response
Poliovirus: Inactivated (fIPV)	injected(i.d.)	IPV-vaccinated Adults USA	Phase I/II (**NCT03922061**)	increased serum neutralizing antibody responses to all three serotypes (PV1, PV2, and PV3); fecal antibody responses absent in both study groups
Poliovirus: Inactivated (IPV)	Injected (i.m.)	IPV-vaccinated Adults Belgium	Phase I (**NCT04232943**)	no difference in systemic or mucosal responses (measured by fecal antibodies and viral shedding post Day28 bOPV1,3 Challenge)

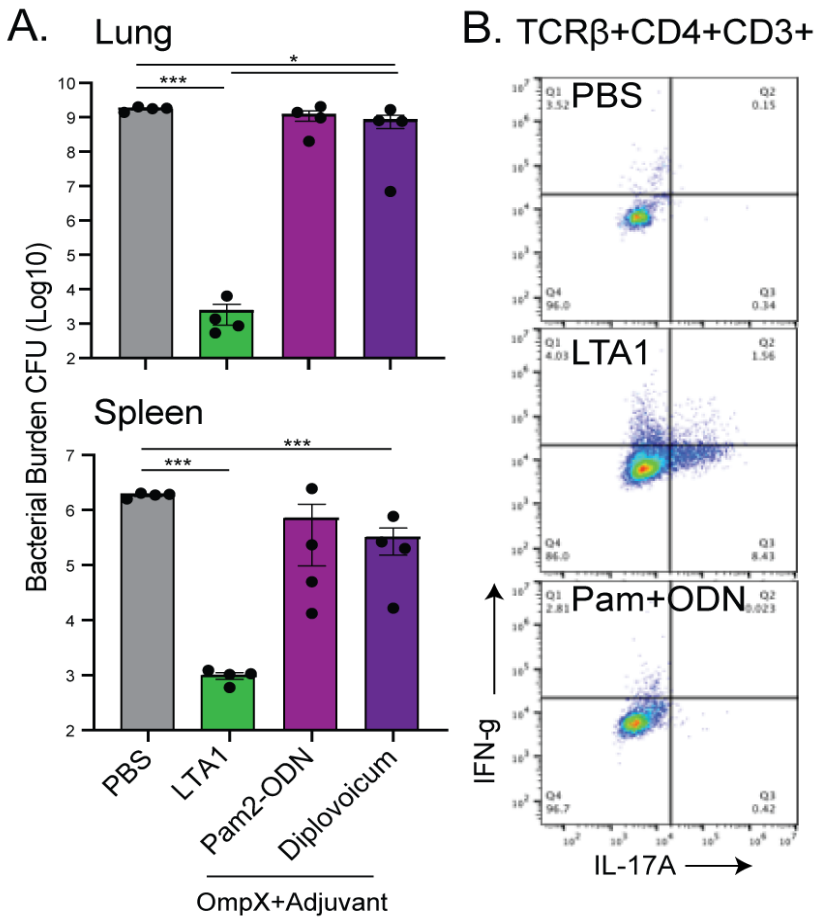
*Planned studies include DNA/protein **HIV** vaccine (NCT04826094) and Injected **Shigella** vaccine (NCT05961059)

