



RXKINETIX™
DRUG DELIVERY TECHNOLOGY

Pluronic® F127–Based Systemic And Mucosal Vaccine Delivery Systems

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Innovative Administration Systems for Vaccines

Rockville, MD

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RxKinetix, Inc.

Product Platforms

ProGelz™ : Reverse thermal gelation based drug delivery

- RK-0202 – treatment for oral mucositis
- HemaGel™ - growth factor delivery
- ProJuvant™ – vaccine delivery
- CTAD – Concentrated therapeutic antibody delivery

Micronix™: Supercritical fluid based particle engineering

- Controlled/immediate release drug delivery (days – months)
- Proteins, peptides, small molecules, genetic materials

ProGelz™

Proprietary polymer gel formulation

- Delivers high protein doses preserving structure and activity
- Reverse thermogelation
- Multiple administration route possibilities
- Bioadhesive penetration enhancer
- Extensive safety history in humans
- Granted patents for the delivery of proteins and peptides

ProJuvant™

Novel Vaccine Delivery Vehicle

- As single/reduced dose injectable formulation
- As mucosal adjuvant/delivery vehicle
 - *Westerink et al. (2002) Vaccine 20:711–723*

ProJuvant™ Is A Two-Component Immune Response Enhancer

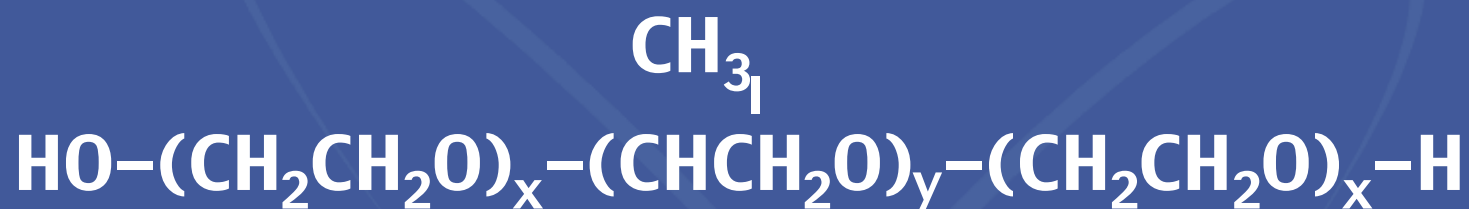
Pluronic® F127

- Biocompatible polyethylene oxide, polypropylene oxide block co-polymer

Adjuvant/penetration enhancer

- *Chitosan*
 - Cationic polymer of N-acetylglucosamine and D-glucosamine
 - Low order toxicity and biodegradable
 - Penetration enhancer and immunological adjuvant
- *CpGs*
 - Immunostimulatory DNA sequences

Structure Of Non-Ionic Block Co-Polymers



<u>Polymer</u>	<u>MW</u>	<u>x</u>	<u>y</u>
F1 27	12,600	100	65
CRL 1 005	12,600	7	207
L1 21	4400	5	70

Experimental Design I: Systemic Administration

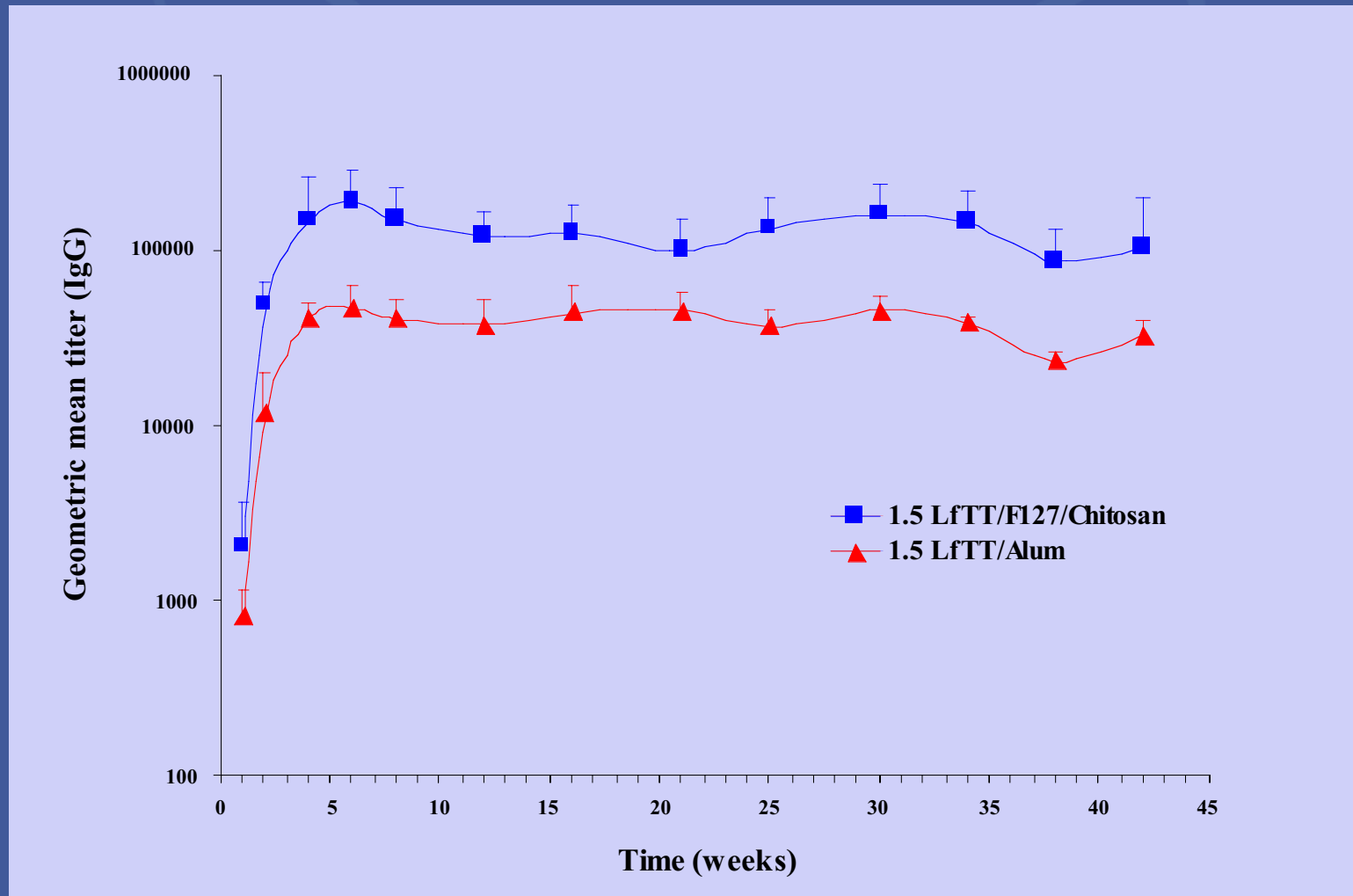
ProJuvant™ Formulation

- Pluronic F127
- Adjuvant
 - Chitosan or CpG
- Antigen
 - Tetanus toxoid (TT)
 - Diphtheria toxoid (DT)
 - Recombinant anthrax protective antigen (rPA)

