Selecting potent adjuvants for antibody vaccines against viruses

Kevin Saunders, PhD

Associate Director

Duke Human Vaccine Institute

NIH NIAID Adjuvant Call

13 September 2023

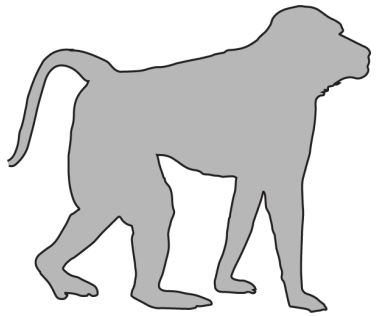
National Institute of Allergy and Infectious Diseases

CHAVD
Duke Consortia for HIV/AIDS Vaccine Development

Goals of our vaccine designs

- **Elicit neutralizing antibodies with extremely high cross-reactivity against a viral pathogen.**
  - **Primary targets are HIV-1 and Betacoronaviruses**
- **Promote affinity maturation of antibodies which leads to cross-reactivity.**
- **Elicit durable, high titers of these neutralizing antibodies.**

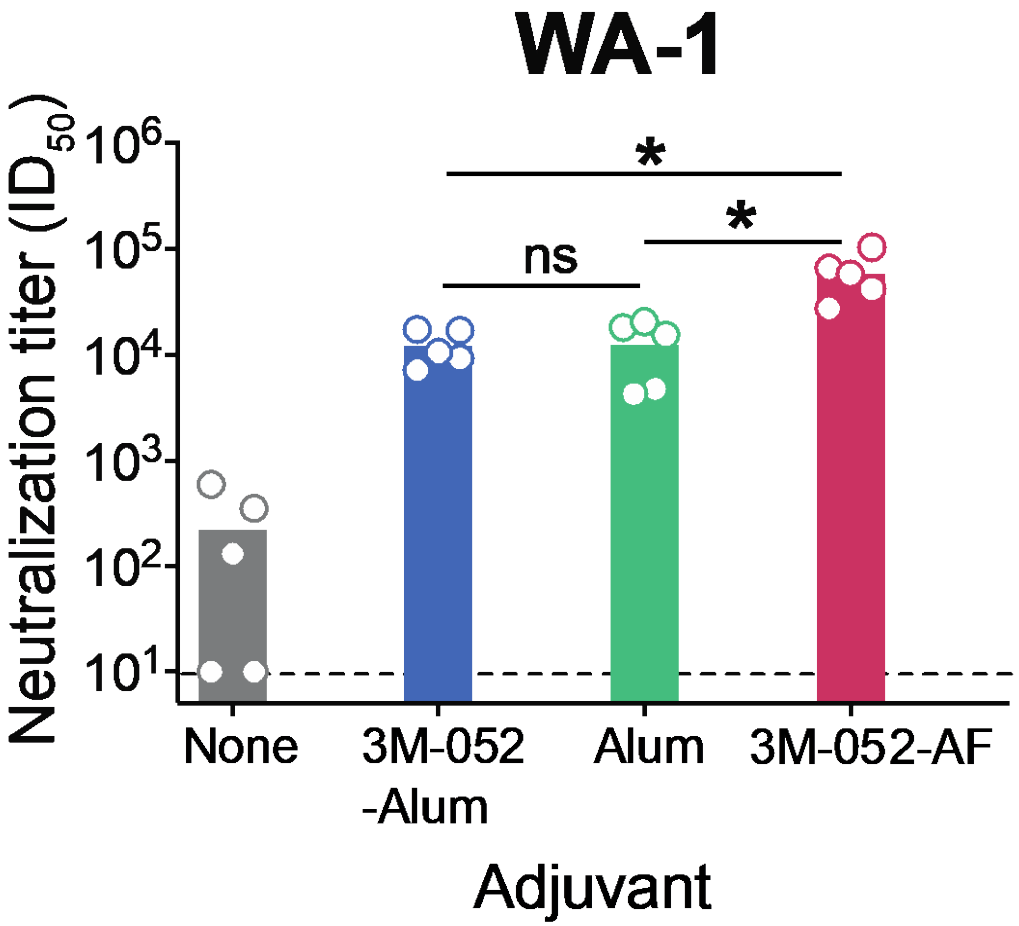
Adjuvant is critical for induction of SARS-CoV-2 neutralizing antibodies



Model: Cynomolgus macaques (n=5)
Route of administration: Intramuscular x3
Adjuvant: Varied

Immunogen	Adjuvant
RBD-scNP +	3M-052-Alum Alum 3M-052-AF

Serum neutralization titer after 3 immunizations in PSV



Li D, Saunders KO et al. Nature Communications
David Montefiori

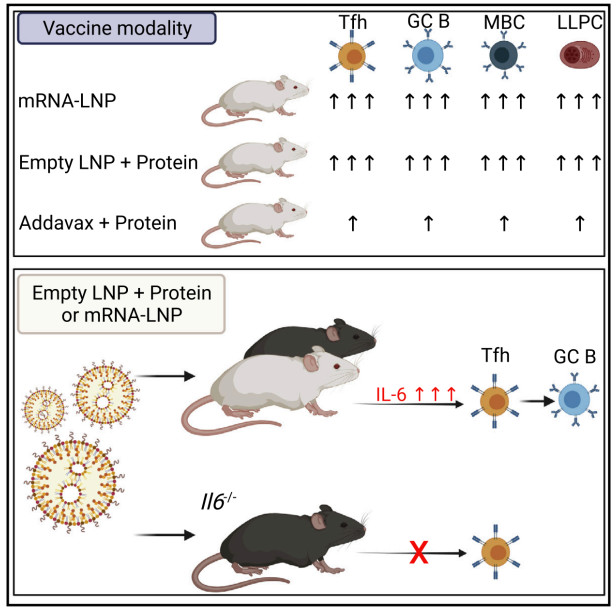
Empty lipid nanoparticles function as an adjuvant for protein subunit vaccine

Article

Immunity

Lipid nanoparticles enhance the efficacy of mRNA and protein subunit vaccines by inducing robust T follicular helper cell and humoral responses

Graphical abstract



Authors

Mohamad-Gabriel Alameh, István Tombácz, Emily Bettini, ..., Botond Z. Igyártó, Michela Locci, Norbert Pardi

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In brief

The mechanism of action of nucleoside-modified mRNA-LNP vaccines is unknown. Alameh et al. demonstrate that LNPs can possess adjuvant activity and promote robust induction of Tfh cell, B cell, and humoral responses when utilized in mRNA and protein subunit vaccines in mice. IL-6 induction and the ionizable lipid component are critical for the adjuvant activity of LNPs.

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TLR7/8 agonists are potent activators of humoral immunity

SCIENCE IMMUNOLOGY | RESEARCH ARTICLE

HIV

3M-052, a synthetic TLR-7/8 agonist, induces durable HIV-1 envelope–specific plasma cells and humoral immunity in nonhuman primates

Sudhir Pai Kasturi[1]*, Mohammed Ata Ur Rasheed[1,2]*, Colin Havenar-Daughton[3], Mathew Pham[1], Traci Legere[1], Zarpheen Jinnah Sher[1], Yevgeny Kovalenkov[1], Sanjeev Gumber[1], Jessica Y. Huang[1], Raphael Gottardo[4], William Fulp[4], Alicia Sato[4], Sheetal Sawant[5,6], Sherry Stanfield-Oakley[5], Nicole Yates[5,6], Celia LaBranche[5], S. Munir Alam[5], Georgia Tomaras[5,6], Guido Ferrari[5,6], David Montefiori[5], Jens Wrammert[1], Francois Villinger[1,7], Mark Tomai[8], John Vasilakos[8], Christopher B. Fox[9,10], Steven G. Reed[9,11], Barton F. Haynes[5], Shane Crotty[3,12], Rafi Ahmed[1,2†], Bali Pulendran[1,13†]

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

HIV

Stabilized HIV-1 envelope immunization induces neutralizing antibodies to the CD4bs and protects macaques against mucosal infection

Kevin O. Saunders[1,2,3,4]*, Robert J. Edwards[1,5]†, Kedamawit Tilahun[1,5]†, Kartik Manne[1,5]†, Xiaozhi Lu[1,5], Derek W. Cain[1,5], Kevin Wiehe[1,5], Wilton B. Williams[1,2,4], Katayoun Mansouri[1,5], Giovanna E. Hernandez[1,5], Laura Sutherland[1,5], Richard Scearce[1,5], Robert Parks[1,5], Maggie Barr[1,5], Todd DeMarco[1,5], Chloe M. Eater[1,5], Amanda Eaton[1,2], Georgeanna Morton[6], Benjamin Mildenberg[6], Yunfei Wang[1,5], R. Wes Rountree[1,5], Mark A. Tomai[7], Christopher B. Fox[8], M. Anthony Moody[1,9], S. Munir Alam[1,5], Sampa Santra[6], Mark G. Lewis[10], Thomas N. Denny[1,5], George M. Shaw[11], David C. Montefiori[1,2], Priyamvada Acharya[1,2]*, Barton F. Haynes[1,4,5]*

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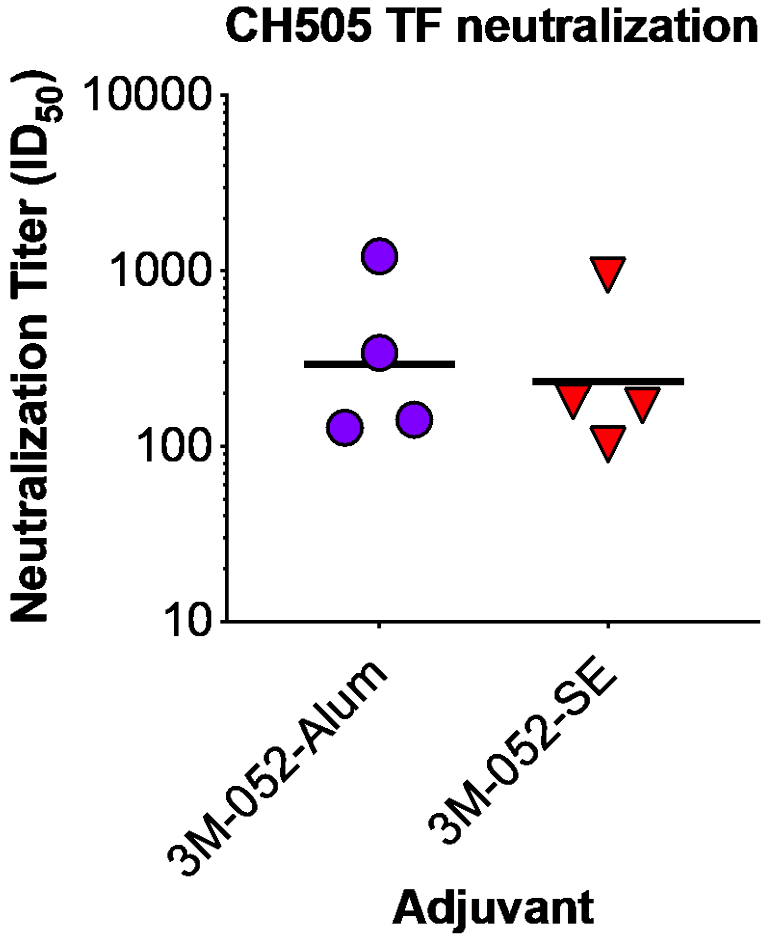
Adjuvants currently under investigation in our Phase I trials

- TLR agonists
- TLR7/8 agonist
- 3M-052
- Lipid nanoparticle
- Cationic lipid
- Acuitas lipid composition

Criteria to consider for adjuvant selection

- Is the immunogen unaffected by the adjuvant?
- Define adjuvant or adjuvant formulations that can translate from animal models to clinical use.
- Are there first in human studies already completed? Was reactogenicity acceptable/mild?