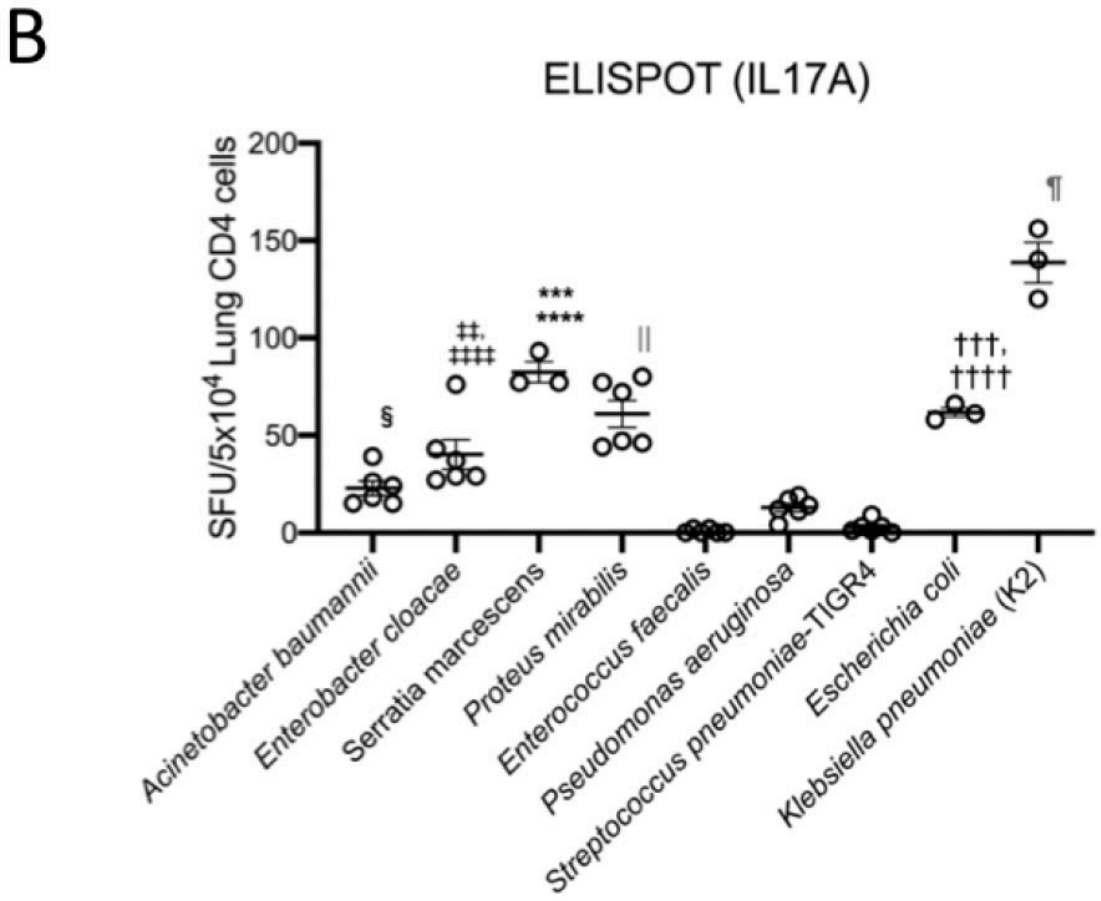
Upcoming Clinical Trial: LTA1

CladeVAX

subunit vaccine against *Klebsiella pneumoniae* & related Enterobacteriaceae causing pulmonary disease







Iwanaga. 2021 Sci Immunology.

dmLT and LTA1 Adjuvants

Elizabeth B. Norton, MPH, PhD

enorton@tulane.edu

*Use QR codes to link to NIH database for published studies in pre-clinical animal models (including for HIV, Klebsiella, Shigella, and many more)

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AAHI adjuvant portfolio, Christopher Fox, SVP, Formulations, AAHI, US

Bacterial Enzymatic Combinatorial Chemistry (BECC) TLR4 Ligands for Use as Vaccine Adjuvants

(*BECC Family of Adjuvants*)

Bob Ernst, PhD
Dr. Paul & Mrs. Jean Corcoran Endowed Professor and Chair
Distinguished University Professor
Department of Microbial Pathogenesis
University of Maryland, Baltimore
Contact: rkernst@umaryland.edu