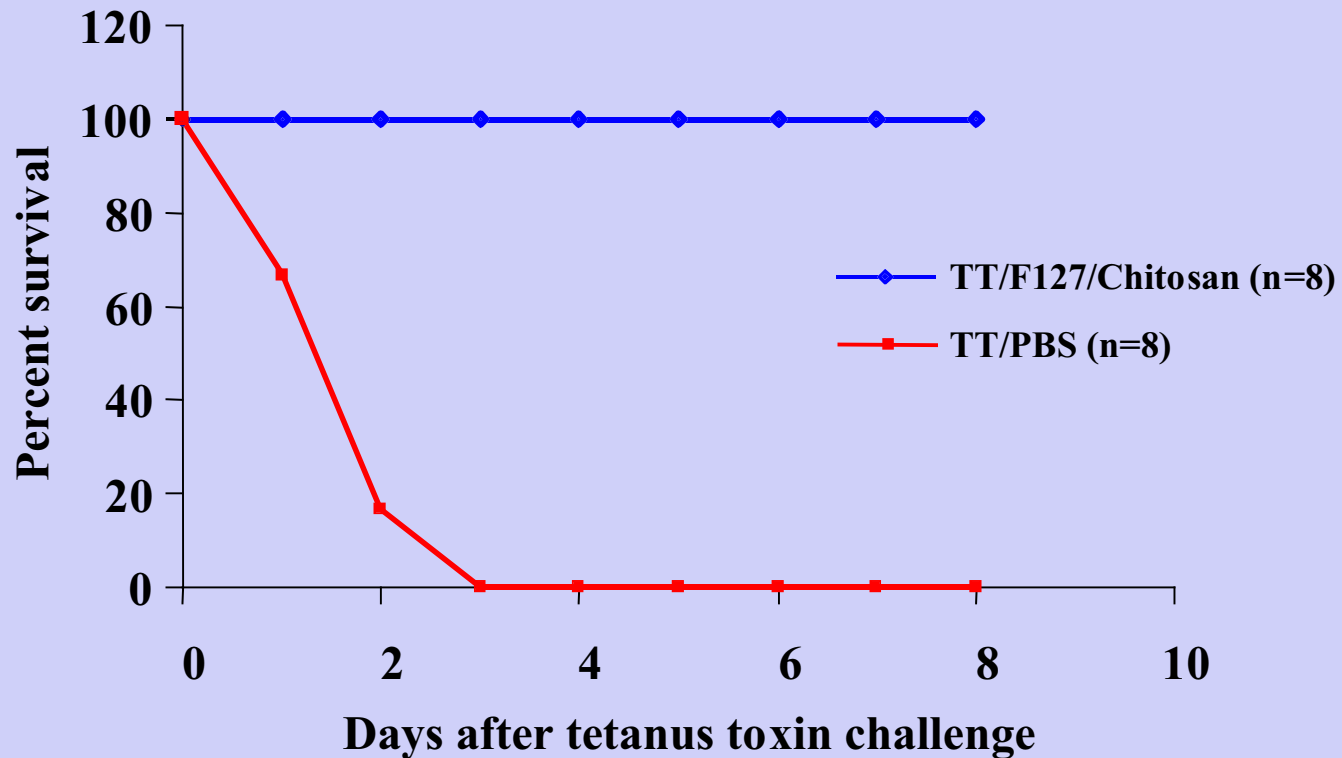
Experimentation

- subcutaneous immunization
 - IgG titers in serum samples measured by ELISA and toxin neutralization assay

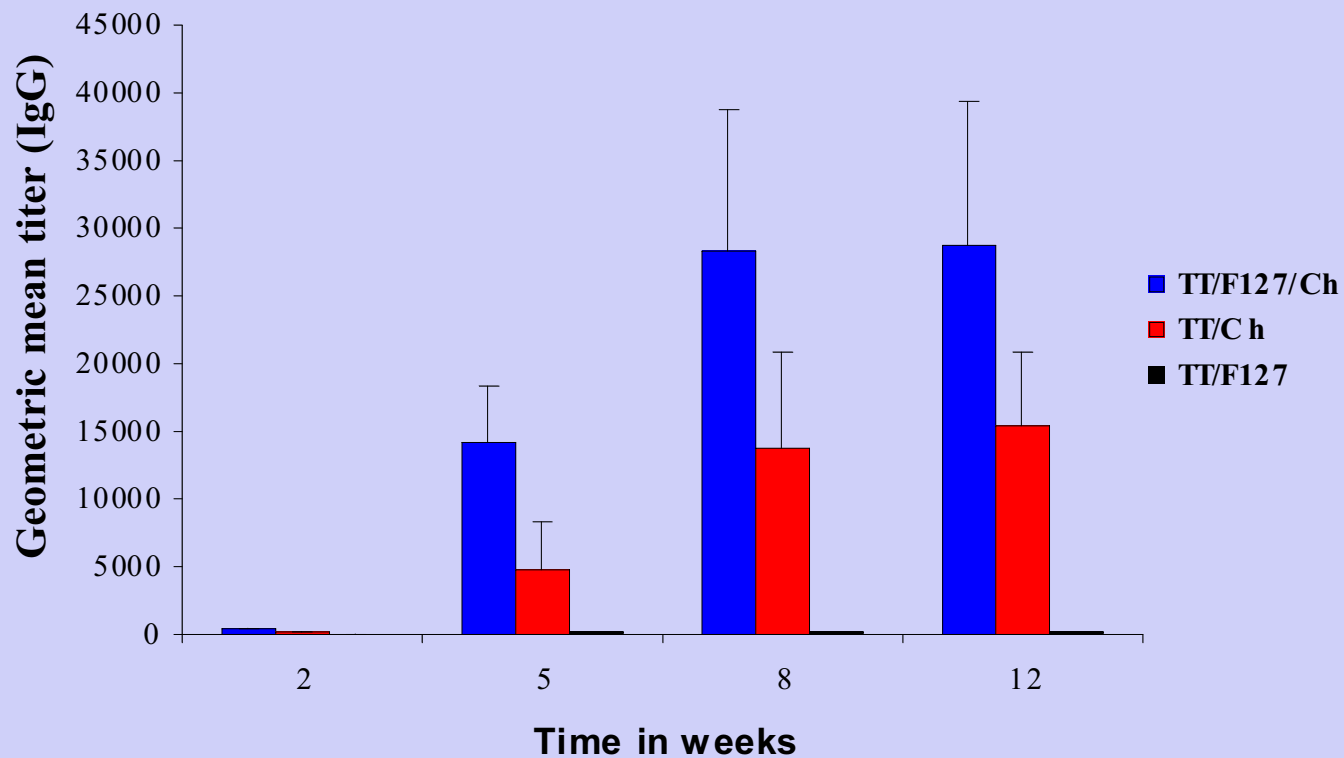
ProJuvant™ Elicits A Long-Lived IgG Antibody Response After Single Injection In Mice



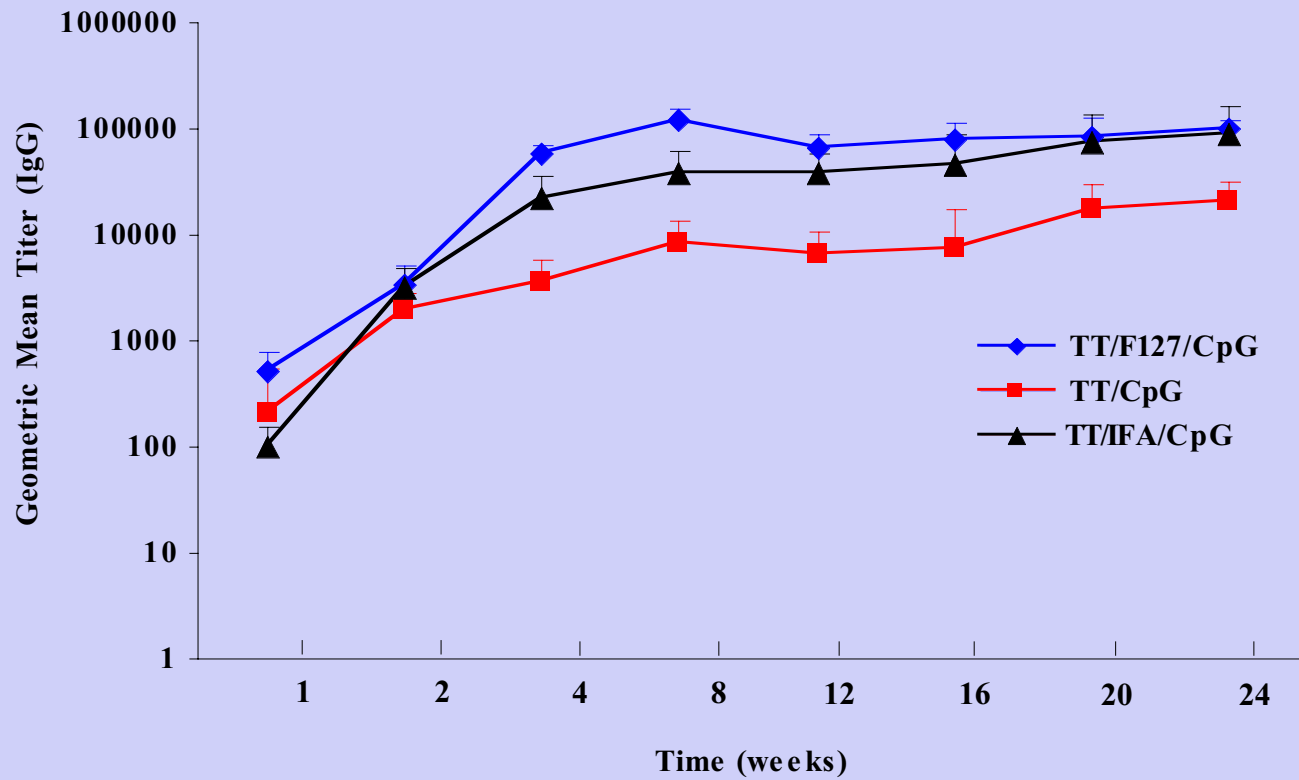
ProJuvant™ Protects Mice From Lethal Challenge With Tetanus Toxin