Both formulations of 3M-052 elicit comparable autologous tier 2 neutralizing antibody titers



- Post 5 immunizations

David Montefiori
Amanda Eaton

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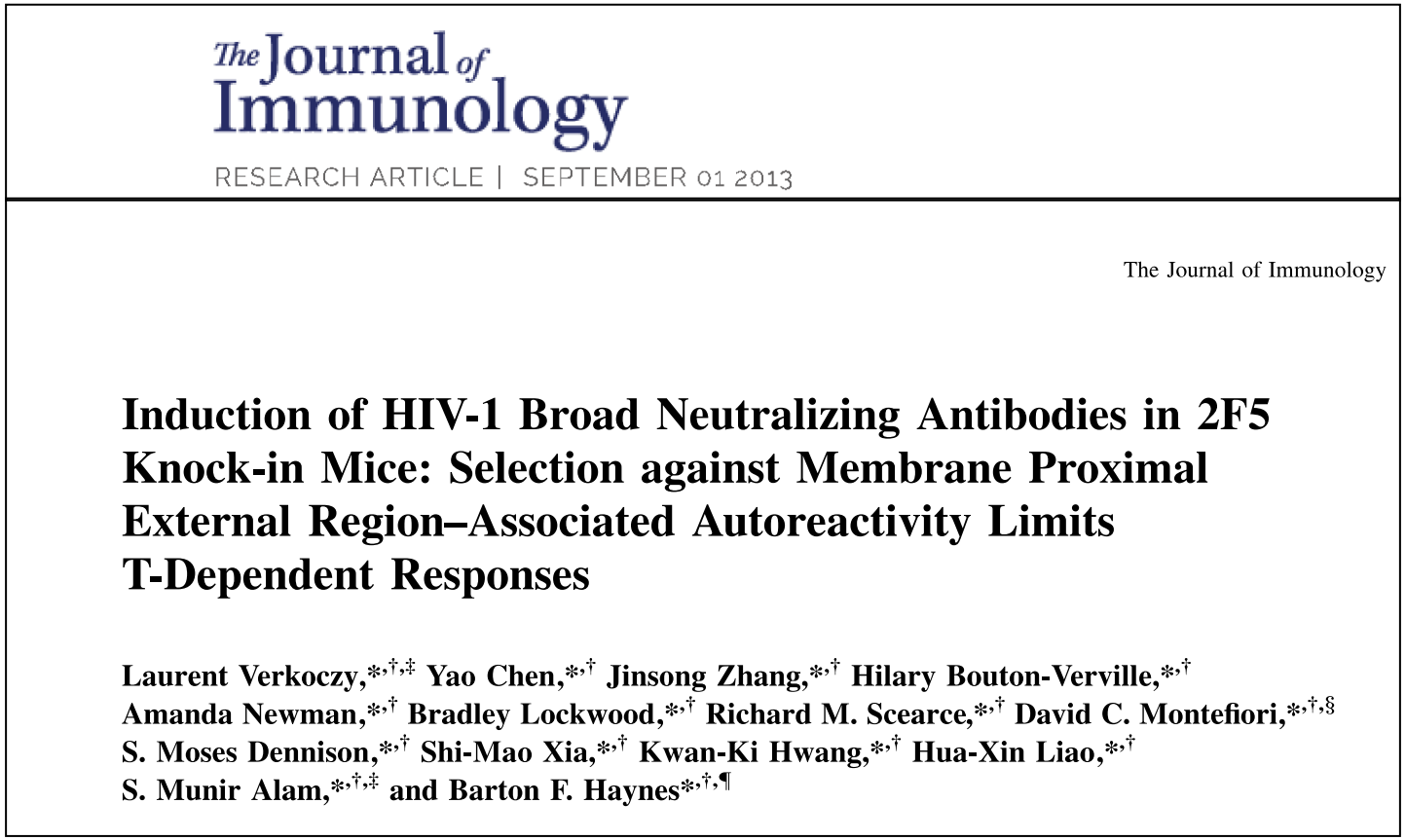
Animal model selection

- **Are the targets for the adjuvant present in various animal model systems?**

- **If the animal models have the target molecule, which animal models are predictive of the human antibody response.**

TLR4 agonists induced HIV-1 antibodies in mice



The Journal of Immunology

RESEARCH ARTICLE | SEPTEMBER 01 2013

Induction of HIV-1 Broad Neutralizing Antibodies in 2F5 Knock-in Mice: Selection against Membrane Proximal External Region–Associated Autoreactivity Limits T-Dependent Responses

Laurent Verkoczy,*,†,‡ Yao Chen,*,† Jinsong Zhang,*,† Hilary Bouton-Verville,*,† Amanda Newman,*,† Bradley Lockwood,*,† Richard M. Scearce,*,† David C. Montefiori,*,†,§ S. Moses Dennison,*,† Shi-Mao Xia,*,† Kwan-Ki Hwang,*,† Hua-Xin Liao,*,† S. Munir Alam,*,†,‡ and Barton F. Haynes*,†,¶

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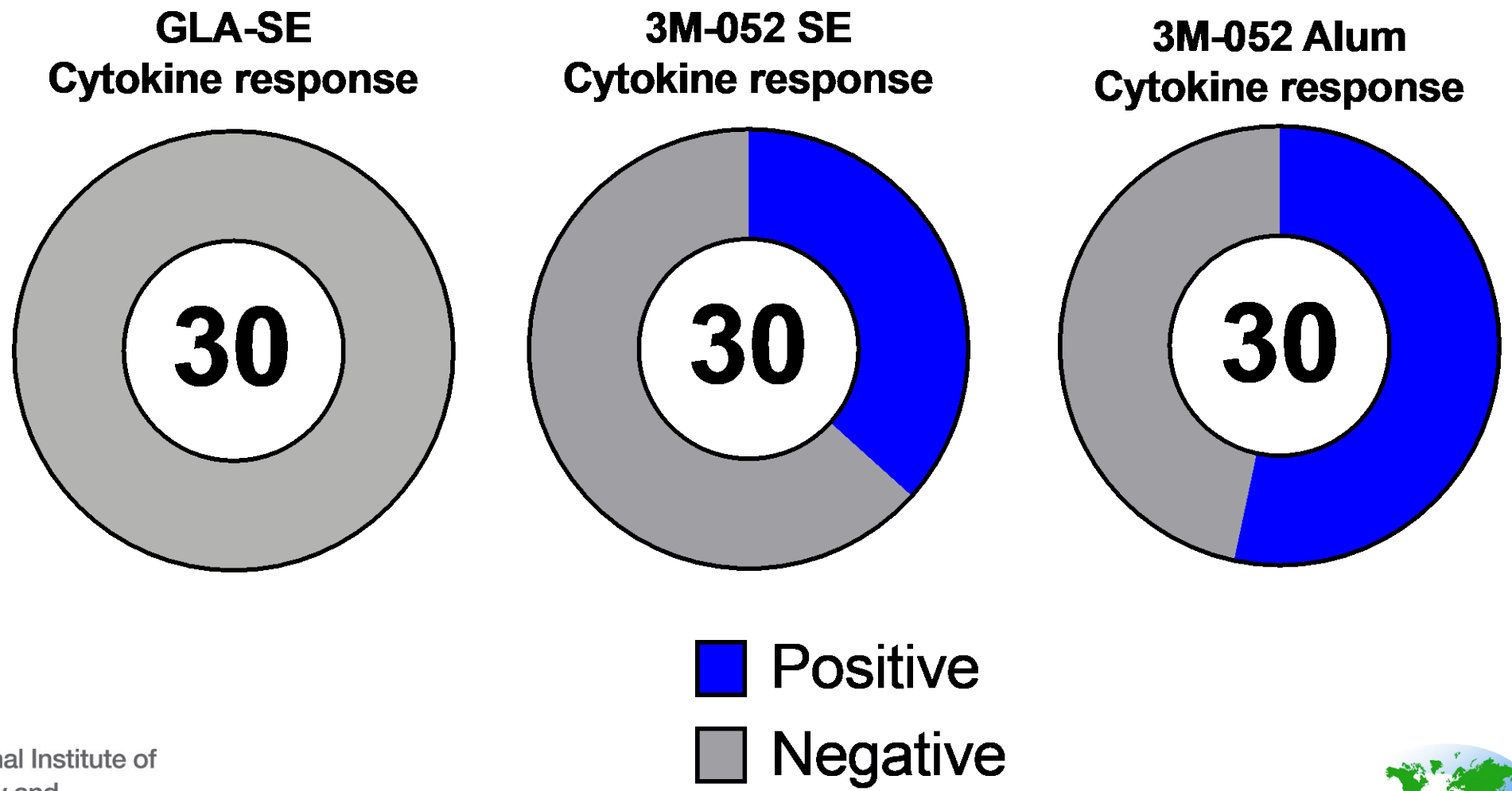
TLR7/8 agonist 3M-052 induced higher titers of autologous tier 2 nAbs in rhesus macaques than TLR4 agonist GLA-SE

Adjuvant

David Montefiori
Amanda Eaton

Unlike TLR7/8 agonist 3M-052, TLR4 agonist GLA-SE does not activate the monkey immune system



Differences in TLR4 expression could lead to differences in adjuvant performance in various species

TLR4 mRNA expression in different cell types across species			
Cell Type	**Human**	**Monkey**	**Mouse**
Plasmacytoid Dendritic cells	**-**	**-**	**+**
Immature dendritic cells	**+**	**+**	**+**
Lymphoid cells (B and T cells)	**-/+**	**-/+**	**++**

Vaure Céline, Liu Yuanqing. Frontiers in Immunology. 2014. 5. 10.3389/fimmu.2014.00316

Adjuvants currently under investigation in our Phase I trials

TLR agonists

TLR7/8 agonist

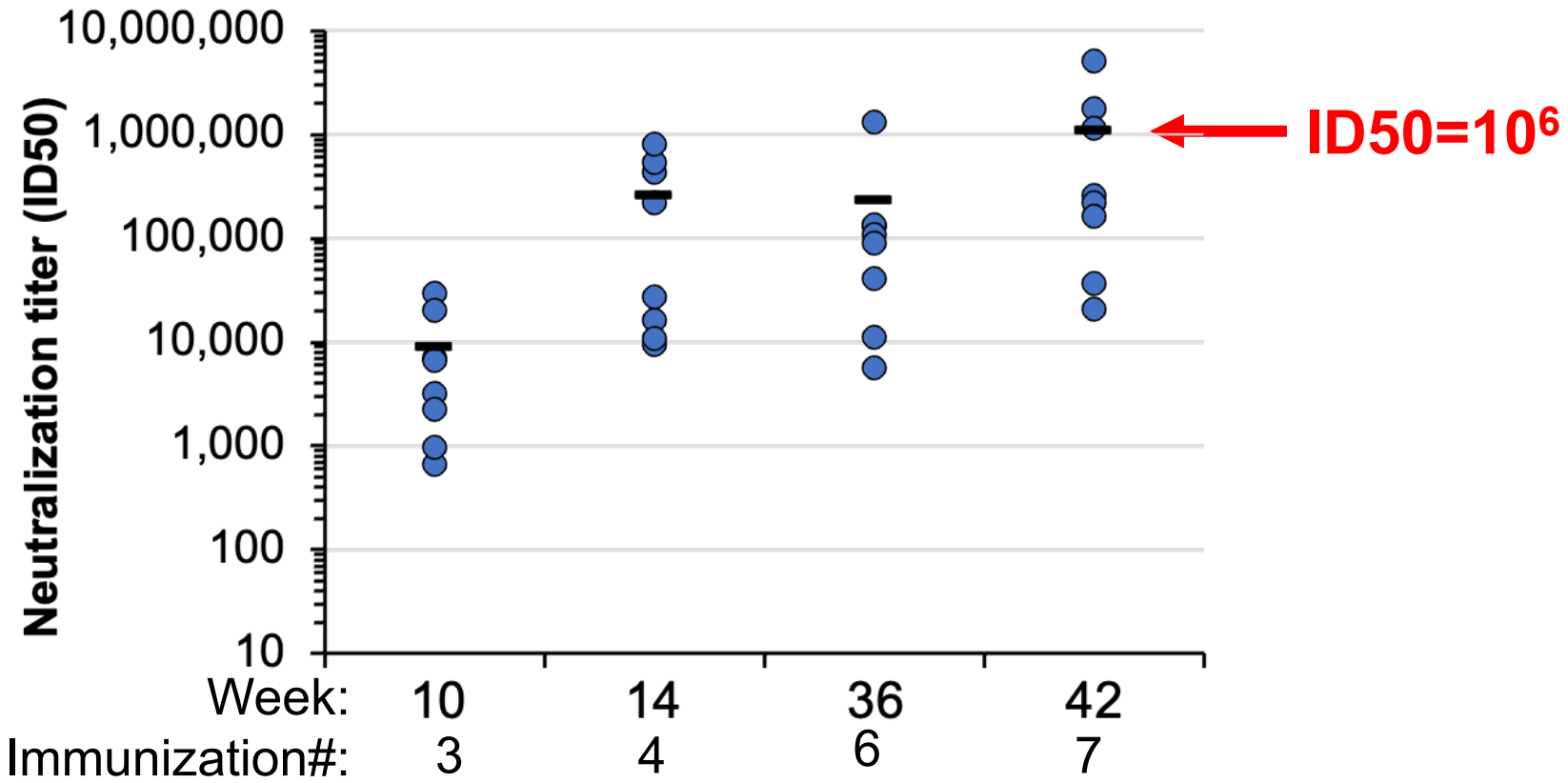
3M-052

Lipid nanoparticle

Cationic lipid

Acuitas lipid composition

LNP-adjuvanted Env Vaccination Elicits Potent Autologous Tier 2 Virus Neutralization in Monkeys