BECC438b BECC438s BECC470b BECC470s

NIAID Vaccine Adjuvant Compendium - https://vac.niaid.nih.gov/

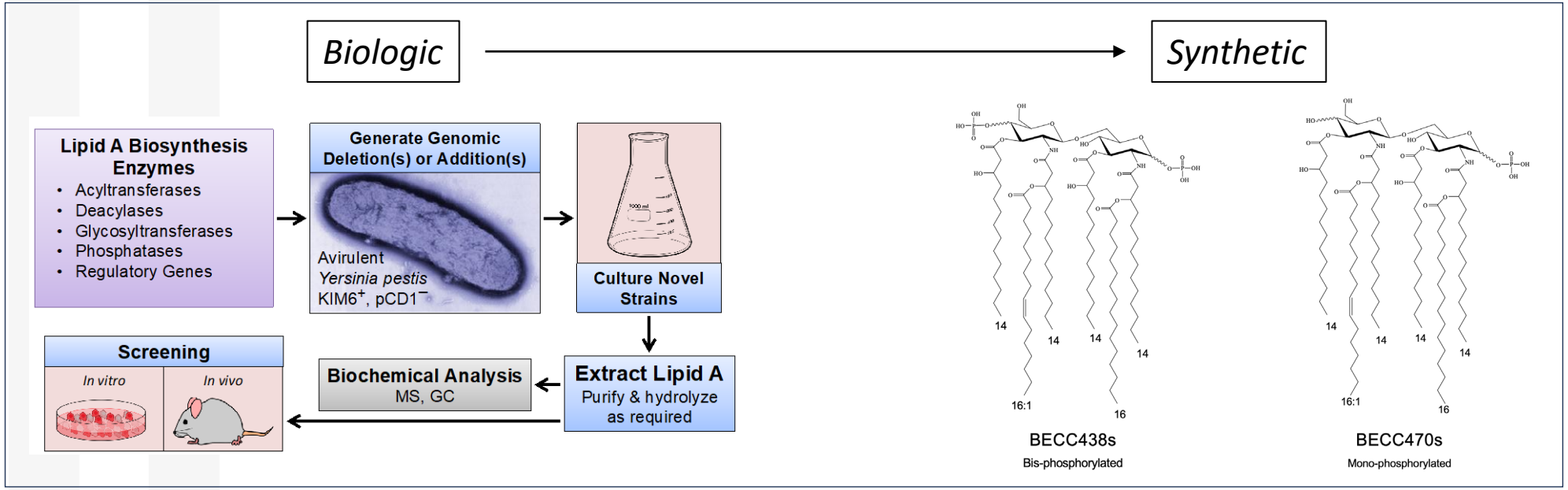
Adjuvant Development Contract, NIAID DAIT
Maribel Miranda, Contracting Officer
Kentner Singleton, Program Officer

BECC Technology: *A Novel Adjuvant Engine Platform*

A robust system designed to augment rapid vaccine innovation

UNIVERSITY of MARYLAND BALTIMORE

- **Bacterial Enzymatic Combinatorial Chemistry**
  - Enables quick & efficient engineering of lipid A mimetics from biological to synthetic
    - 10 to 14 days from creation to lead biological compound *in vitro* analysis
    - Facilitates customization of the immunostimulatory properties of a final agonist/antagonist structure
- Lead synthetic molecules currently available for vaccine development – BECC438s and BECC470s



Partners

BECC Manuscripts

BECC Technology: *Exceeding the Capabilities of Current Adjuvants*

UNIVERSITY of MARYLAND BALTIMORE

BECC Development Lifecycle - Immunology to Manufacturing

Robust Immune Response

- Balance Th1/Th2
- Increased IgG2b and IgG3 titers
- Increased T-cell responses
  - Tfh, central, effector

Memory and Aged Response

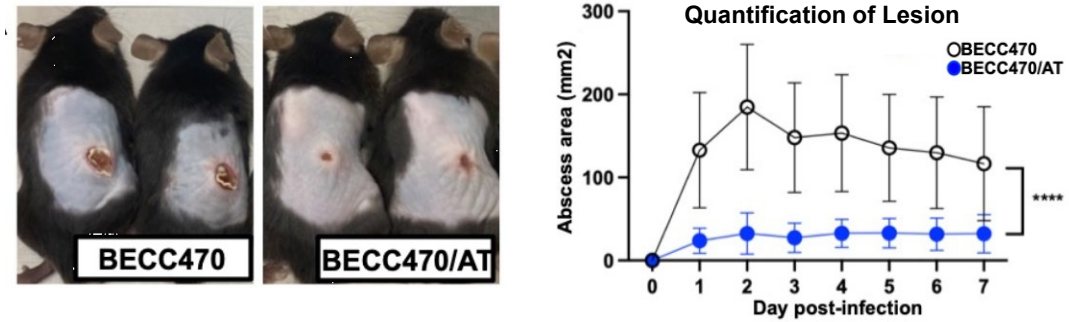
- Memory response out to 48 months
- Increased B-cell memory
- Efficacy in aged animals
  - **Influenza**, mice, 12 month
  - ***P. aeruginosa***, mice, 18 month

Breath in bacterial and viral model systems

- **Viral** – RSV, HPV, SARS2 RBD and spike, Influenza H1 and H5
- **Bacterial** – *B. pertussis, Y. pestis, P. aeruginosa, S. aureus, Shigella ssp.*
- **Ongoing** – *M. tuberculosis*