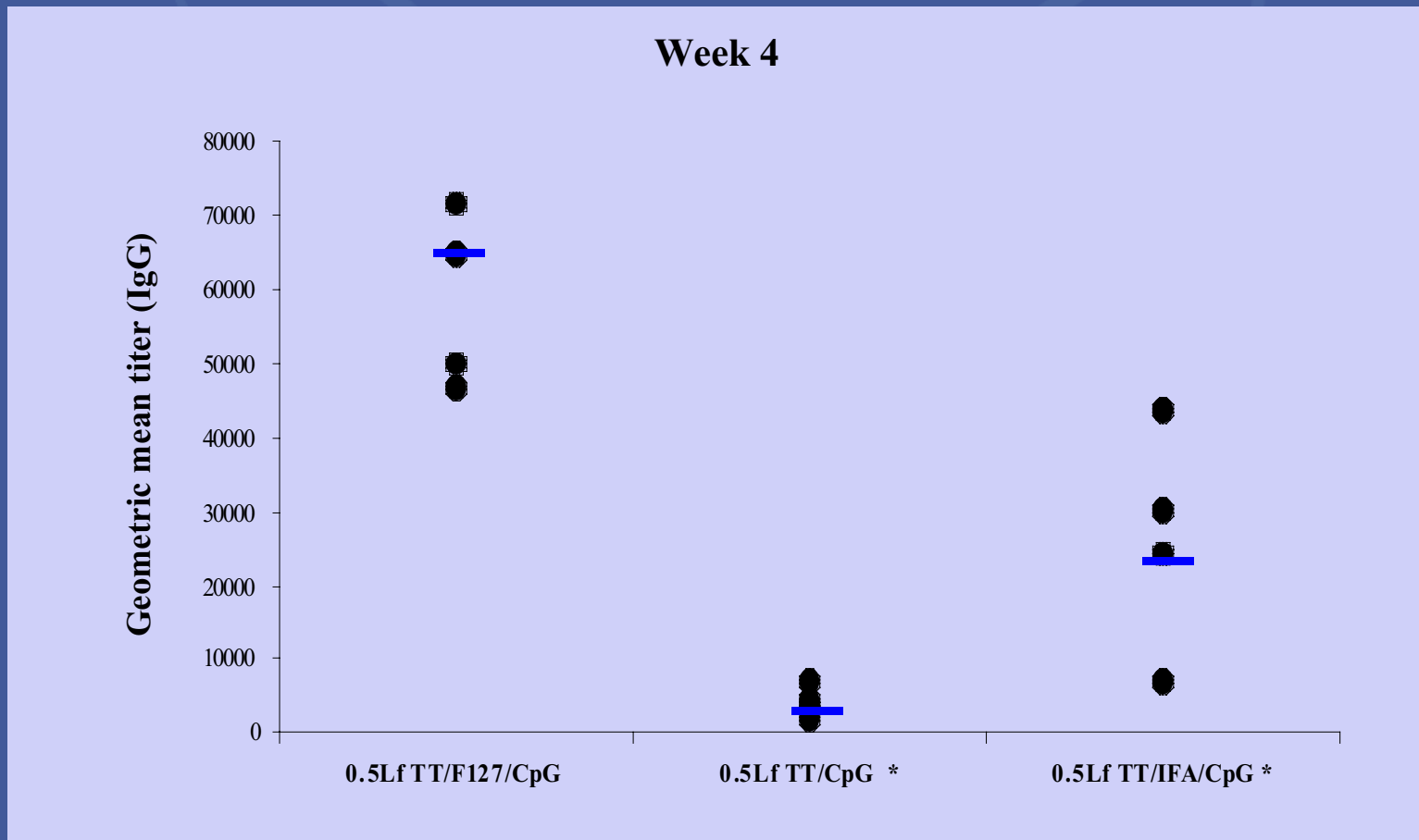
ProJuvant™ Is Superior To Either Component Alone



