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Comprehensive T cell antigen discovery using a genomic approach

Jessica Baker
Genocea Biosciences

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Comprehensive T cell antigen discovery using a genomic approach

Jessica Baker Flechtner, PhD

Vaccine Technology IV – May 20-25, 2012

BusinessWeek
"One of World's Most Intriguing Startups"

Fierce 15 WINNER
FierceBiotech

"Best Vaccine Startup"
worldvaccine CONGRESS 2008

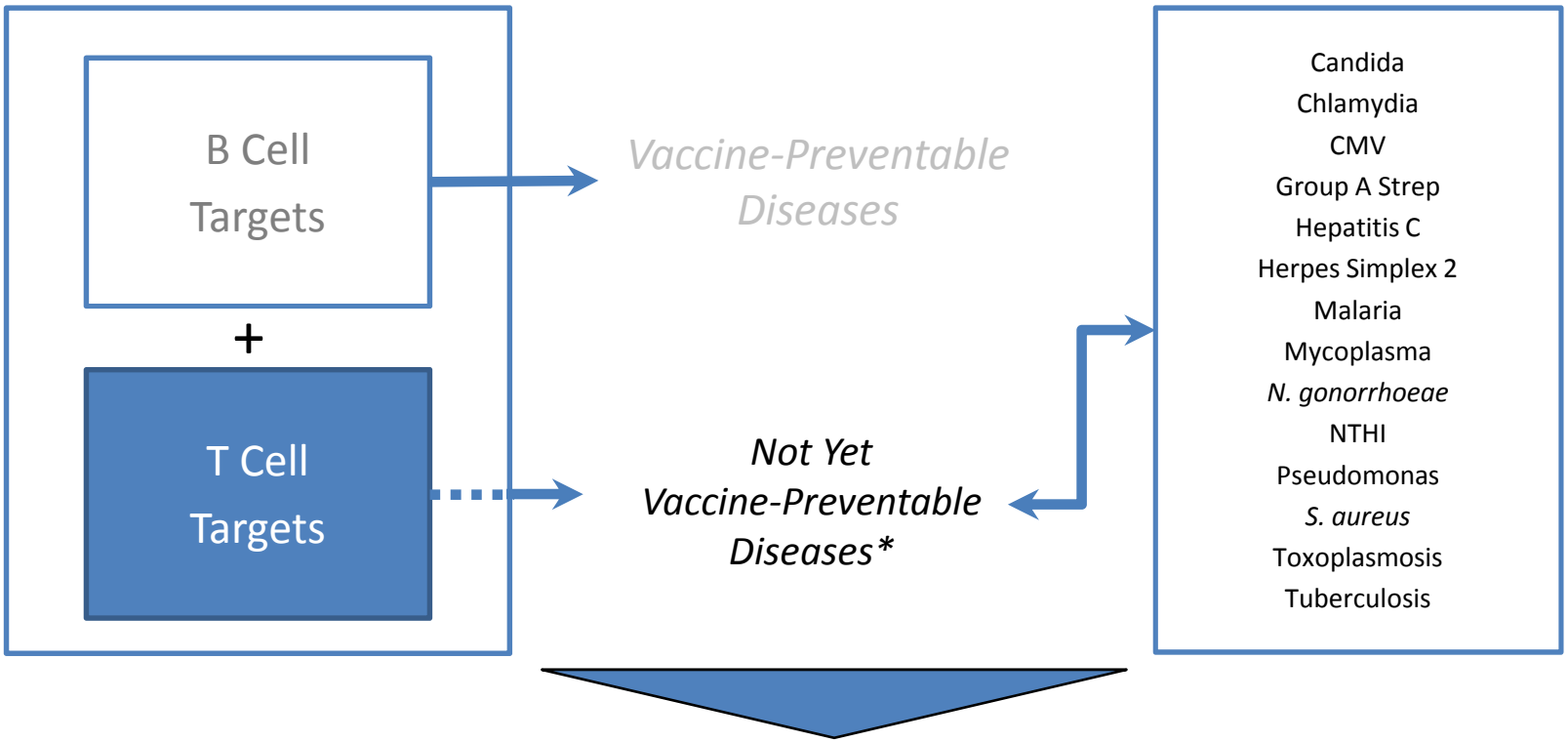
Genocea Background

- Location: Cambridge, MA
- Platform: Licensed from Harvard Medical School, UC Berkeley
- Headcount: 35 (19 with MS, PhD, or MD)
- Funding: $61 million in venture and $6.7 million grant funding

INVESTORS	GRANT SOURCES
POLARIS VENTURE PARTNERS Johnson & Johnson DEVELOPMENT CORPORATION luxcapital SR·one SKYLINE VENTURES	PATH A catalyst for global health National Institutes of Health Department of Defense United States of America

Antigen Discovery Platform (ATLAS™)