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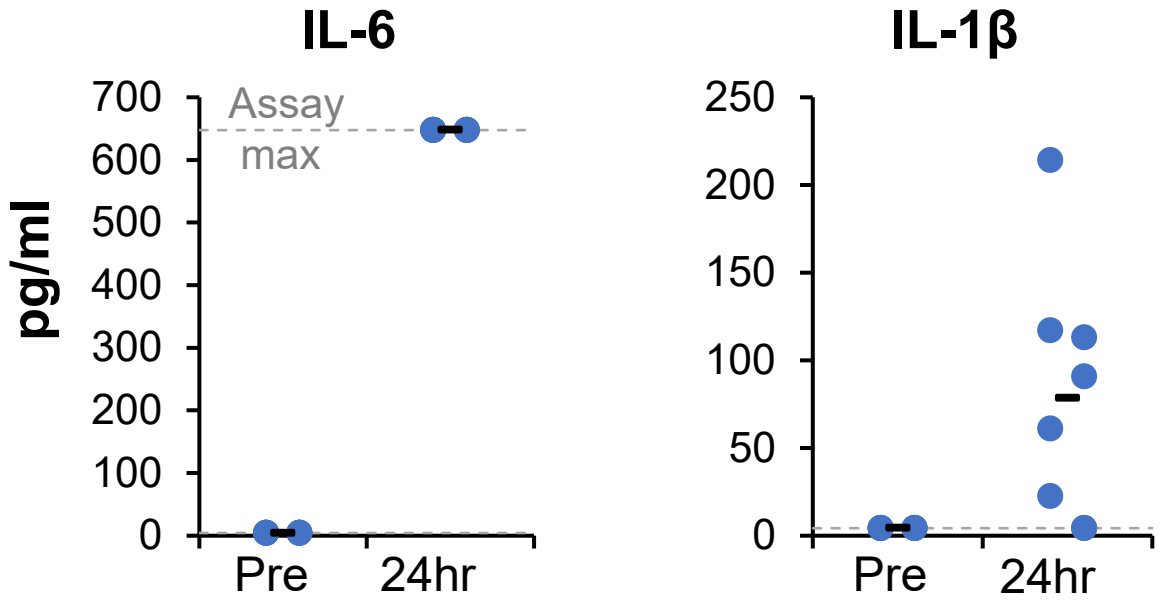
Cytokines Induced by LNP/Env Immunization



Cytokines Modestly Increased

MCP-1
VEGF

Cytokines Decreased

IL-12
RANTES

Cytokines Unchanged

FGF Basic	MIP-1b	I-TAC
GCSF	IL-15	MIF
IL-10	EGF	IL-4
Eotaxin	IL-5	IL-8
IL-17a	HGF	
MIP-1a	IFNg	
GM-CSF	CCL22	

P<0.05, Pre vs. 24 hr, Wilcoxon Exact Tests

Note: High dose of mRNA-LNP used for immunizations (1 mg per monkey)

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Conclusions and summary

- **Adjuvants for HIV-1 Env and CoV spike vaccination are critical for induction of neutralizing antibodies.**
- **Immunogen stability in adjuvant is also a critical aspect to consider.**
- **Careful consideration of adjuvant target expression in model systems is needed to ensure adjuvant performance.**
- **We are currently investigating TLR7/8 agonists and lipid nanoparticles as potent adjuvants in humans.**
- **It is important to test formulations that can be manufactured and used in humans.**

Collaborators

Duke Human Vaccine Institute

- **Barton Haynes**
  - Dapeng Li
  - Robert Parks
  - Maggie Barr
  - Laura Sutherland
  - Cynthia Bowman
  - Grace Stevens
  - Charlie Mu
  - Richard Scearce
  - Victoria Lee
  - Meg Deyton
  - Amanda Newman
  - Whitney Edwards
- **David Montefiori (Neutralization)**
  - Amanda Eaton
- **Derek Cain (Flow Cytometry)**
  - Aria Arus-Altuz
  - Steve Slater
- **Wes Rountree (Statistics)**
- **Munir Alam (Biophysics)**
- **RJ Edwards (Negative Stain EM)**
  - Katayoun Mansouri

Duke Human Vaccine Institute

- **Kevin Saunders**
  - Esther Lee
  - Alecia Brown
  - Xiaozhi Lu
  - Dylshan Malewana
  - James Counts
  - Lena Smith
  - Jingjing Li
  - Joe Zhou
  - Savanna Toure
  - Rebecca Williams
  - Tess Overton
  - Jordan Flemming
  - Tyler Gavitt
  - Severin Coleon
  - Andrew Foulger
  - Chuancang Jiang
  - Elizabeth Donahue
  - Fangping Cai
  - Katrina Hodges
  - Li Zhu
  - Joena Bal
  - Marcela Velasquez
  - Kushal Gandhi

Upenn (mRNA vaccines)

- **Drew Weissman**
  - Norbert Pardi

Acuitas Therapeutics (LNPs)

- Ying Tam
- Christopher Barbosa

AAHI (Adjuvants)

- Chris Fox
- Corey Casper

3M Company

- Mark Tomai

BIOQUAL (NHP studies)

- Mark Lewis

UNC Chapel Hill (CoV mouse and neutralization)

- **Ralph Baric**
  - David Martinez
  - Alexandra Schaefer

NIAID Program and Product Development teams

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U.S. Department of Health and Human Services (HHS)
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Division of AIDS (DAIDS)
Duke University School of Medicine

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The State of North Carolina though the Federal CARES Act

Duke Consortia for HIV/AIDS Vaccine Development (CHAVD) #UM1-AI144371

The impact of formulation on adjuvanted vaccine immune responses

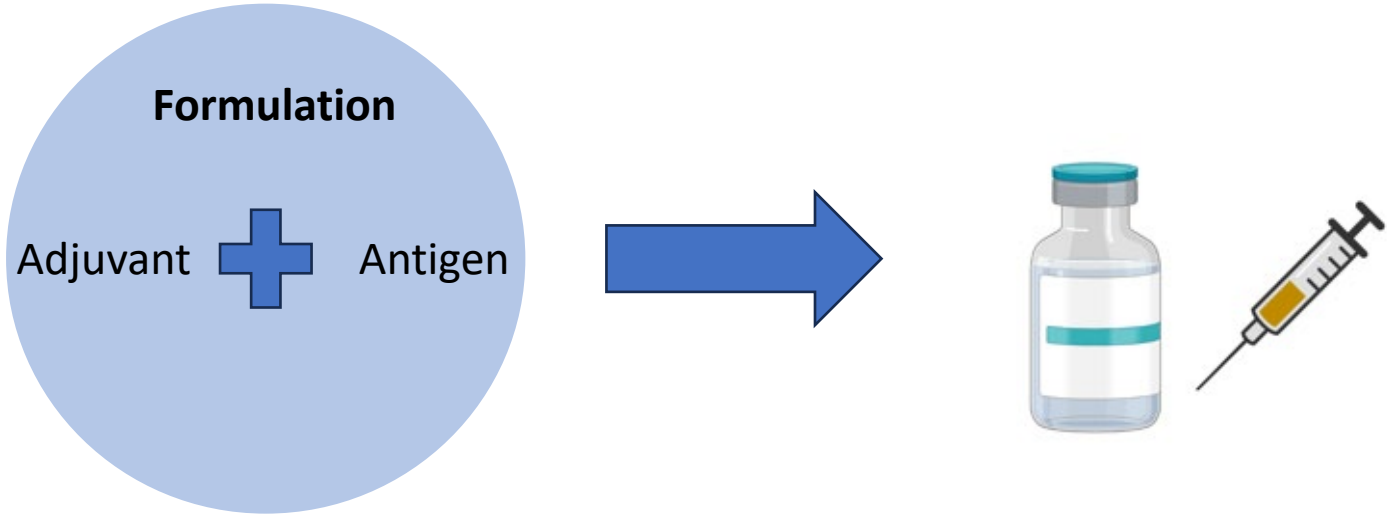
Shannon Miller, PhD
Inimmune
in collaboration with the University of Montana
Sept 13, 2023
GVIRF Webinar

1121 E Broadway, Suite 121, Missoula, MT

Adjuvanted vaccine formulations: often forgotten but always important

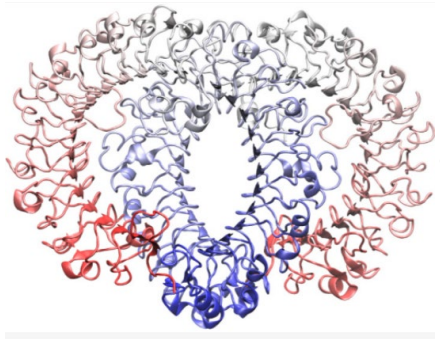
- Formulation is the “glue” that holds a vaccine together
- Formulations affect:
  - Whether or not antigen and adjuvant are co-delivered
  - Cellular uptake and post-injection trafficking
  - Vaccine stability
  - Cost and ease/complexity of manufacturing
  - Immune response!

- The line between adjuvant and formulation can be blurry
  - Some formulations induce immune responses without the addition of an adjuvant

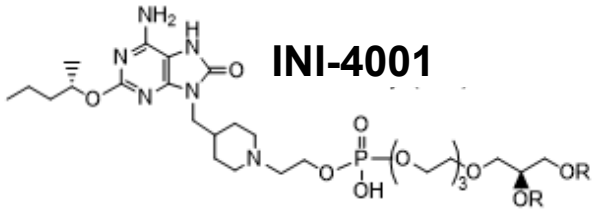


Small molecule pattern recognition receptor agonists as adjuvants

INI-4001: TLR7/8 agonist



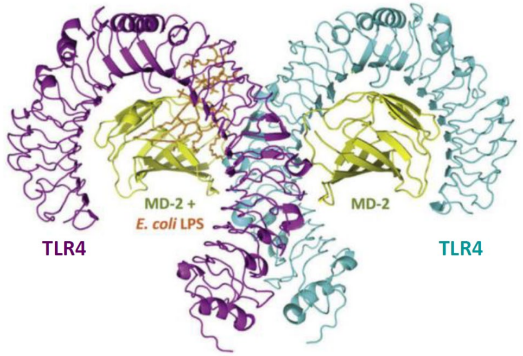
TLR7



INI-4001

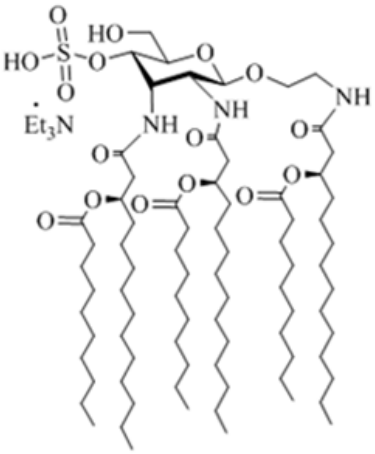
Gentile, Francesco, et al. "Structure based modeling of small molecules binding to the TLR7 by atomistic level simulations." *Molecules* 20.5 (2015): 8316-8340.