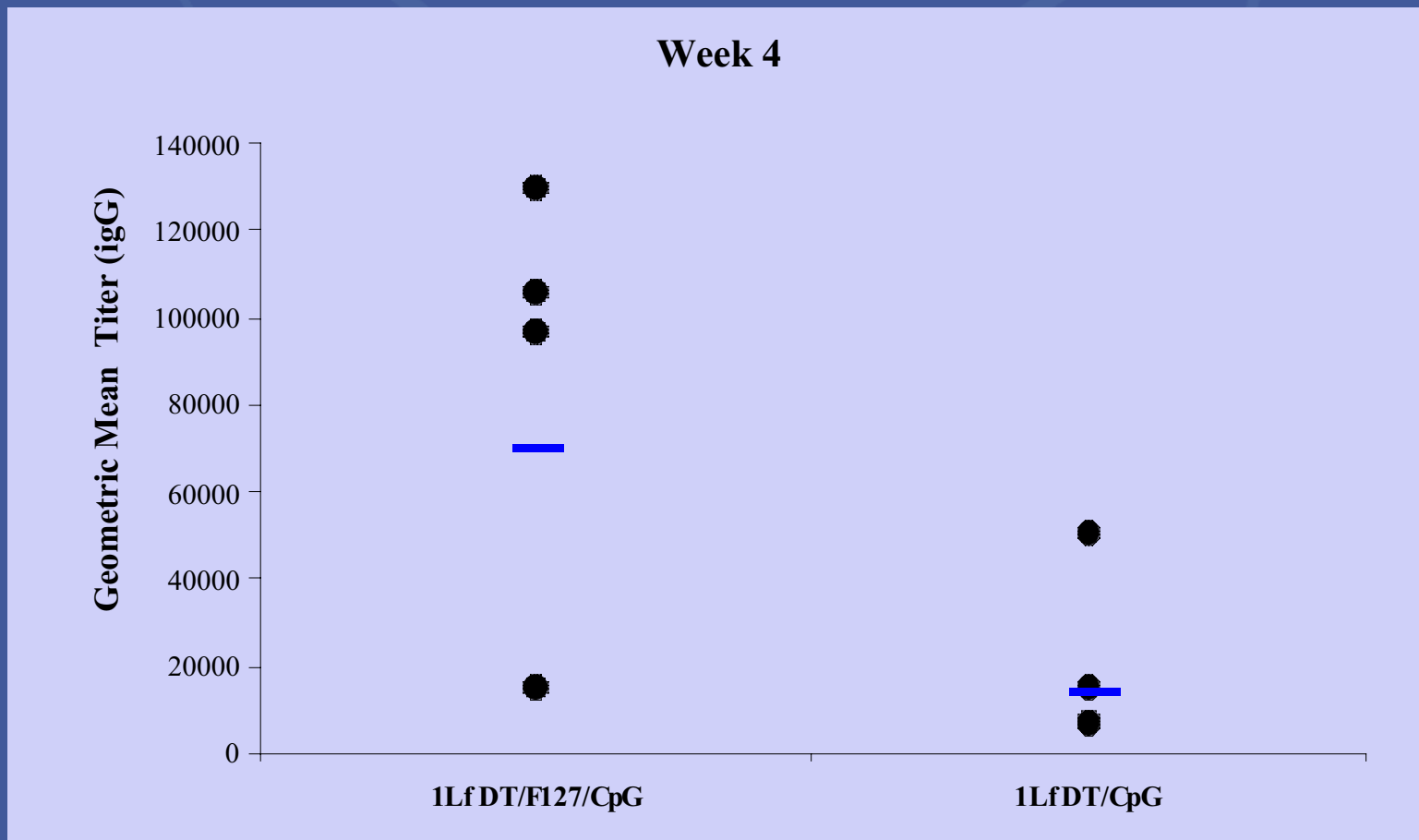
ProJuvant™ Comparison With IFA



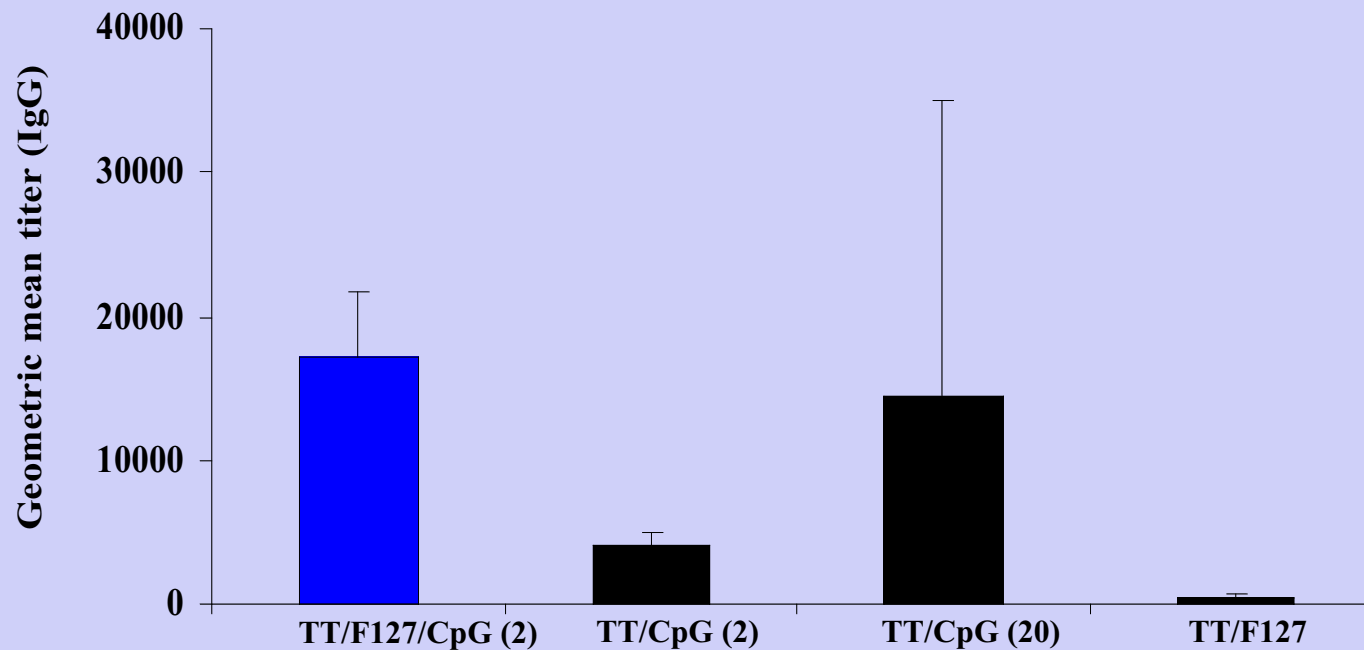
ProJuvant™ Elicits Improved IgG Titers With Tetanus Toxoid