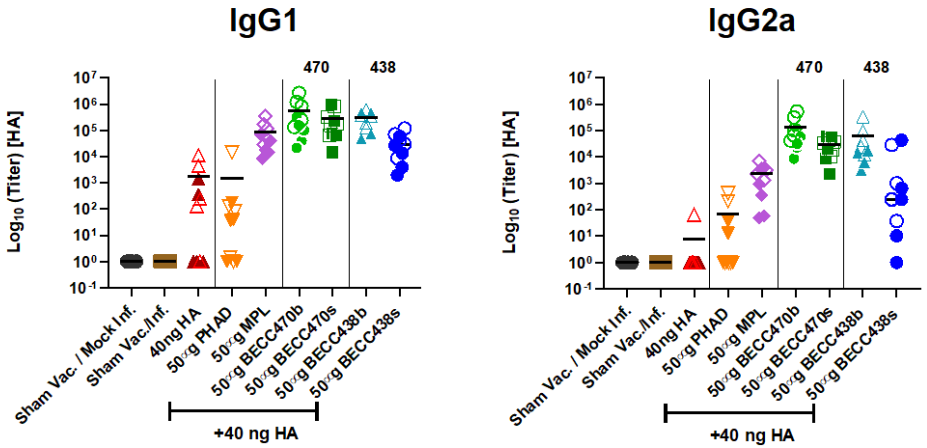
Red – WHO priority pathogen list for vaccine development

S. aureus Dermonecrotic Model



Antigen: detoxified a-toxin (AT – 1 µg), **BECC470** (50 µg), **C57/BL/6**, 1-week prime boost

Influenza Challenge Model



Antigen: H1 HA (40 ng), **BECC438/BECC470** (50 µg), **C57/BL/6**, 2-week prime boost

BECC Technology: *Exceeding the Capabilities of Current Adjuvants*

UNIVERSITY of MARYLAND BALTIMORE

BECC Development Lifecycle - Immunology to Manufacturing

Antigen and Dose Sparing

- Up to 1000-fold less antigen
  - **H1 HA** – 40 ng
  - **Quadrivalent** – 125 ng
  - **H1ssF** – 200 ng
- 1-2 fewer doses
- **Cross protection** – Influenza, HPV

Animals and Administration

- **Animals** – mice, rabbit, dog, baboon
- **Administration** – IM, IN, microneedles

Toxicity

- **Rabbit** - Single dose, Labcorp
- Well-tolerated as a single IM administration
  - **synthetic** - 50 µg/dose
  - **biologic** - 1000 µg/dose

Formulation

- Bedside (admix)
- Biosimilar: AS01, AS03, AS04
- Emulsion
- Biophysical characterization

Stability

- **Aqueous** - >10 months (4ºC)
- **Powder** - >1 year (-20ºC)
- **Emulsion** - 2 weeks (40ºC)

Synthetic Manufacturing

- **Preclinical** – gram plus quantities available
- **Clinical** – GMP production identified, CMC protocol established, favorable regulatory pathway as a chemical entity

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Céline Lemoine
Head of VFI laboratory Lausanne

VACCINE FORMULATION INSTITUTE

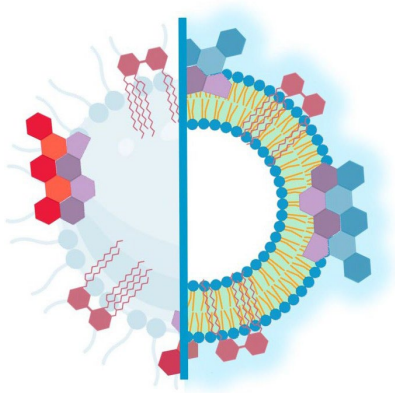
VFI adjuvant portfolio

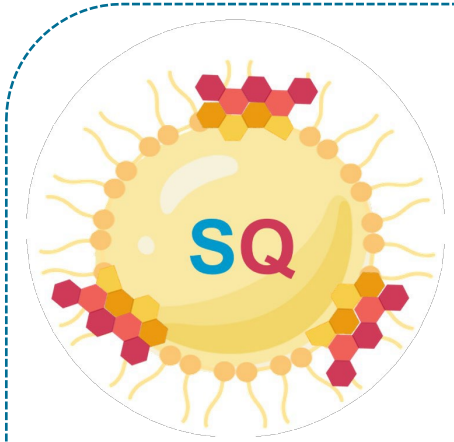
GVIRF Webinar - Vaccine Adjuvants for Global Health

Session III: Access to Adjuvants

September 13th, 2023

VFI adjuvant portfolio





Cholesterol

Quillaja saponaria extract

Synthetic TLR4

Open access

SEPPIC

R&D

Late development → GMP manufacture in 2024

Commercial

Vaccine Adjuvant Compendium

Adjuvants developed with the support from the European Commission (EC), US-HHS BARDA and the Bill & Melinda Gates Foundation (BMGF)