INI-2002: TLR4 agonist



Protein Data Bank ID 3FXI

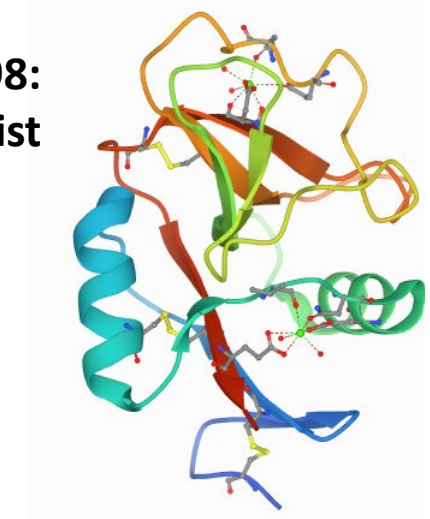
TLR4

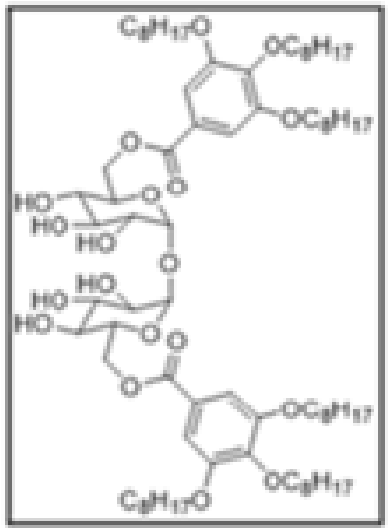


INI-2002

Mincle

UM-1098: Mincle agonist

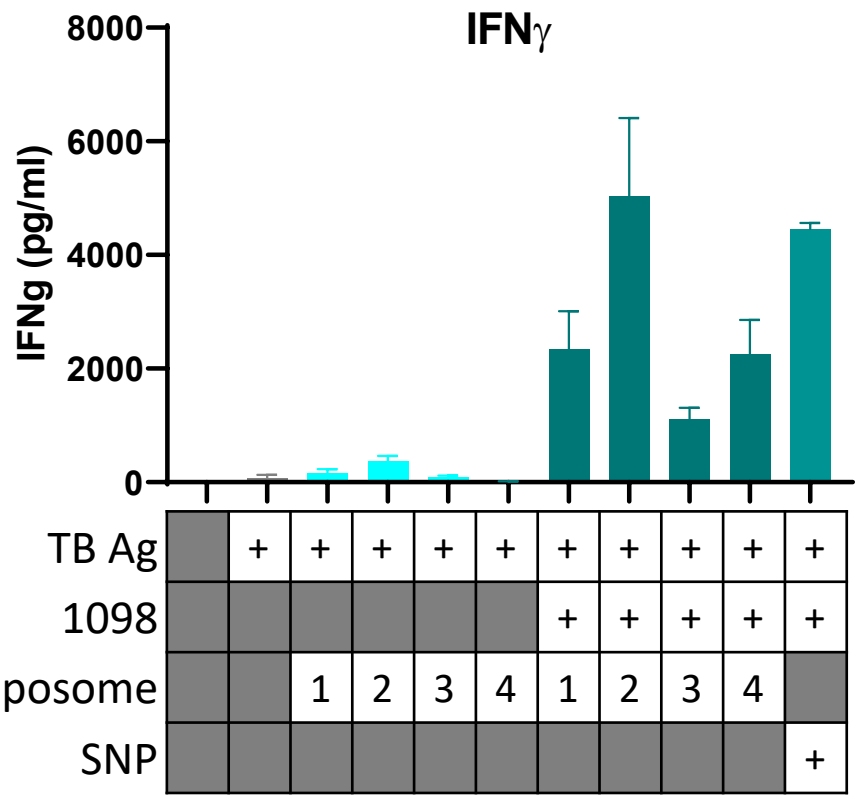


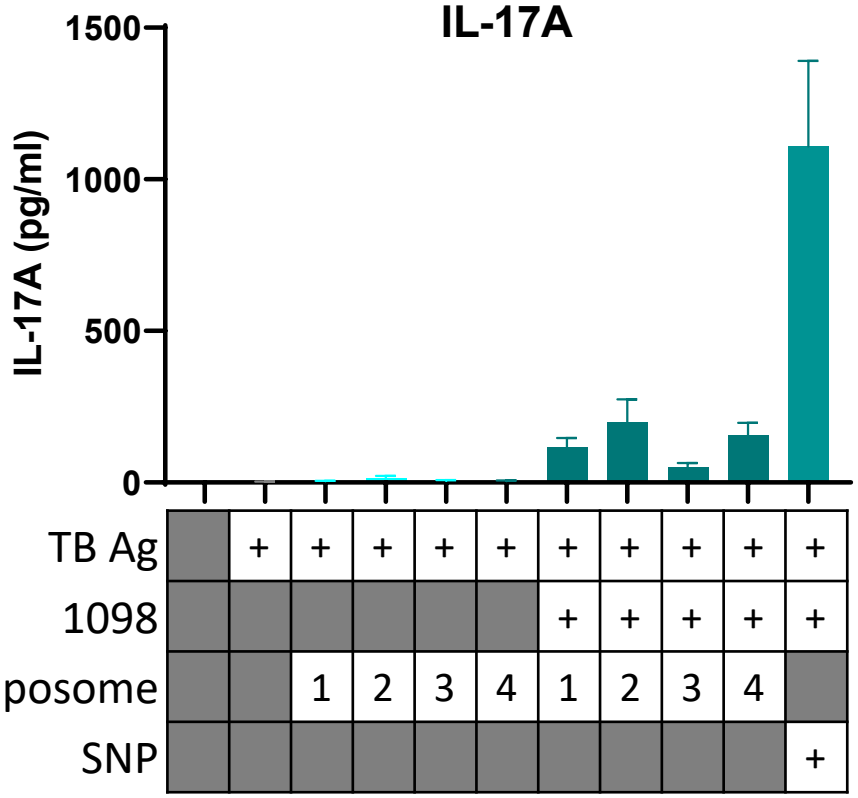


UM-1098

The Th1/Th17 polarizing ability of UM-1098 is dependent on formulation

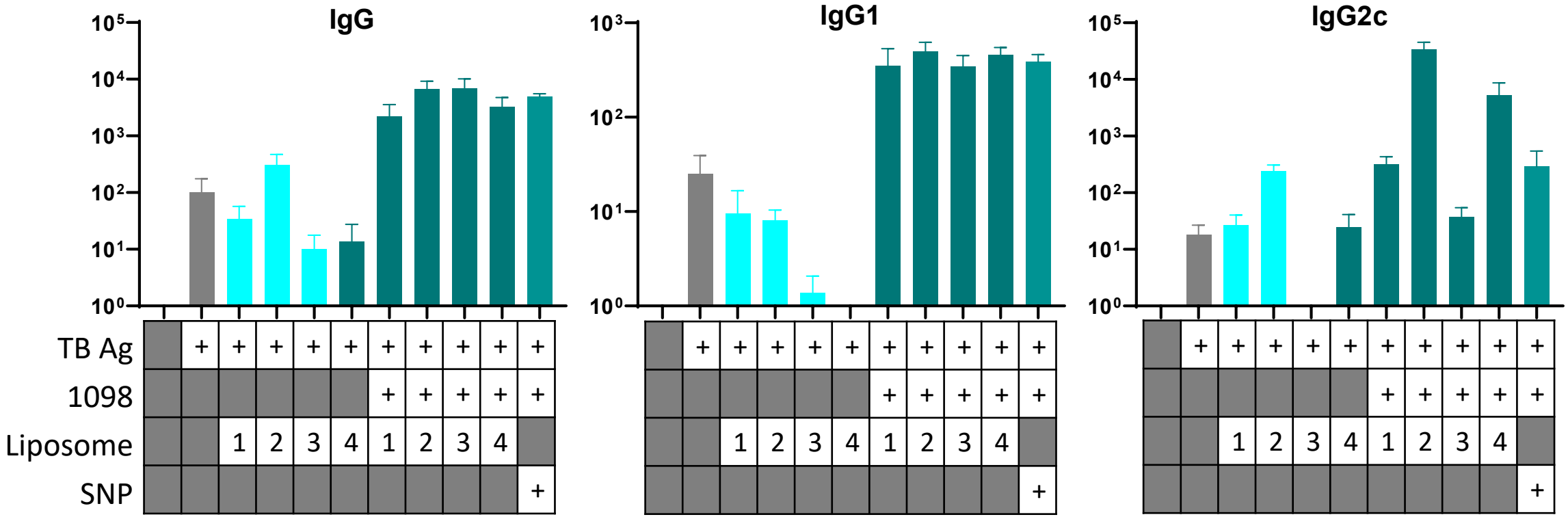
Antigen: Mtb purified protein





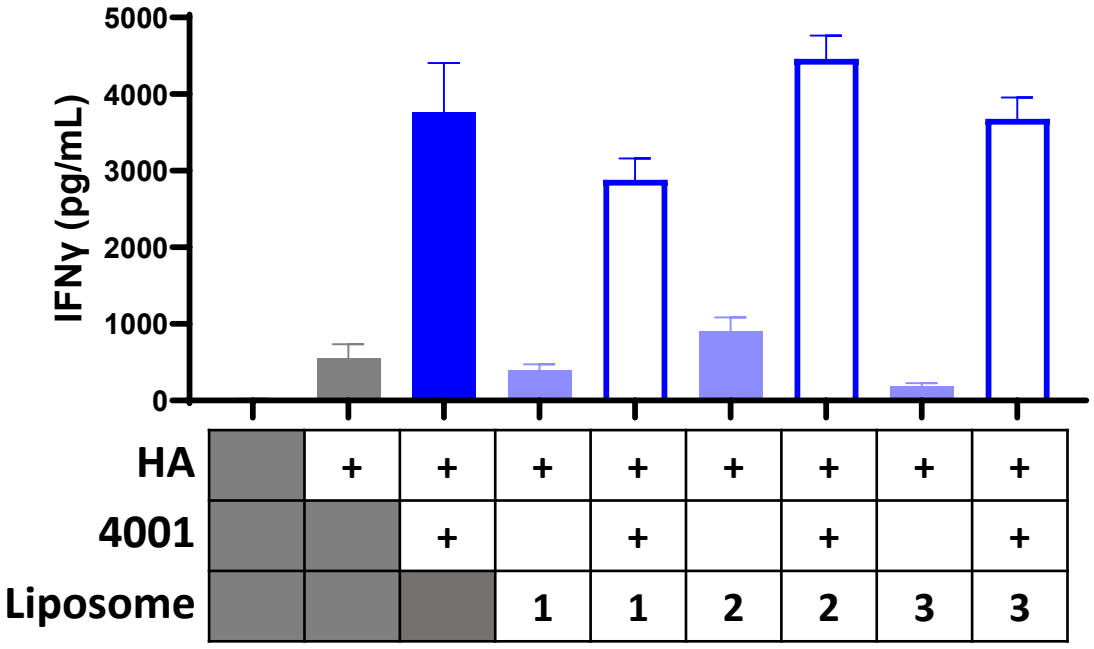
IgG2c responses are particularly sensitive to formulation changes in UM-1098 adjuvanted vaccines

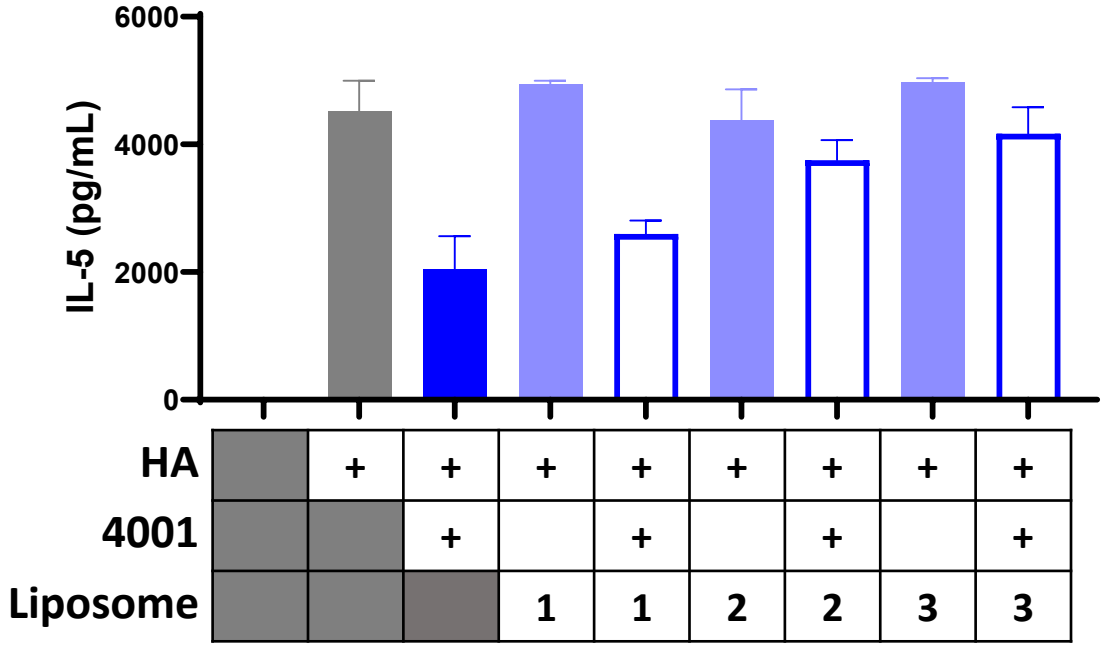
Antigen: Mtb purified protein



The immune response to INI-4001 adjuvanted vaccines can be broadened through the use of different formulations