ProJuvant™ Elicits Improved IgG Titers With Diphtheria Toxoid



ProJuvant™ Allows For TEN-Fold CpG Dose Reduction

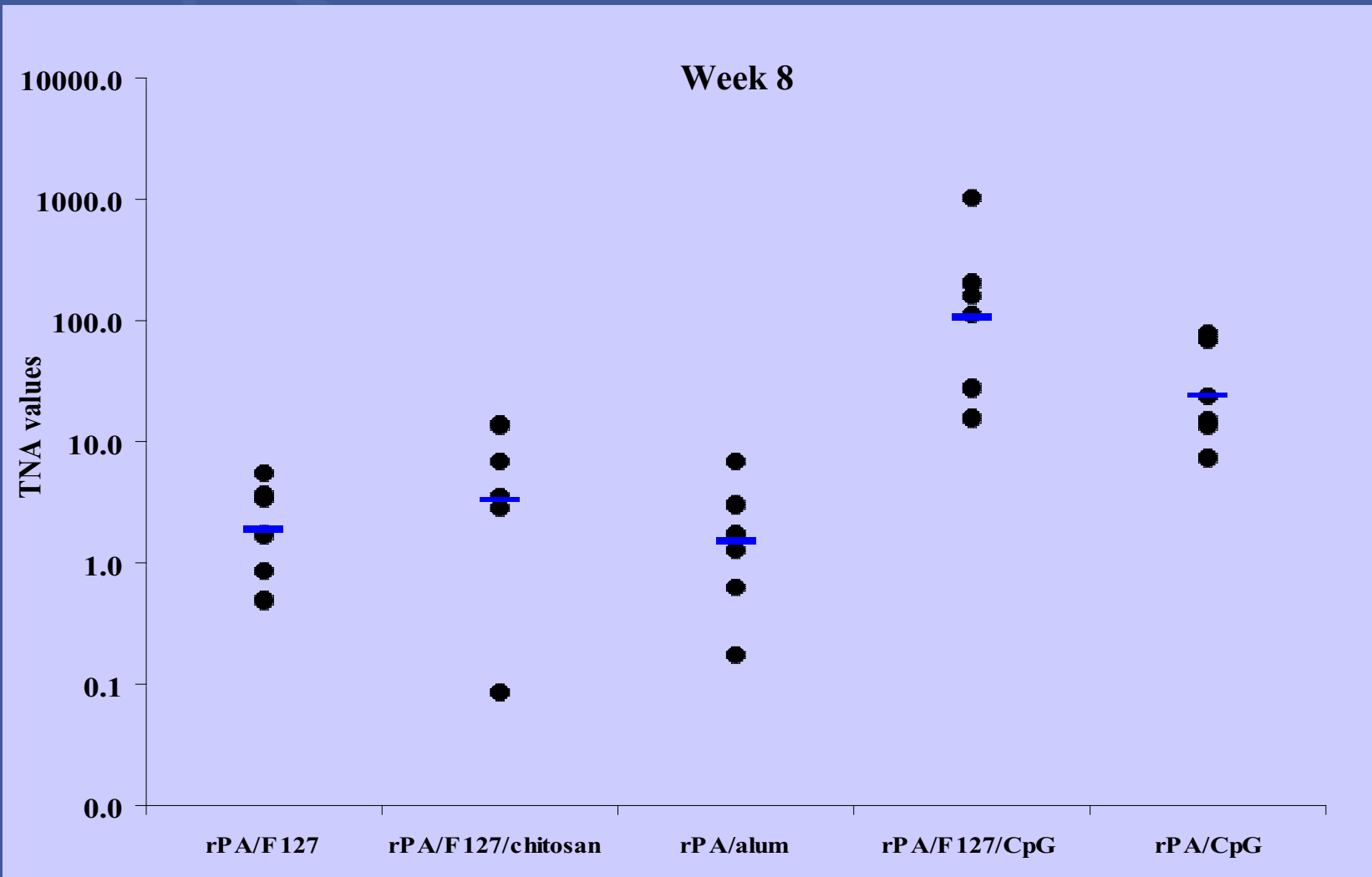


Anthrax Vaccine Delivery System

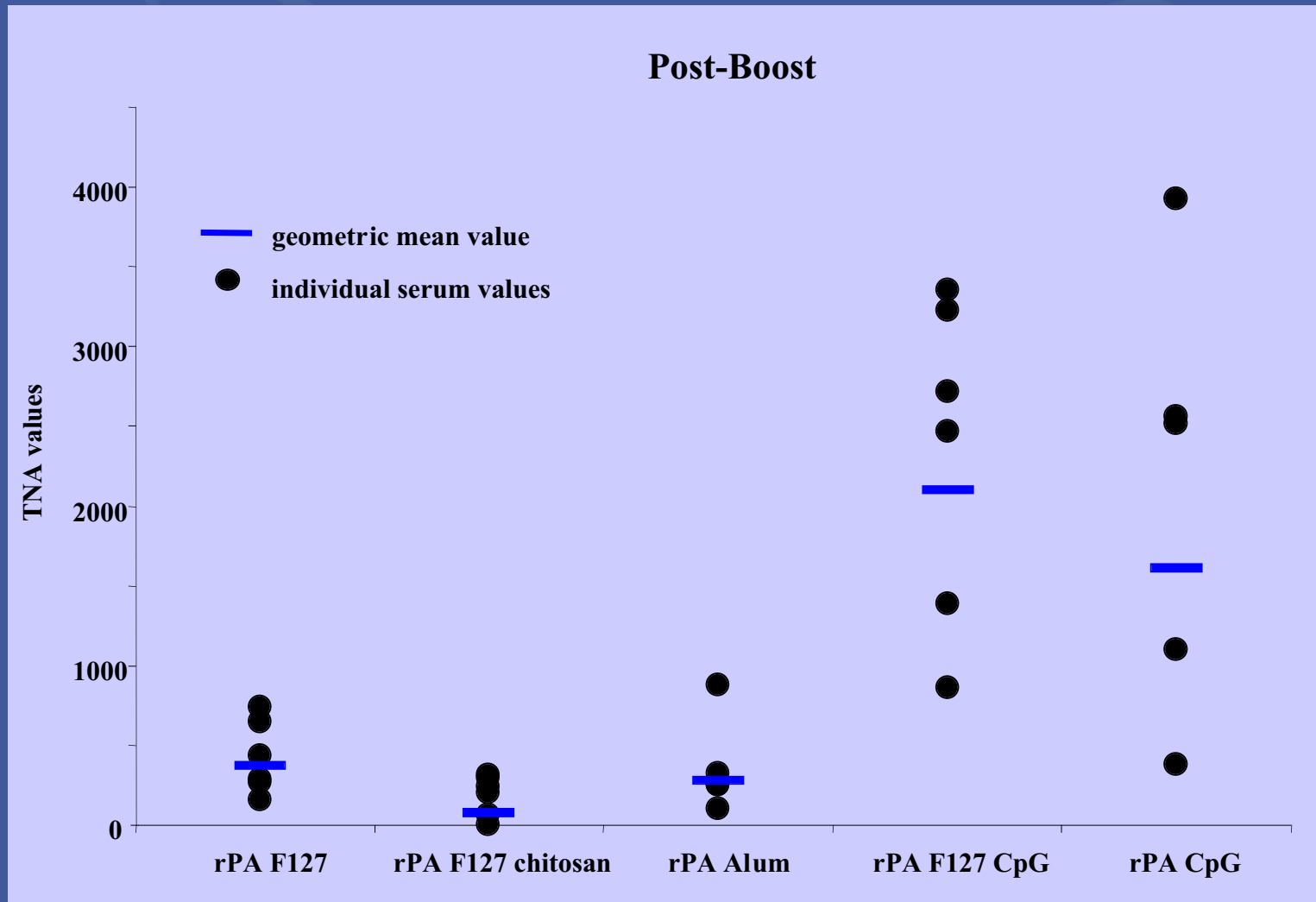
Anthrax Protective Antigen (rPA)

- Antibody response against PA commensurate with protection against anthrax
- Primary component of licensed US vaccine
- Released from bacteria as non-toxic monomer
- Combines with lethal factor (LF) and edema factor (EF) on target cell surface
- Lethal Toxin: cell bound complexes of PA and LF
- Edema toxin: PA and EF

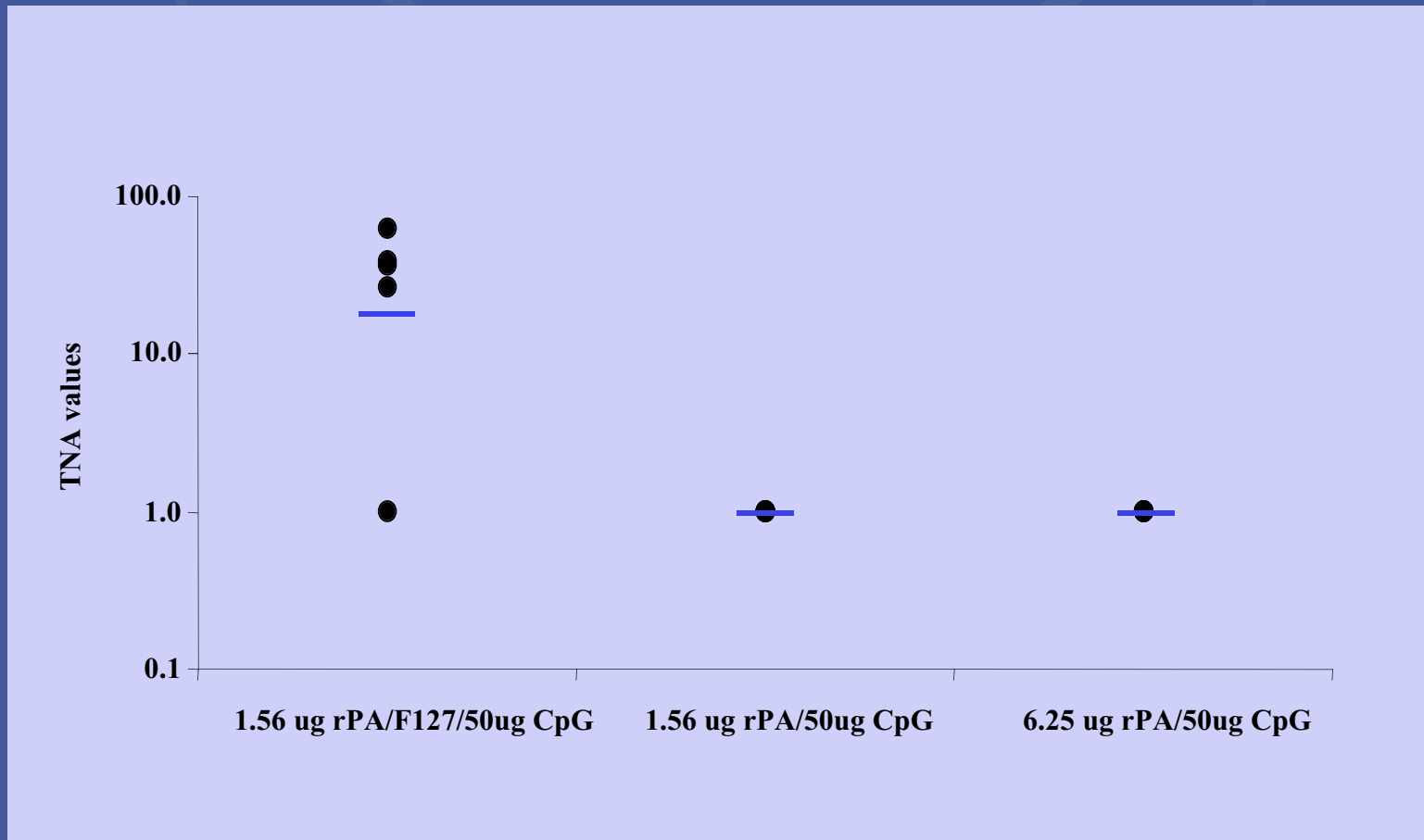
ProJuvant™ Elicits Toxin Neutralizing Antibodies I