Sepivac SWE™ adjuvant for Global Health vaccines

50 mL

1 L

10 L

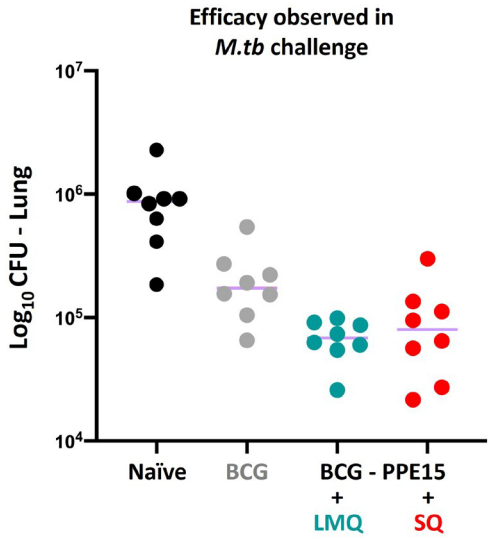
Sepivac SWE™

- ✓ **Open-access** without any licensing agreement
- ✓ **GMP grade**
- ✓ **Industrial scale** produced by Seppic
- ✓ **In several clinical trials - Phase 1 & 2**
- ✓ **Compatible** with various antigens and vaccine types
- ✓ **Dose-sparing**
- ✓ **Stable** for several years at 5°C
- ✓ **One-vial** formulations

VFI adjuvant portfolio to evaluate vaccine candidates

Tuberculosis

(unpublished results - confidential)

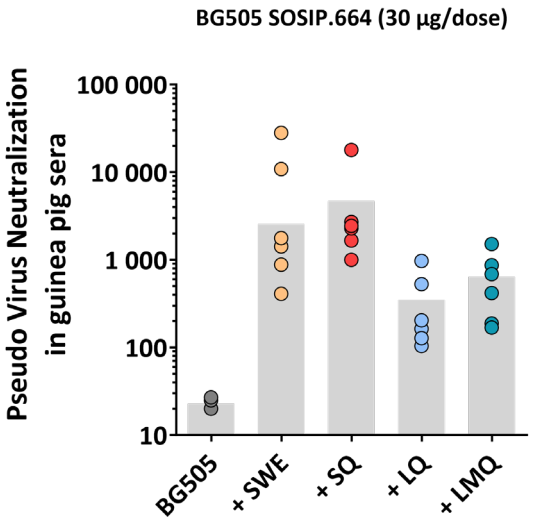


Improved protection
heterologous BCG/adjuvanted prime-boost regimen for **LMQ** and **SQ**

Collaboration with Elena Stylianou & Marcellus Korompis
University of Oxford

HIV/AIDS

(unpublished results - confidential)

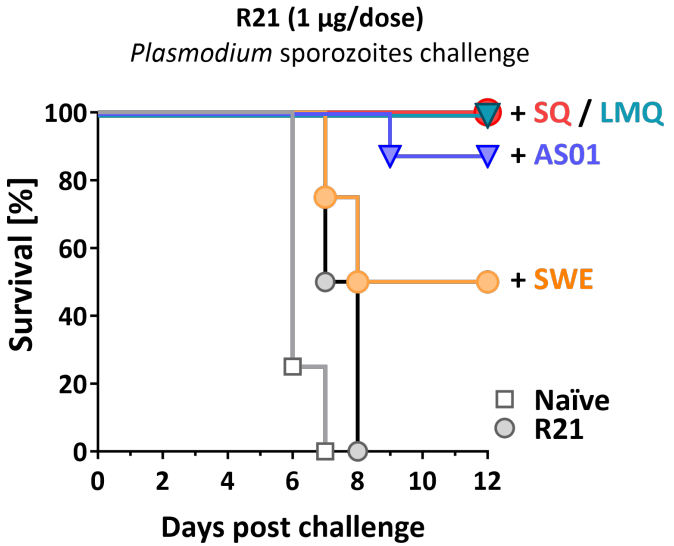


Higher neutralization titers
for emulsion-based adjuvants **SWE** and **SQ**

Collaboration with John Moore – Weill Cornell Medicine
David Montefiori - Duke University Medical Center

Malaria

(unpublished results - confidential)