Antigen: Purified influenza HA





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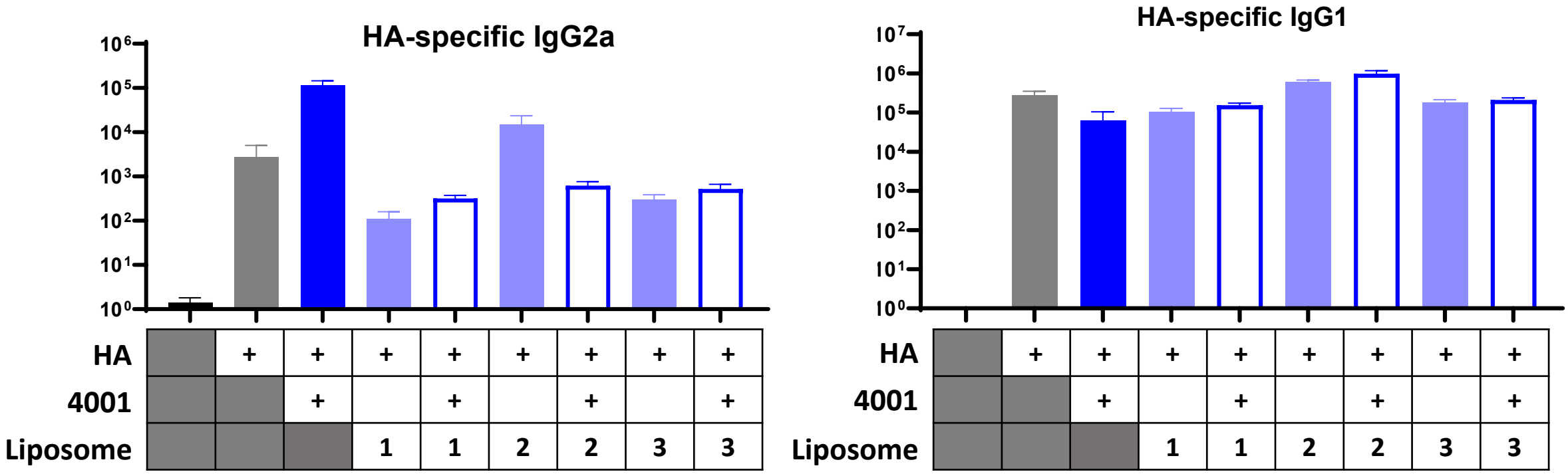
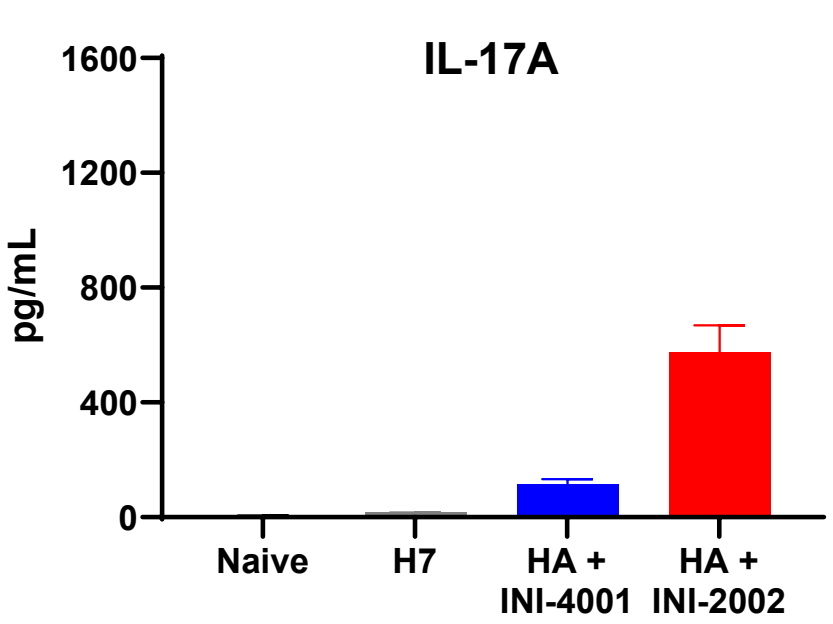
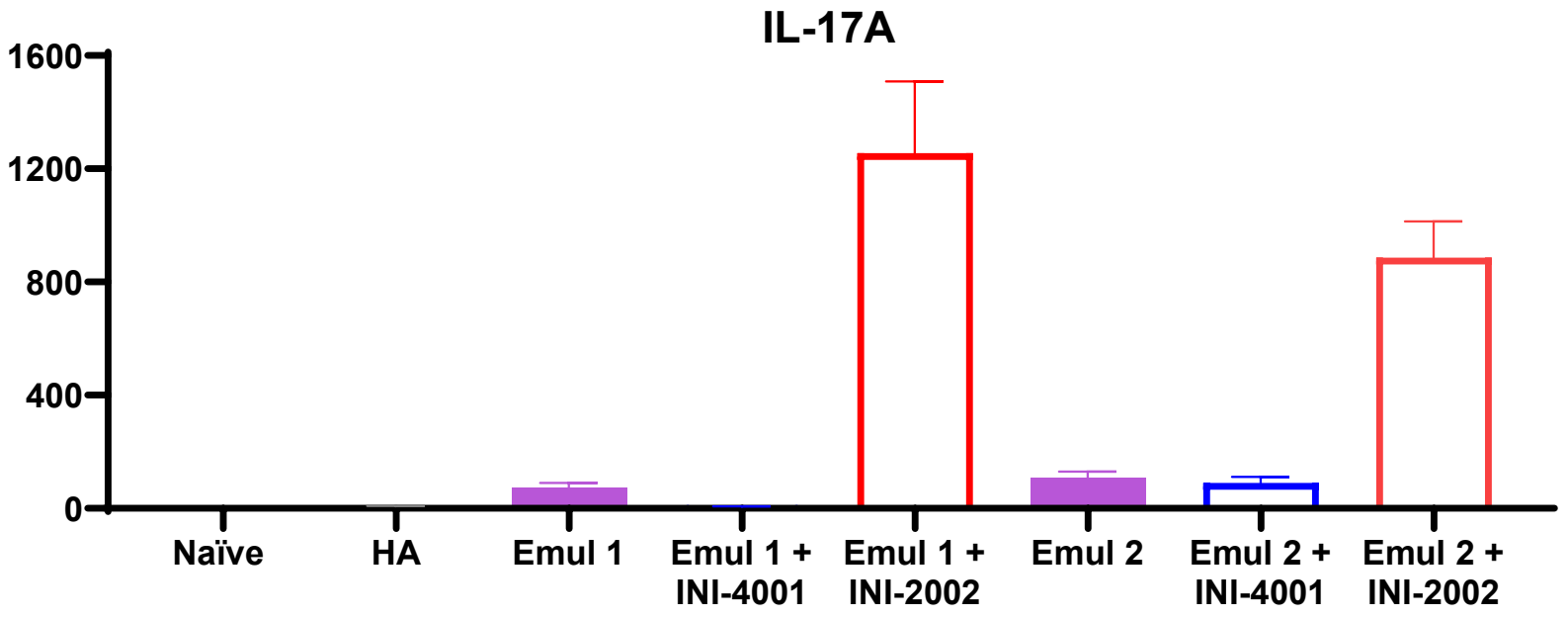