The Problem: A New Approach Needed for T Cell Vaccines

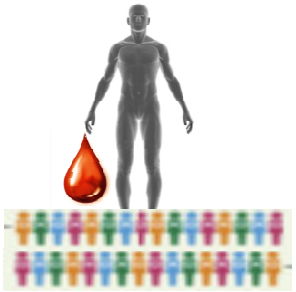


Conventional Antigen Discovery Is Not Applicable to T cell Antigens

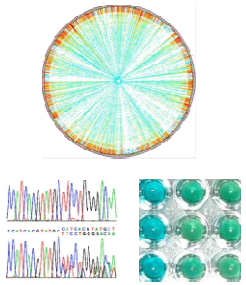
- Ab targets are surface exposed or secreted; T cell targets are any protein
- Too many targets for complex organisms: need rapid screening method
- T cell antigen discovery needs to account for HLA restriction

*Partial list

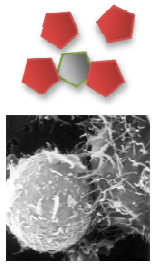
AnTigen Lead Acquisition System (ATLAS™)



1) *Human immune response profiling*

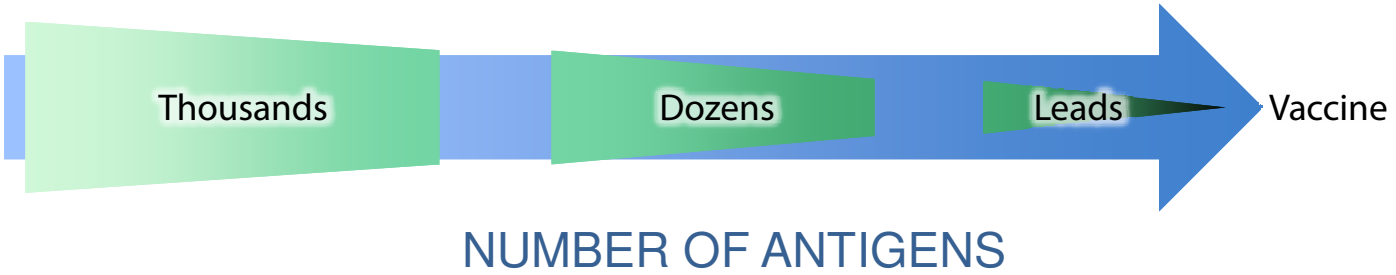


2) *High throughput screening*



3) in silico *validation*

4) in vivo *validation*



Human Immune Response Profiling