Excellent protection
against malaria challenge for **SQ** and **LMQ**

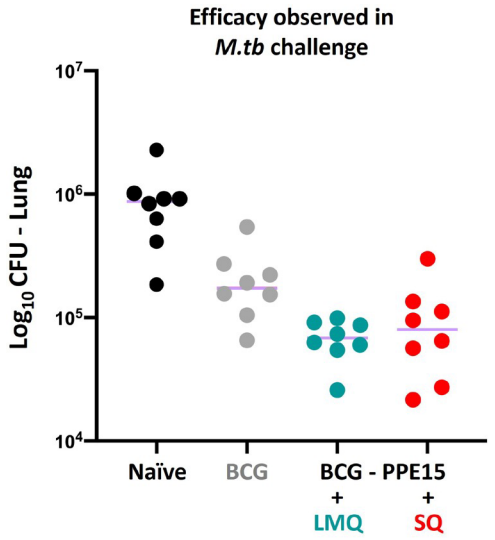
Collaboration with Anita Milicic & Sören Reinke
University of Oxford

Immune mechanism investigations are reported here:
Reinke et al. **2023.** *Cell Reports Medicine*

VFI adjuvant portfolio to evaluate vaccine candidates

Tuberculosis

(unpublished results - confidential)



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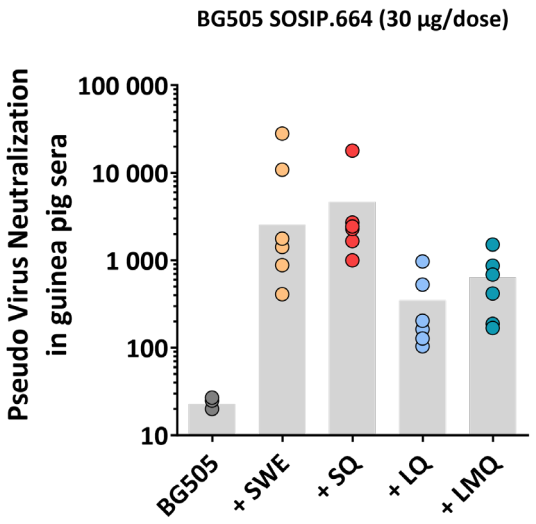
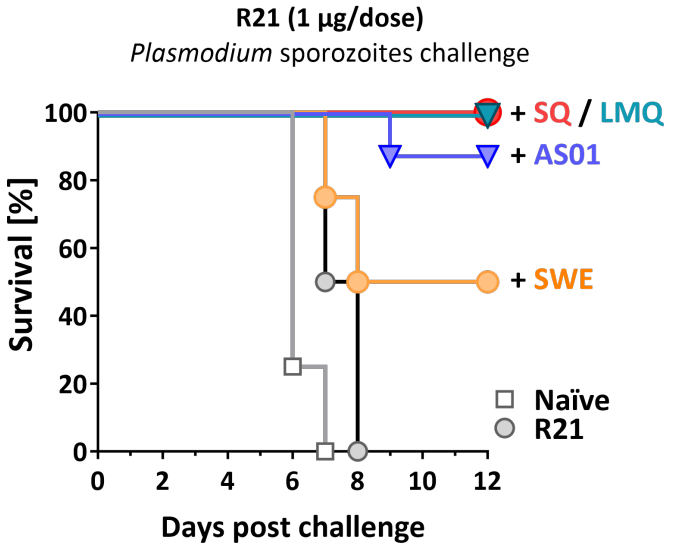


Malaria

(unpublished results - confidential)



More Vaccine Indications

Group A Strep: Rivera-Hernandez et al. *mBio.* **2020.** doi: 10.1128/mBio.00122-20.
MERS: O'Donnell et al. *Front. Immunol.* **2022.** doi: 10.3389/fimmu.2022.976968.
COVID-19: Dalvie et al. *PNAS* **2021**, doi: 10.1073/pnas.2106845118.