Emulsion formulations enhance INI-2002-driven Th17 but not INI-4001-driven Th17

Antigen: Purified influenza HA

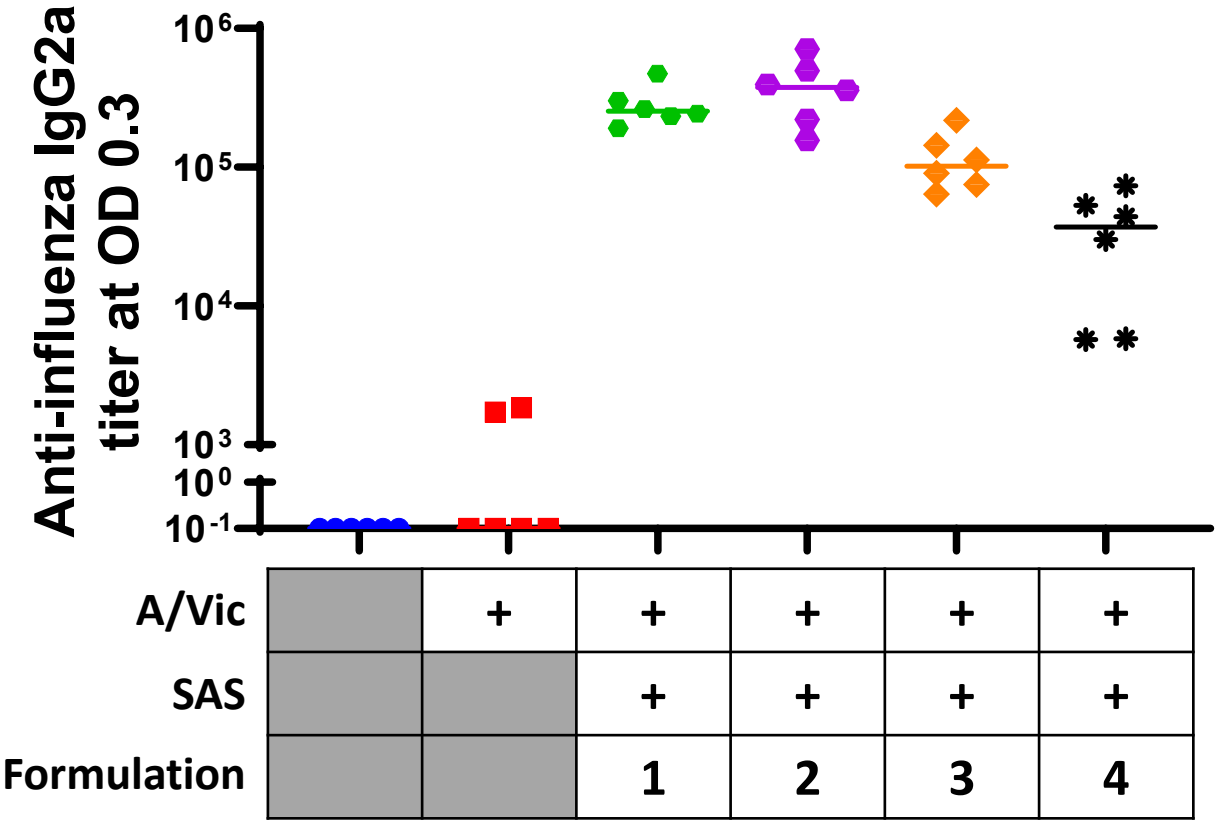


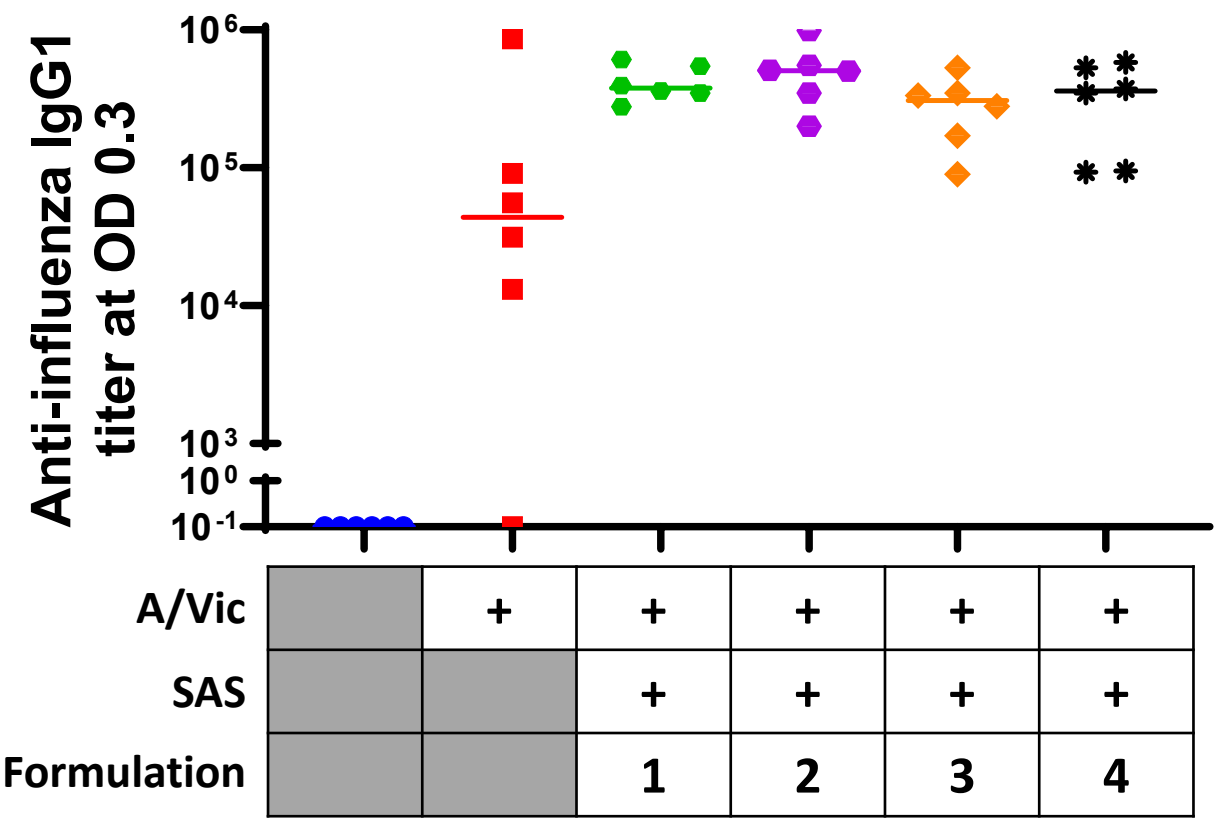


Formulation changes can alter antibody titers without affecting T cell responses

Adjuvant: SAS (synthetic adjuvant system, INI-2002 + saponin)

Antigen: Detergent-split A/Victoria/210/2009 (A/Vic)





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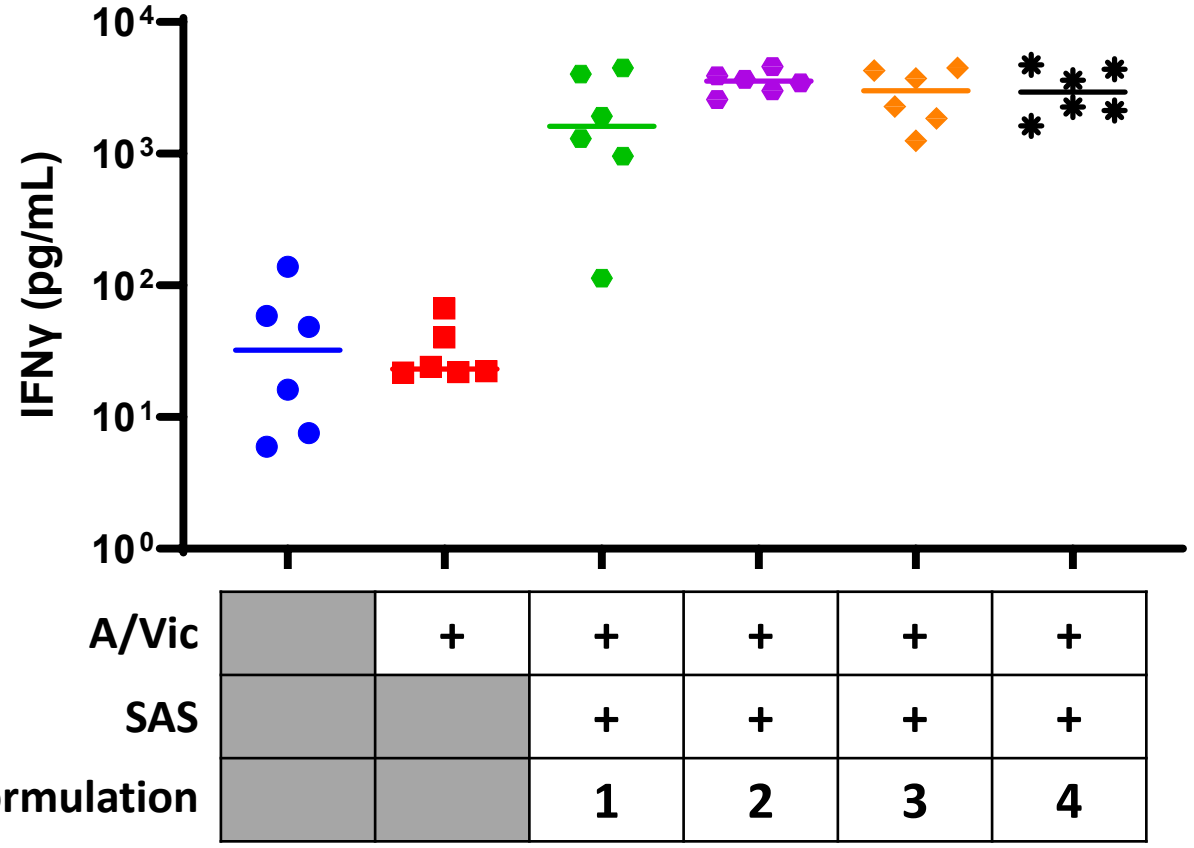

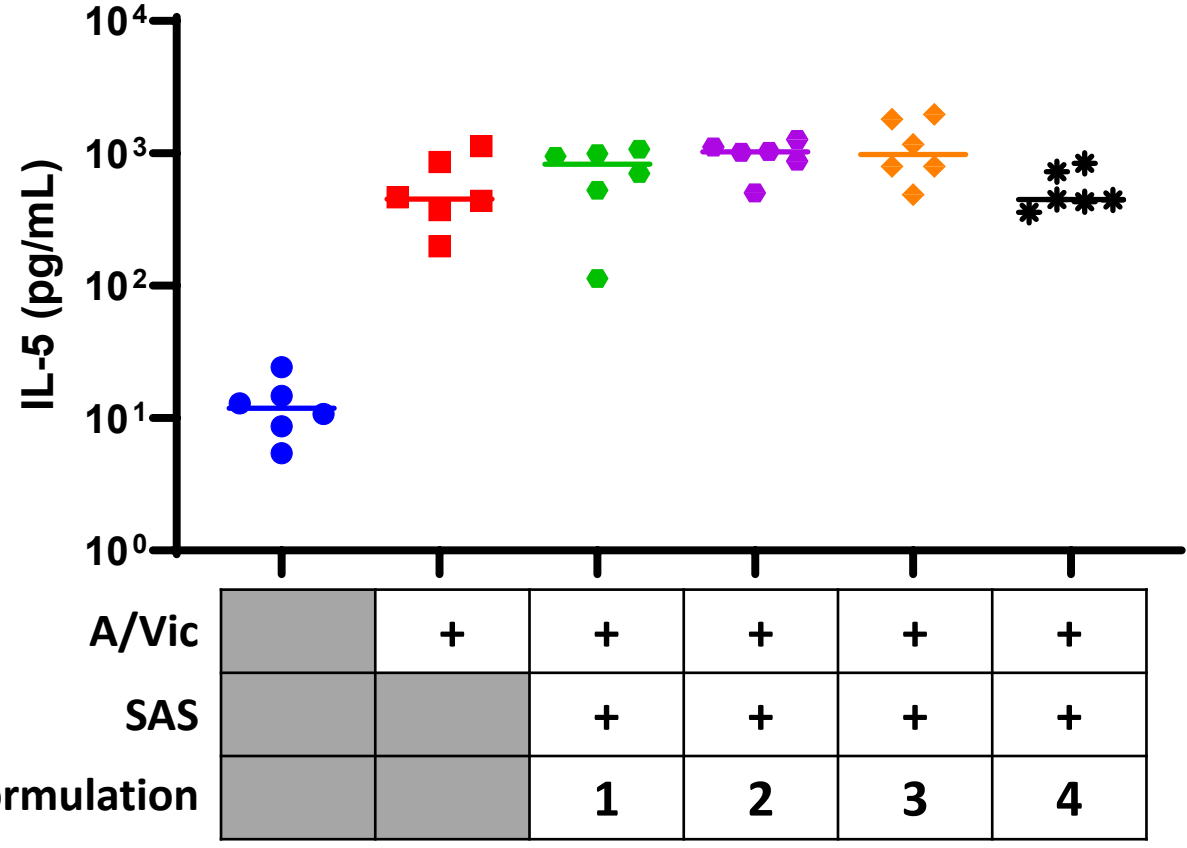

Formulation selection: Known properties + empirical testing

Knowns

- Co-delivery of adjuvant and antigen tend to produce improved T cell responses
- Formulation size, charge, shape, and “softness” have all been shown to change delivery of drugs and vaccines in various ways that can, to some extent, be predicted

Empirical Testing

- Addition of antigen or changing the antigen can alter the above-mentioned formulation properties
- Combination of adjuvant and formulation excipients can result in unexpected immune responses
- Species specificity
  - Similar responses in various animal models (e.g. mice, rats, ferrets, dogs, pigs, primates) increase confidence that results will translate to humans

Thank you!

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Adjuvant Performance in Target Populations RV460 HIV Vaccine Clinical Trial in Kenya

Josphat Kosgei, MBChB, MSc, DLSHTM
RV460 Principal Investigator

GVIRF Webinar
Vaccine Adjuvants for Global Health
September 13, 2023

WRAIR
Walter Reed Army Institute of Research

ClinicalTrials.gov ID: NCT04826094

RV460 Project Information

Clinical Site:

- KEMRI/US Army Medical Research Directorate-Africa (USAMRD-A), Clinical Research Centre; Kericho, Kenya. PI: Dr. Josphat Kosgei

IND Sponsor:

- National Institute of Allergy and Infectious Diseases (NIAID) , Division of AIDS (DAIDS)

Funding Source:

- Congressionally Directed Medical Research Program (CDMRP), United States Army Medical Research Acquisition Activity (USAMRAA) - CA# W81XWH-18-2-0040. Dr. Gary Matyas, Award PI

Clinical Phase & Target Population:

- Phase 1; 126 healthy, HIV-negative male and female participants aged 18 to 40 years

Study Initiated in March 2021

Trial Objectives

- The **primary objective** of the study is to assess the safety, reactogenicity and tolerability of the various adjuvant formulations with both HIV Env-C Plasmid DNA and gp145.

- The **secondary objectives** are to:
  - Determine whether the adjuvants improve the immunogenicity of the DNA priming.
  - Determine whether the addition of ALF43 to the Rehydragel®/HIV Env gp145 C.6980 protein boost further improves the immune response to gp145.
  - Determine whether adjuvants improve humoral responses.
  - Evaluate the influence of adjuvants on cellular immune responses.
  - Describe mucosal humoral responses in cervicovaginal and rectal secretions and semen.

Trial Scientific Questions

- Can adjuvants improve DNA priming?
- Can adjuvants further improve protein boosting?

Study Products

Env-C Plasmid DNA

Manufactured by Waisman Institute through a sub-award to Dr. Shan Lu, University of Massachusetts Medical Center. Clade C gp120 (93MW965.26) was cloned into pSW3981 vector. The dose administered was 2 mg.

HIV Env gp145 C.6980 Protein

Developed under contract by ABL with MHRP investigators. Manufactured for human clinical trials under DAIDS contract. The dose administered was 100 µg.

dmLT

A heat-labile enterotoxin B (R192G/L211A) will be provided by PATH. It was administered at 50 µg/dose on a patch at the site of the DNA injection.

ALF43

Manufactured by Avanti Polar Lipids and vialed at WRAIR PBF. The dose was 200 µg 3D-PHAD® (synthetic monophosporyl lipid A). It is supplied as a lyophilized product.

Rehydragel®

Vialed at the VRC at a concentration of 5 mg/ml of Al^{3+} in water. The dose for the trial was 500 µg Al^{3+}.