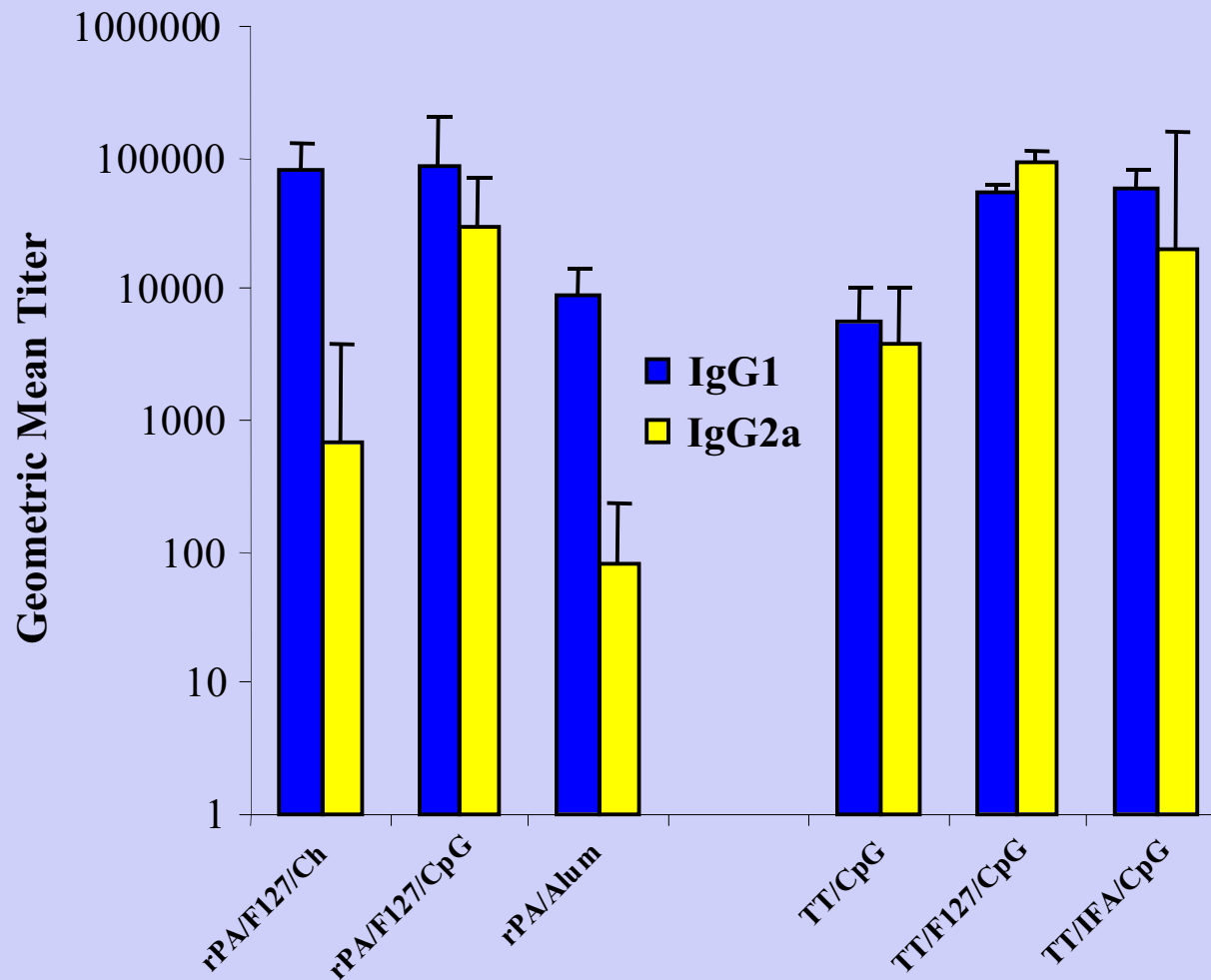
ProJuvant™ Elicits Toxin Neutralizing Antibodies II



ProJuvant™ Elicits Toxin Neutralizing Antibodies III. In Rabbits



IgG Subclass Distribution



Experimental Design II: mucosal administration

Formulation

Pluronic F127 – Chitosan – Tetanus toxoid (TT)