Take Home Messages

- ✓ **One adjuvant does not fit all vaccine antigens**
- ✓ **Formulation studies are critical to confirm antigen/adjuvant compatibility and interpret data**

VFI manuscripts

Please contact us if you are interested to learn more about VFI adjuvants

GENEVA

VFI Geneva laboratories
Rue du Champ-Blanchod 4
1228 Plan-les-Ouates
Switzerland

contact@vformulation.org

LAUSANNE

VFI Lausanne laboratories
Route de la Corniche 5
1066 Epalinges
Switzerland

www.vaccineformulationinstitute.org

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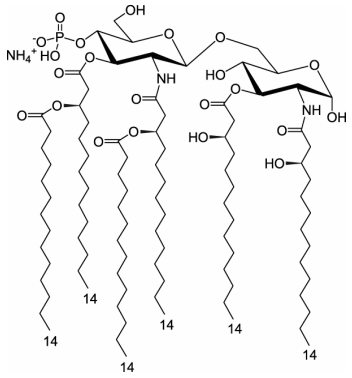
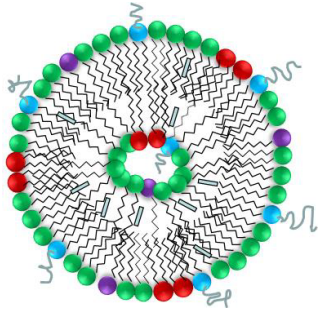
AAHI Adjuvant Formulation Portfolio

AAHI ACCESS TO ADVANCED HEALTH INSTITUTE



Molecular Adjuvant
(TLR ligands, saponins)



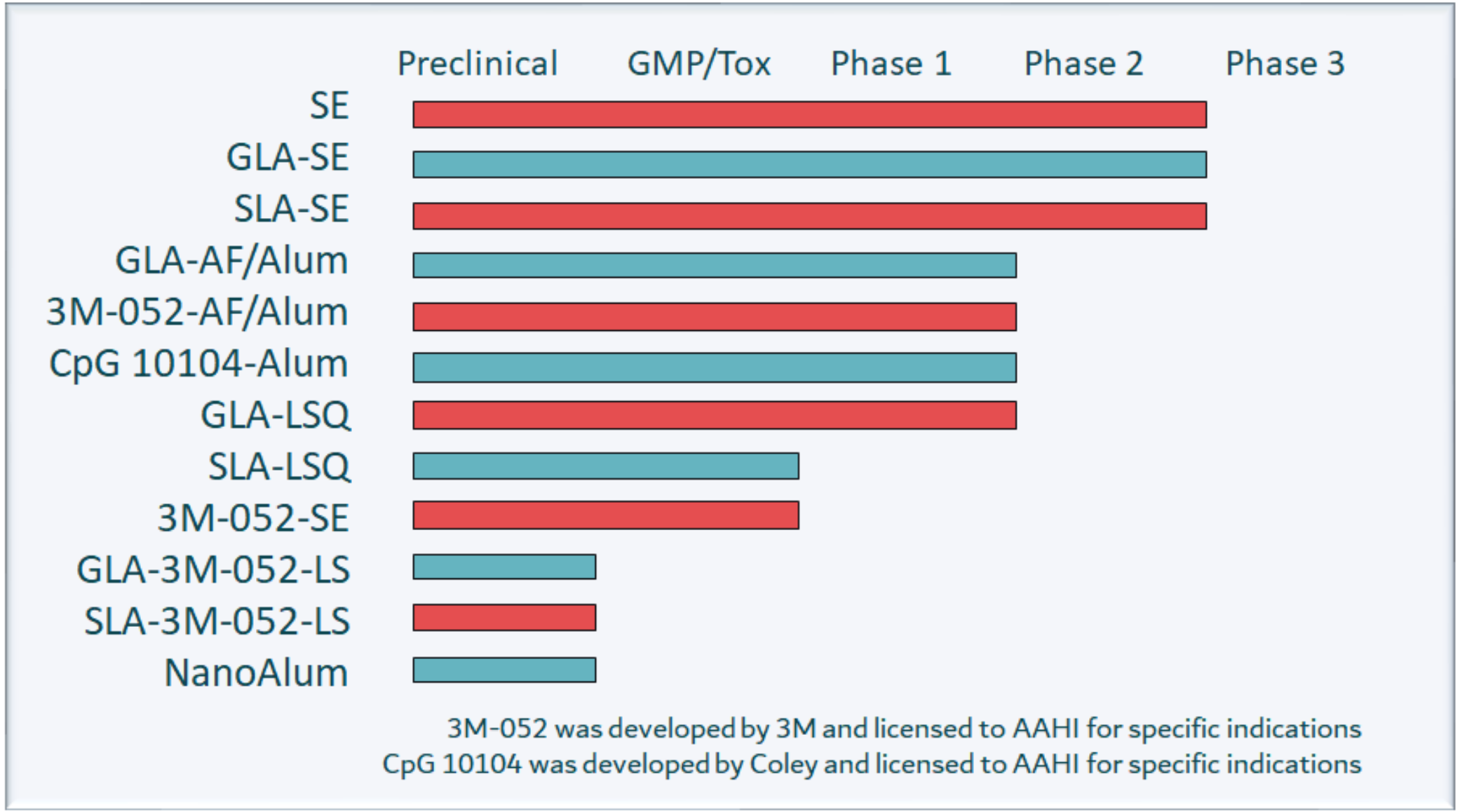
Formulation Platform
(emulsions, liposomes, aluminum salts)