UMASS

WRAIR
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PATH

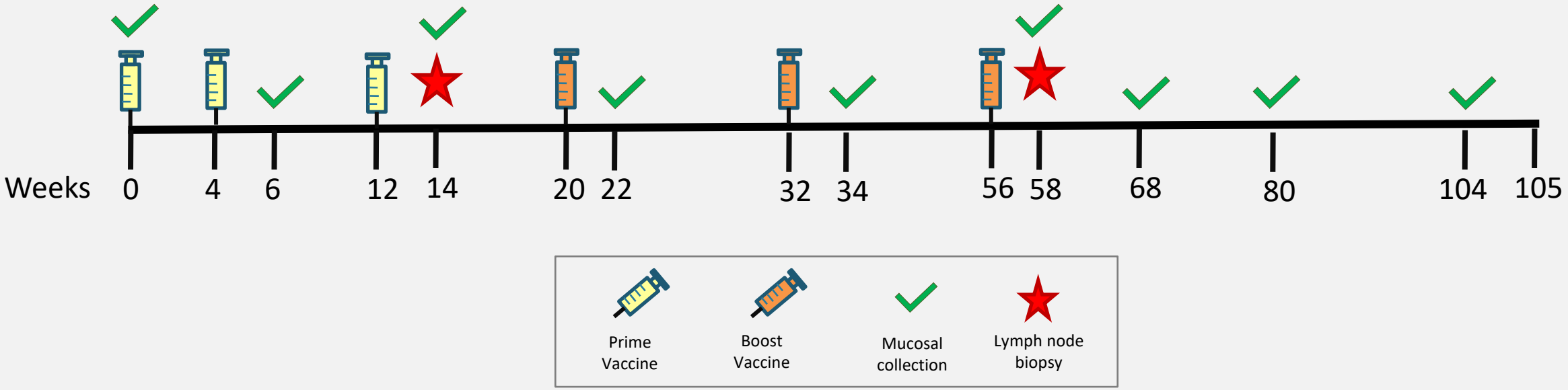
RV460: Adjuvants for DNA Priming *and* Protein Boosting

Dr. Gary Matyas, CA PI

Group	V/P	Prime at Weeks 0, 4, 12	Boost at Weeks 20, 32, 56
1	15/3	DNA alone	gp145 + Rehydragel®
2	15/3	DNA alone	gp145 + ALF43 + Rehydragel®
3	15/3	DNA + dmLT (TCI)	gp145 + Rehydragel®
4	15/3	DNA + dmLT (TCI)	gp145 + ALF43 + Rehydragel®
5	15/3	DNA + ALF43	gp145 + Rehydragel®
6	15/3	DNA + ALF43	gp145 + ALF43 + Rehydragel®
7	15/3	DNA + gp145 + ALF43	DNA + gp145 + ALF43 + Rehydragel®

- The vaccines were given by intramuscular injection into the deltoid muscle, excluding the dmLT adjuvant which was given by transcutaneous immunization (TCI).
- RV 460 is the first to evaluate the dmLT delivered by TCI.

Study Procedures



- Each participant is followed for 108 weeks (105 weeks of clinic visits and then contact by phone once weekly for an additional 3 weeks to inquire about medically attended AEs)
- Optional procedures:
  - Inguinal lymph node excision
  - Mucosal collections include cervicovaginal secretions, semen, and rectal sponge secretions.

Study Status & Population

- Screening and Enrollment
  - Screening/consenting started 09 February 2021
  - Enrollment/ vaccination began 15 March 2021
  - Enrollment concluded 07 January 2022

	Male	Female	Total
Screened/Consented	106	172	278
Enrolled	55	82	**137**

- Demographics:
  - Median age of 30 years (range 21-40yo);
  - Majority female (59.8%);
  - Single never married (36.5%);
  - Occupation ranged but largest category farmer (37.2%)

Vaccination Summary by Group

	Prime Vaccinations			Boost Vaccinations		
Study Group	**Vaccine 1**	**Vaccine 2**	**Vaccine 3**	**Vaccine 4**	**Vaccine 5**	**Vaccine 6**
ITT Total (N= 126 + 11 replacements)	137	121	118	124	118	117

- All vaccinations are complete
- Clinical follow-up visits will conclude in January 2024

Local Reactogenicity

Symptom	Prime vaccinations (Vaccines 1,2,3)	Boost Vaccinations (Vaccines 4, 5, 6)
	N=137	**N=127**
Pain/Tenderness	28(20.4%)	28(21.9%)
Swelling/Induration	5(3.6%)	6(4.7%)
Itching	14(10.1%)	7(5.5%)
Redness/Erythema	4(2.9%)	2(1.5%)
Hardness	3(2.1%)	2(1.5%)
Warmth	10(7.2%)	4(3.1%)
Any Local Reaction	**36(26.2%)**	**29(22.7%)**

Systemic Reactogenicity

Symptom	Prime vaccinations (Vaccines 1,2,3)	Boost Vaccinations (Vaccines 4, 5, 6)
	N=137	**N=127**
Headache	54(39.3%)	23(18.0%)
Temperature	15(10.8%)	20(15.6%)
Chills	17(12.3%)	9(7.0%)
Dizziness	22(16.0%)	10(7.8%)
Tiredness/Fatigue	39(28.4%)	9(7.0%)
Nausea	12(8.7%)	5(3.9%)
Muscle pain/myalgia	20(14.5%)	12(9.4%)
Joint pain/arthralgia	16(11.6%)	3(2.3%)
Rash	2(1.4%)	1(0.7%)
Other	2(1.4%)	0
Any Systemic Reaction	**73(53.2%)**	**43(33.7%)**

Safety Review

- Reactogenicity and tolerability of the vaccine has been excellent
- No severe or life-threatening local injection or systemic reactions
- 1 Serious adverse event (SAE)
  - Hospitalization for new onset Type 1 diabetes mellitus in 23 yo female in Group 1 (unrelated to study)
- 2 Potentially immune-mediated medical conditions (PIMMCs)
  - Type 1 diabetes mellitus (as noted above)
  - Graves' disease in 27 yo female in Group 3 (unrelated to study)
- No deaths

Interim analysis:
Focusing on DNA prime vaccinations

Group	V/P	Prime at Weeks 0, 4, 12
1	15/3	DNA alone
2	15/3	DNA alone
3	15/3	DNA + dmLT (TCI)
4	15/3	DNA + dmLT (TCI)
5	15/3	DNA + ALF43
6	15/3	DNA + ALF43
7	15/3	DNA + gp145 + ALF43

Env-C Plasmid DNA

Clade C gp120 (93MW965.26) was cloned into pSW3981 vector.

dmLT

A heat-labile enterotoxin B (R192G/L211A).

ALF43

The dose was 200 µg 3D-PHAD® (synthetic monophosporyl lipid A).

HIV Env gp145 C.6980 Protein

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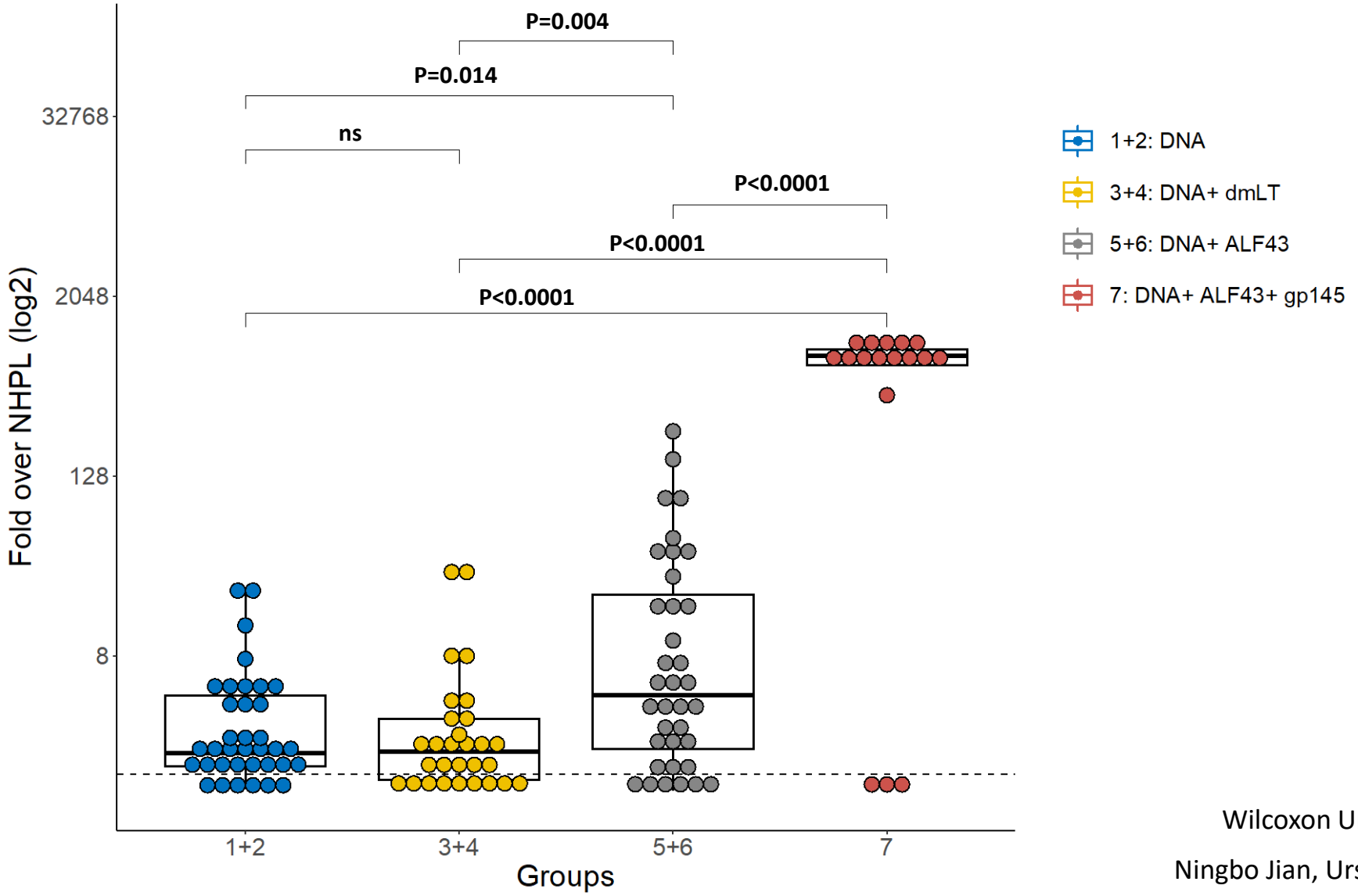
MHRP