Experimentation

Systemic prime (TT/PBS) and intranasal boost

OR

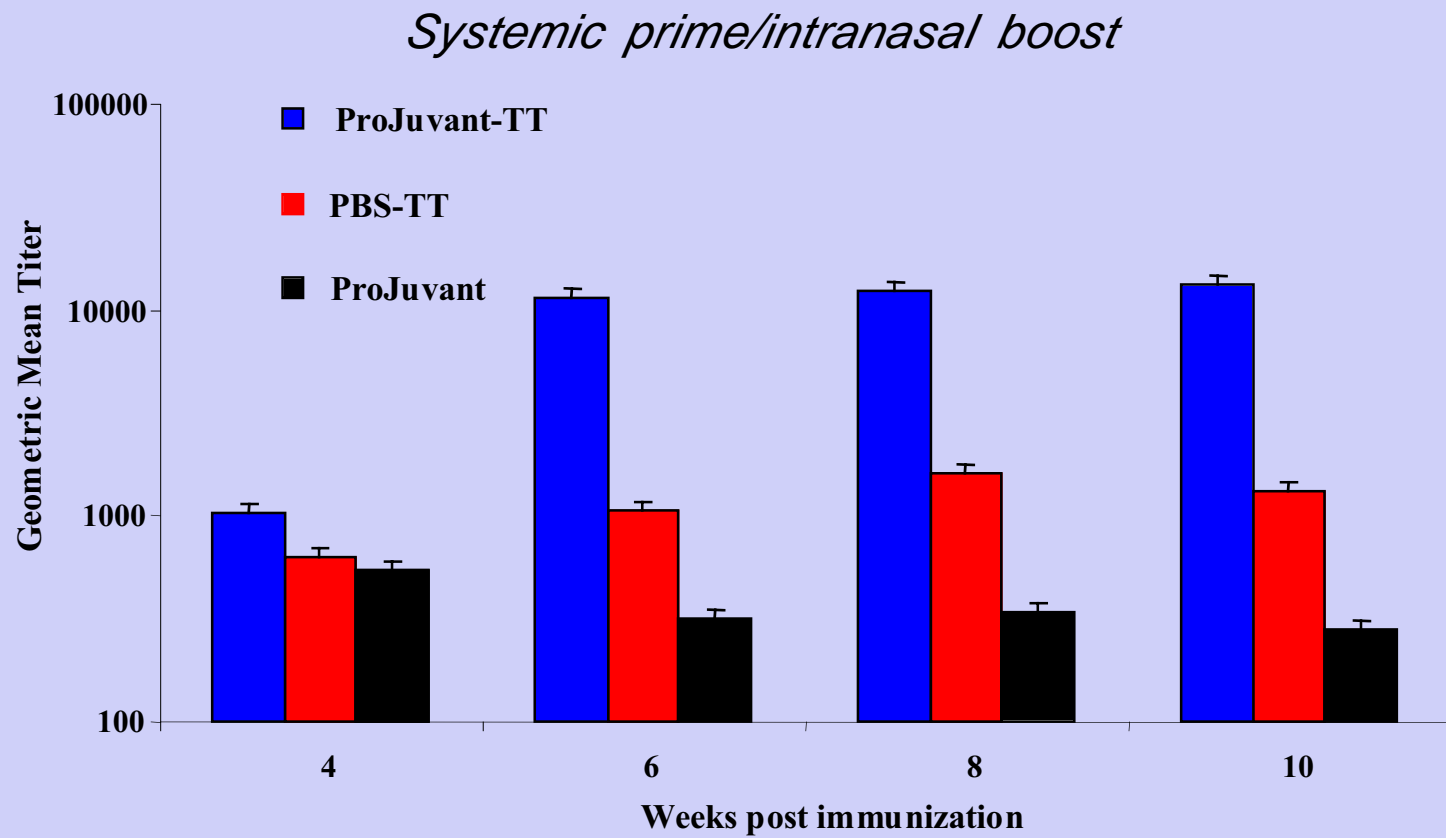
Intranasal prime and boost

Assay

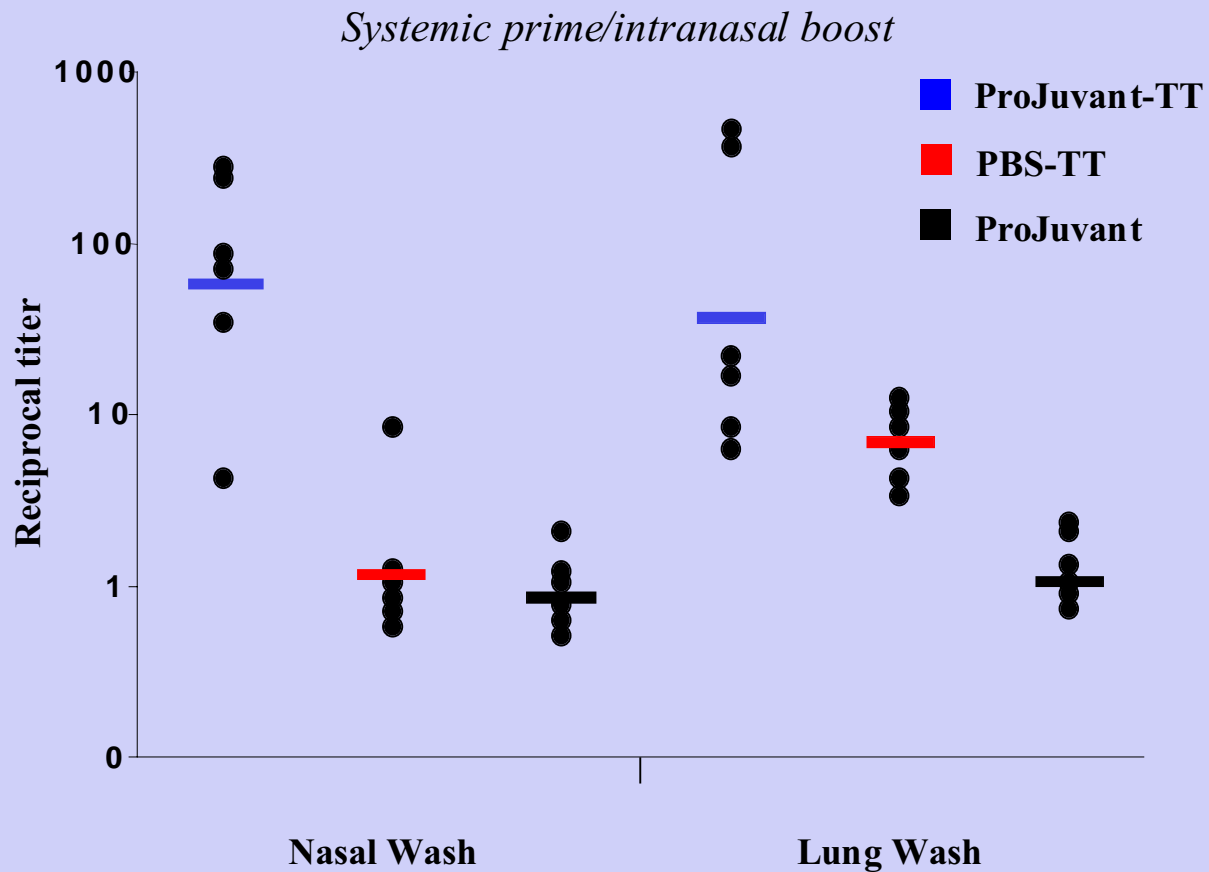
IgG titers in serum samples

IgA and IgG titers in nasal and lung washes

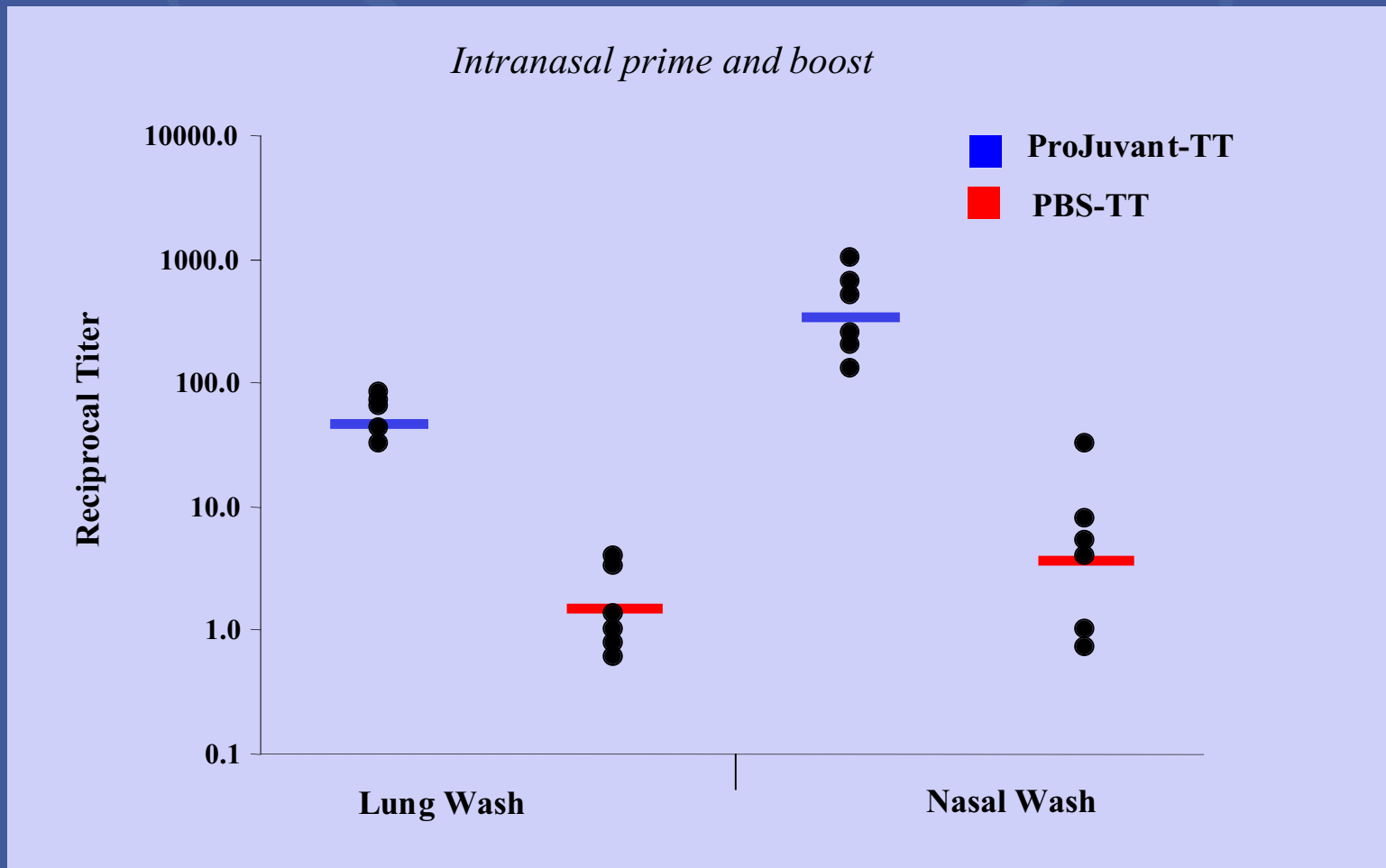
ProJuvant™ Elicits A Systemic IgG Response With Intranasal Administration



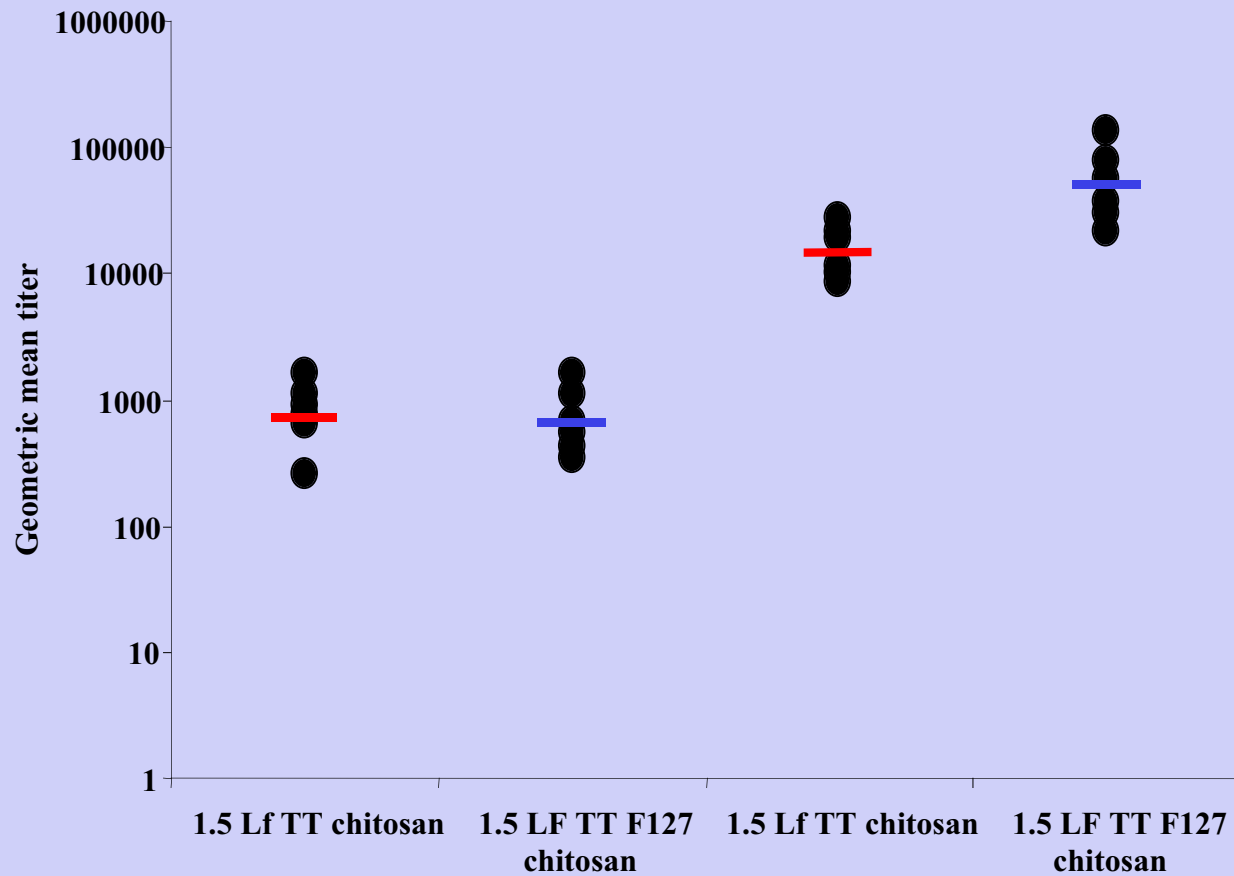
ProJuvant™ Elicits An IgA Response With Intranasal Administration