Emulsions	Liposomes	Aluminum salts
GLA-SE (TLR4)	GLA-LSQ (TLR4, QS-21)	GLA-AF/Alum (TLR4)
SLA-SE (TLR4)	SLA-LSQ (TLR4, QS-21)	3M-052-AF/Alum (TLR7/8)
3M-052-SE (TLR7/8)	GLA-3M-052-LS (TLR4/7/8)	NanoAlum

For more information about each adjuvant formulation, scan QR codes or visit www.aahi.org/formulations

3M-052 was developed by 3M and licensed to AAHI for specific indications

AAHI Adjuvant Formulation Development Stage



Practical Attributes of AAHI Adjuvant Formulations

AAHI ACCESS TO ADVANCED HEALTH INSTITUTE

Sustainable raw materials

npj | vaccines

www.nature.com/npjvaccines

ARTICLE OPEN

Check for updates

Semi-synthetic terpenoids with differential adjuvant properties as sustainable replacements for shark squalene in vaccine emulsions

Manufacturing partners for scalability and global access

Alternative routes of delivery

frontiers in Immunology

Optimizing a Multi-Component Intranasal *Entamoeba Histolytica* Vaccine Formulation Using a Design of Experiments Strategy

In-house R&D and cGMP manufacturing

Thermostable formulation platforms

nature communications

Article

https://doi.org/10.1038/s41467-023-36789-2

Safety and immunogenicity of a thermo-stable ID93 + GLA-SE tuberculosis vaccine candidate in healthy adults

Multiple Phase 1/2 clinical trials

AAHI ACCESS TO ADVANCED HEALTH INSTITUTE

Adjuvant Formulation Capacity Building

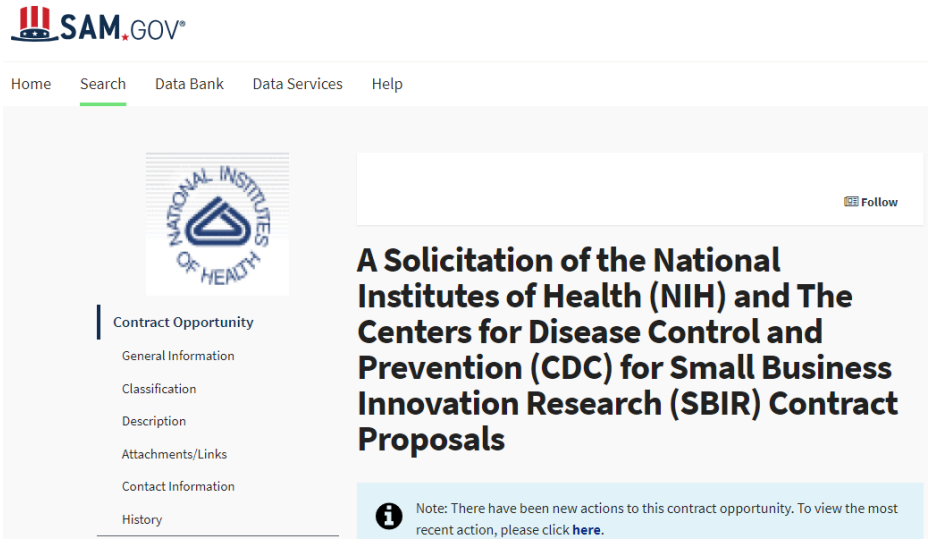
RESEARCH ARTICLE

PLOS ONE Preparedness against pandemic influenza: Production of an oil-in-water emulsion adjuvant in Brazil

AAHI transfers adjuvant formulation and manufacturing know-how to strengthen local development and production capabilities

Funding Opportunities

- SBIR contract program for Adjuvant Discovery; Adjuvant Development
  - Solicitation on the street now (PHS 2024-1 omnibus contract solicitation)
  - Due Nov 7th, 2023
  - Supports screening for novel adjuvants, further development of vaccines with novel adjuvants, production of mimics of advanced adjuvants (late stage or in licensed vaccines)




Thank you!