Cognate vaccine immunogen gp145 Binding Antibody Responses

Luminex

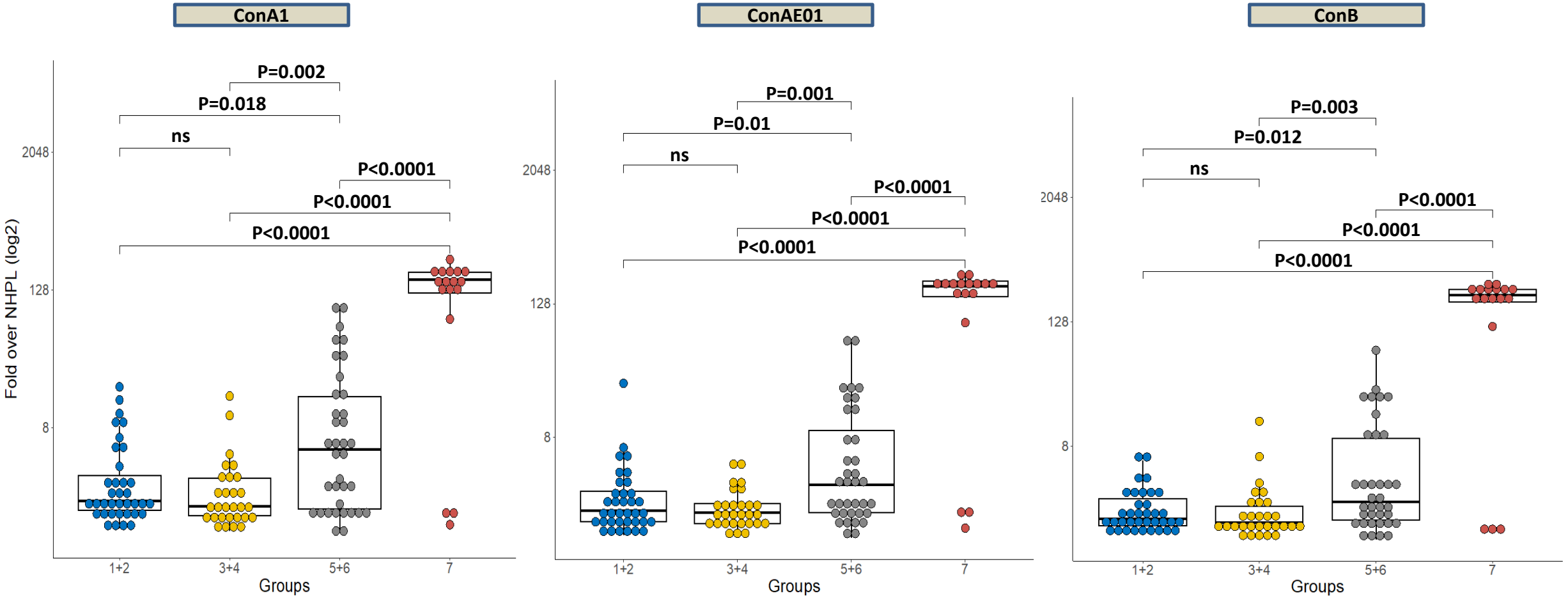


Wilcoxon Unpaired p-values

Ningbo Jian, Ursula Tran, Bonnie Slike

Higher, Cross-clade Antibody Responses in ALF43 Adjuvant Groups

Consensus gp140's



Wilcoxon Unpaired p-values

Ningbo Jian, Ursula Tran, Bonnie Slike

MHRP

Immunogenicity Review

- Binding antibody responses against clade C HIV antigen was detected at visit 11 in >30% of the participants.
  - The majority of these responders are in Groups 5-7.
- Group 7 (DNA + gp145 + ALF43) developed the highest magnitude of antibody binding responses compared to all other groups.
- Groups 5-7 also generated higher, cross-clade antibody responses against gp140 HIV antigens compared to groups that received DNA alone (Groups 1 & 2) or DNA + dmLT (Groups 3 & 4).

- Co-administration of liposomal adjuvant ALF43 along with HIV-1 DNA vaccination improves binding responses against HIV-1.

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All RV460 participants!

GLOBAL INFECTIOUS DISEASES

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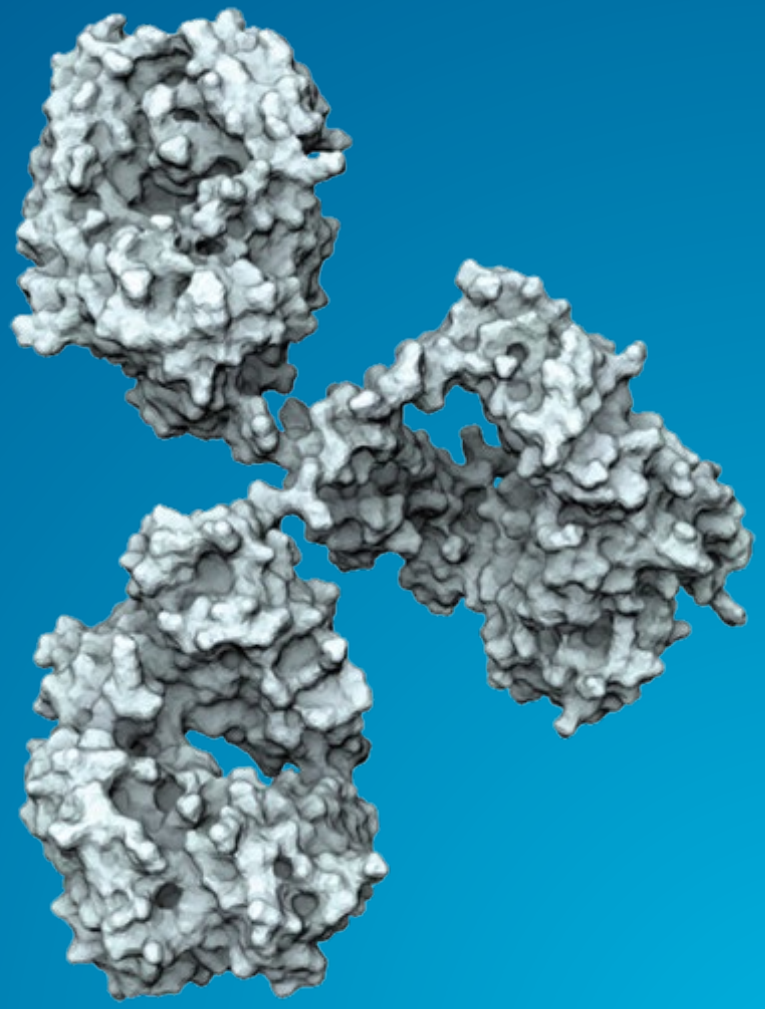
Regulatory Considerations for adjuvants for new and improved vaccines



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IAVI

GVIRF Webinar – Vaccine Adjuvants for Global Health

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As of July 2023

Adjuvants: General Considerations

- Adjuvants have been used for decades to enhance the immune response to vaccine antigens
- Strategies and approaches for the development and delivery of vaccine antigens have expanded over the last several decades
- Broad range of novel products comprised of purified subunit antigens or subunit proteins
- These antigens may require the presence of adjuvants to
  - enhance the immune response to the vaccine antigens
  - reduce the dosing frequency
  - induce cross-protective effects
  - direct the immune response and/or achieve antigen sparing

Novel adjuvants contained in licensed vaccines - Examples

US

- Al^{+++} salts in many vaccines
- Monophosphoryl lipid A (MPL) /$AlOH_3$: AS04
  - Cervarix (human papilloma virus vaccine)
- AS03 (oil-in-water emulsion)
  - Q-Pan (H5N1) monovalent pandemic flu vaccine
- CpG 1018 (oligodeoxynucleotides)
  - Heplisav (rec. Hepatitis B vaccine)
- MF59 (oil-in-water emulsion)
  - Fluad (seasonal influenza vaccine)

Europe

- Al^{+++} salts in many vaccines
- MPL/$AlOH_3$: AS04
  - Fendrix (hepatitis B vaccine)
  - Cervarix (human papilloma virus vaccine)
- MF59
  - Focetria (pandemic influenza vaccine)
  - Fluad (seasonal influenza vaccine)
- AS03
  - Pandemrix (pandemic influenza vaccine)

Adjuvanted Vaccines: Development Strategy

Pre-clinical data supportive of initiating clinical studies

Human clinical safety and efficacy data adequate to support the proposed indication and use

Post-licensure pharmacovi-gilance plan

Goal: Safe, effective, high-quality product of known stability that can be consistently manufactured

Product-related data and testing plans adequate to support the manufacturing process

Manufacturing process ensuring quality product and consistency of manufacture

Facility data: compliance w/cGMPs, manufacturing controls, QA/QC

Adjuvants: Special Considerations

- Substances or combinations of substances used in conjunction with vaccine antigen(s) to
  - Enhance, prolong or modulate the specific immune response to the vaccine antigen to enhance the clinical effectiveness of the vaccine

- Exhibit range of properties that invoke complex immune responses
- Mode of action of adjuvants not always known or not fully understood
- Animal models that predict safety and efficacy of adjuvant-antigen combination not available
- Unique issues to be addressed during preclinical and clinical development of the adjuvanted vaccine formulation

Framework for assessment of adjuvanted vaccines

- WHO guidelines on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines (2013), referred to by various NRAs including FDA and EMA

  https://www.who.int/publications/m/item/nonclinical-evaluation-of-vaccine-adjuvants-and-adjuvanted-vaccines-annex-2-trs-no-987

  - Describes the quality, pharmacological, toxicological, and other information needed to support initiation of clinical trials with a vaccine combined with a novel adjuvant
  - Provides consistent and harmonized guidance on nonclinical testing approaches to support the use of candidate adjuvanted vaccines in all stages of clinical development
  - Describes design elements for first-in-human clinical trials
  - *Caveat:* Many NRAs provide a regulatory and legal classification for the adjuvant component of the vaccine (e.g., excipient, active ingredient or constituent material
    - Depending on the particular definition used by the particular NRA, additional testing may be required

Example: US FDA regulatory definition & considerations: Adjuvants

- Adjuvants are not considered active ingredients
  - 21 CFR 610.15 Constituent Material (*Ingredients, preservatives, diluents, adjuvants)*
- No vaccine adjuvant is authorized in its own right, but only as a component of a particular adjuvanted vaccine
- It is the adjuvanted vaccine formulation, *in toto*, that is tested in clinical trials and licensed, no independent licensure of adjuvants
- Adjuvanted vaccine formulation must be safe and effective
  - Benefits outweighing its risk

Adjuvanted Vaccines: Preclinical Safety

Q*uality:* physicochemical characterization (potency, purity, stability)

Safety:

- Repeat dose toxicity in animal model

  Usually conducted prior to clinical trials

  To identify and characterize potential local and systemic adverse effects

  Histopathology of full tissue list (WHO guidance) for novel adjuvants

- Reproductive toxicity testing

  Conducted in parallel with Phase 3 clinical trials for products intended for use in females of childbearing potential, *or*

  Conducted prior to studies enrolling pregnant women

WHO guidelines on the nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines published in 2013

When & how should the “added benefit” of the adjuvant be demonstrated?

- Manufacturer should provide rationale for the use of adjuvant in their vaccine formulation
  - Preclinical studies (e.g., in *vitro assays* and/or proof-of-concept studies in animal models)
  - Early clinical immunogenicity trials comparing adjuvanted vs. unadjuvanted vaccines to include
    - evidence of enhanced immune response
    - antigen sparing effects, or
    - other advantages
  - If available, information about the presumed mechanism of action of the adjuvant
- Because adjuvants are not considered active ingredients from a regulatory perspective manufacturers are not required to demonstrate the “added benefit” of an adjuvant in comparative phase 3 efficacy and safety trials, e.g.,
  - Studies comparing vaccine antigen with and without adjuvant
  - May be requested on a case-to case basis, e.g.,
    - Safety concerns have been identified
    - Superiority claims

Special Considerations Adjuvanted Vaccines: Clinical Safety Evaluation

- Benefits from incorporating or adding an adjuvant to any vaccine formulation need to be balanced with the risk of adverse reactions
- Suggested comparisons (early in clinical development, i.e., Phase 1 & 2):
  - Adjuvanted vaccine vs. saline placebo
  - Adjuvanted vaccine vs. unadjuvanted antigen
- Specific inquiries regarding symptoms consistent with autoimmune and neuroinflammatory diseases
- Longer post-vaccination follow-up than is typical for non-adjuvanted vaccines
  - Typically 12 months following vaccination
  - Follow-up SAEs, new-onset medical conditions, “adverse events of special interest”
- Safety experience with the same adjuvant formulated with other vaccine antigens may also contribute to the adjuvant's safety evaluation

Special Considerations Adjuvanted Vaccines: Clinical Safety Evaluation

Duration of follow-up

- Some potential adverse events beginning after vaccination may not be recognized or diagnosed until much later
- Trade-off: Longer duration can increase identification of potential AEs, but may also increase noise
- Longer follow-up is often routinely obtained in efficacy studies, but increases the complexity where product is evaluated based on immunogenicity
  - Adverse events of “special interest” (AESI)
    - Focus on autoimmune/autoinflammatory diseases
    - Examples
      - Neuroinflammatory disorders (e.g., optic neuritis, transverse myelitis)
      - Musculoskeletal and connective tissue diseases (e.g., RA, SLE, Wegener’s)
      - GI disorders (e.g., Crohn’s disease, ulcerative colitis)

Summary

- Regulatory pathways supporting development and approval of vaccines formulated with novel adjuvant are the same as for unadjuvanted vaccines
- Efficient planning of the development pathway for any adjuvanted vaccine requires careful attention to preclinical testing, study design, dosing decisions, and safety monitoring
- Although manufacturers are not required to demonstrate the “added benefit” of adjuvanted *vs* unadjuvanted vaccines in clinical comparative phase 3 studies, manufacturers should provide a justification for including an adjuvant in the vaccine
- Evaluation of safety of an adjuvanted vaccine needs to include special safety considerations