ProJuvant™ Elicits An IgA Response With Intranasal Administration



ProJuvant™ As Intranasal Booster: comparison with chitosan alone



Experimental Design III: mucosal administration

STTR Phase I grant

PI: Julie Westerink, MD, Medical College of Ohio

Formulations

Pluronic F127

One of four immunomodulators

PspA from *S. pneumoniae*

Administration

Intranasal administration: 0, 2 and 4 weeks

Assay

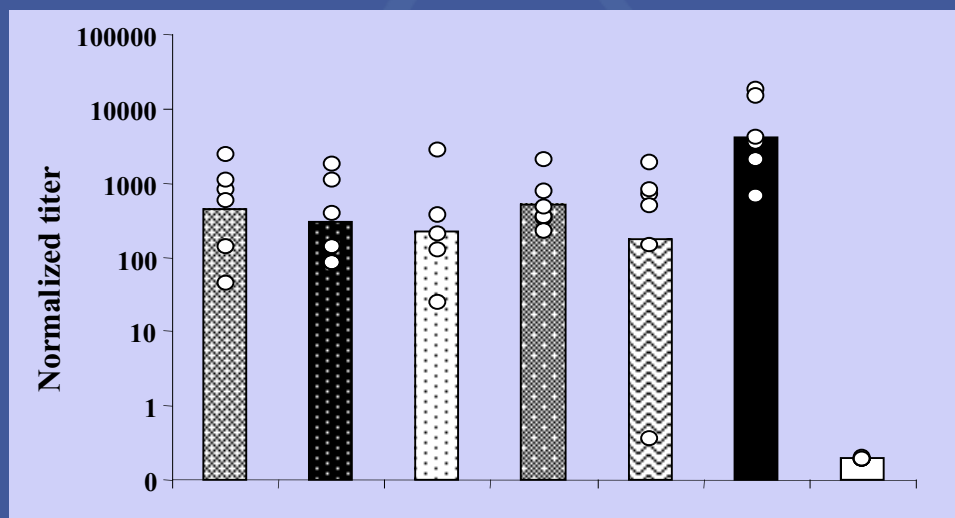
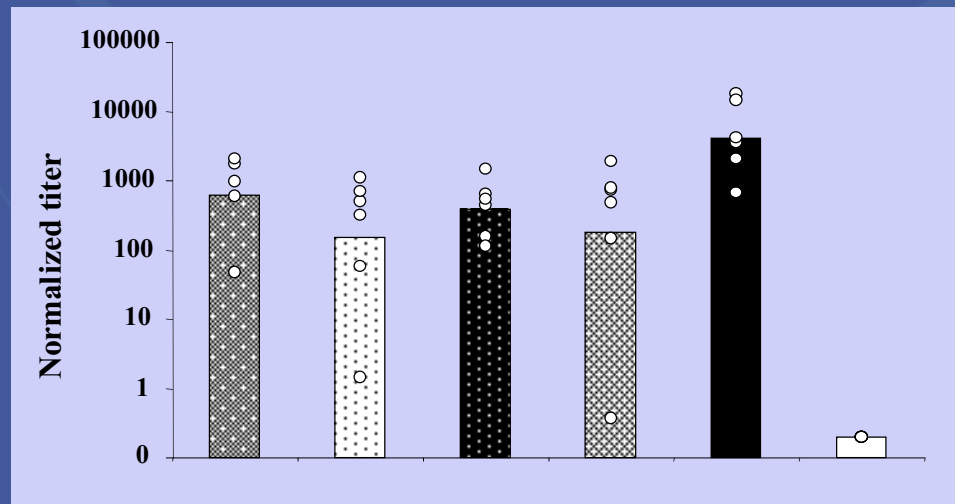
IgG titers in serum samples

IgA and IgG titers in nasal and vaginal washes

Opsonophagocytic activity

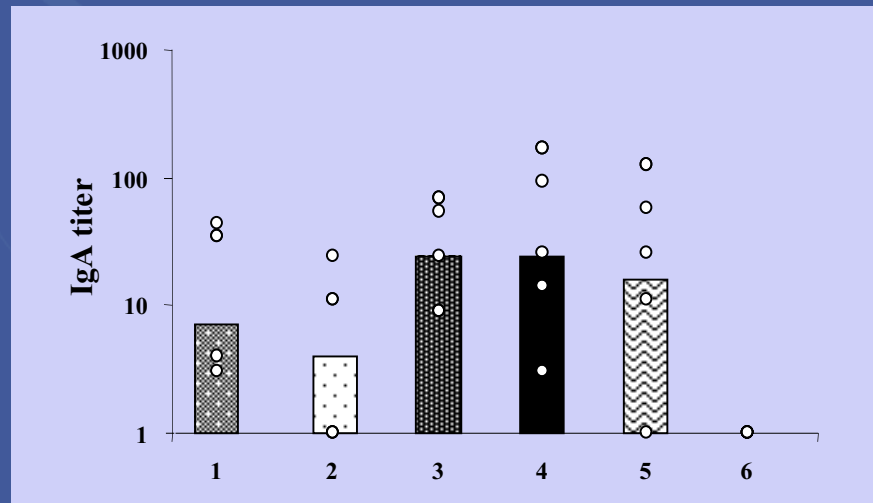
Challenge with lethal and non lethal serotypes

Intranasal administration of PspA in F1 27 based formulations: IgG systemic response

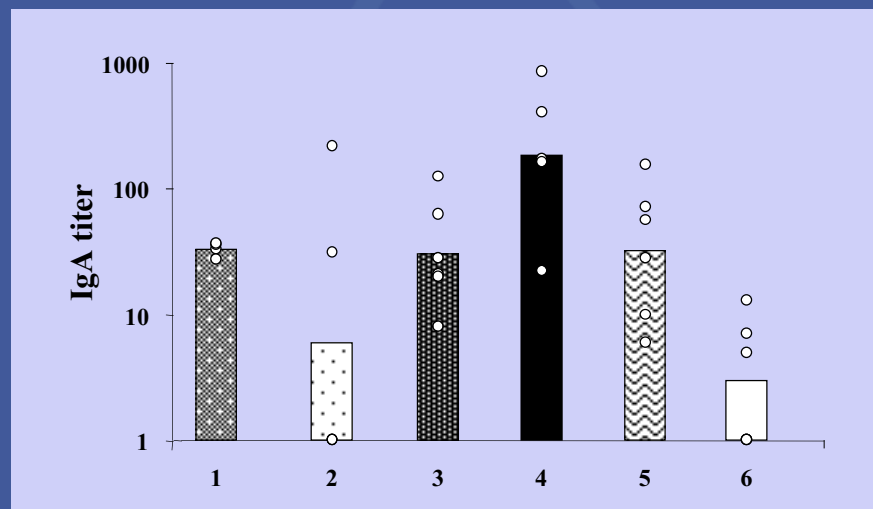


Intranasal administration of PspA in F127 based formulations: IgA mucosal response

Nasal Wash



Vaginal Wash



Conclusions

- **ProJuvant™: Formulations of Pluronic® F127 with different adjuvants**
- **As mucosal adjuvant/delivery vehicle**
 - Specific systemic IgG response
 - Specific IgA response at proximal and distal mucosal surfaces
- **As single/reduced dose injectable formulation**
 - Long-lived IgG antibody response
 - Protective immunity elicited
 - Effective with variety of antigens

Collaborators/Consultants

- **Medical College of Ohio**
 - Louise Smithson
 - Julie Westerink
- **University of Colorado Health Sciences Center**
 - John Cambier
 - John Carpenter
- **RxKinetix Inc.**
 - Joan Blonder
 - Binhan Lin
 - Gary Rosenthal
 - Adrian Samaniego
 - Marazban Sarkari
 - Kathleen Stone
 - Evie Verderber



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