Define disease cohorts → Recruit subjects, Collect PBMCs → Output

Effective Immune Response

Ineffective Immune Response

Deleterious or Negative Sequellae

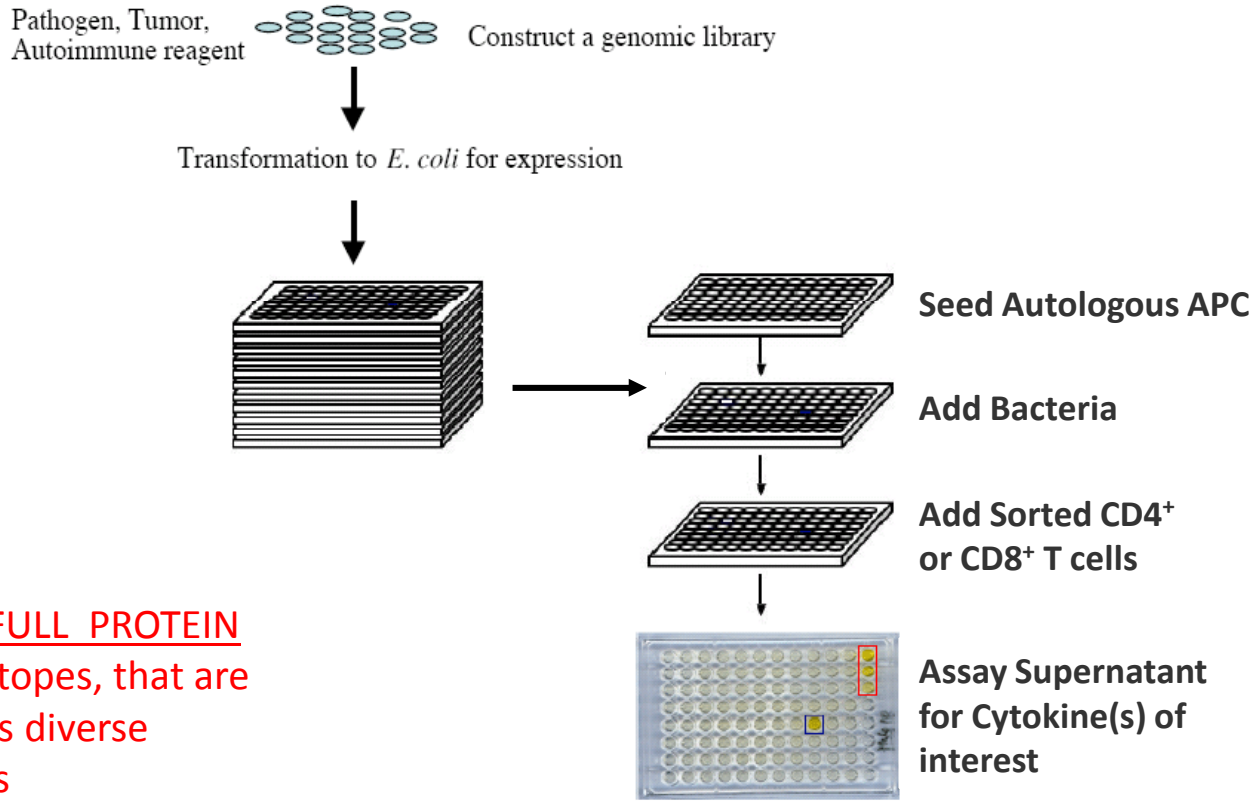
Key Considerations

- HLA diversity
- Age
- Gender
- Cohort size needed for statistical power

Clinical basis for identifying immune response differences

ATLAS™ Workflow

- High-throughput protein screening of any disease-causing agent to identify protective T cell antigens* for effective vaccines



*ATLAS™ discovers FULL PROTEIN ANTIGENS, not epitopes, that are broadly seen across diverse human populations

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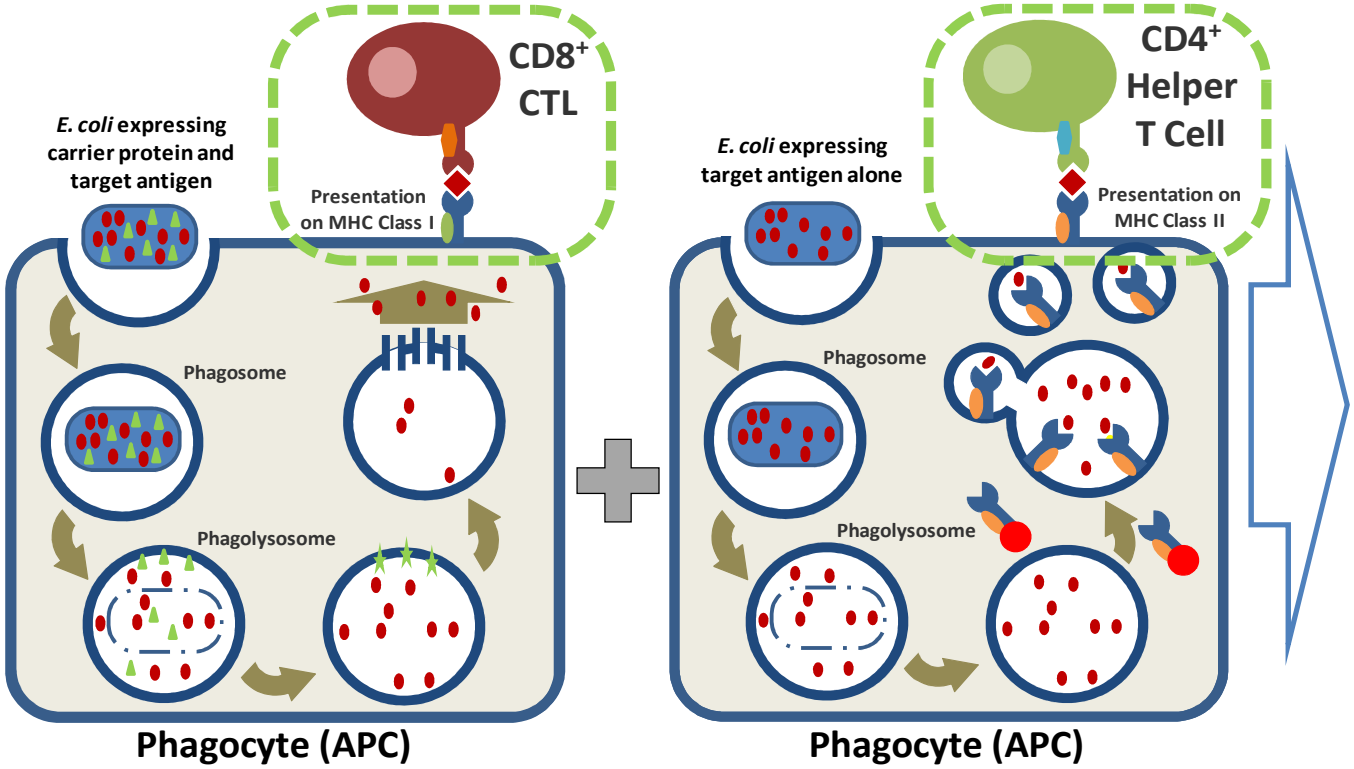
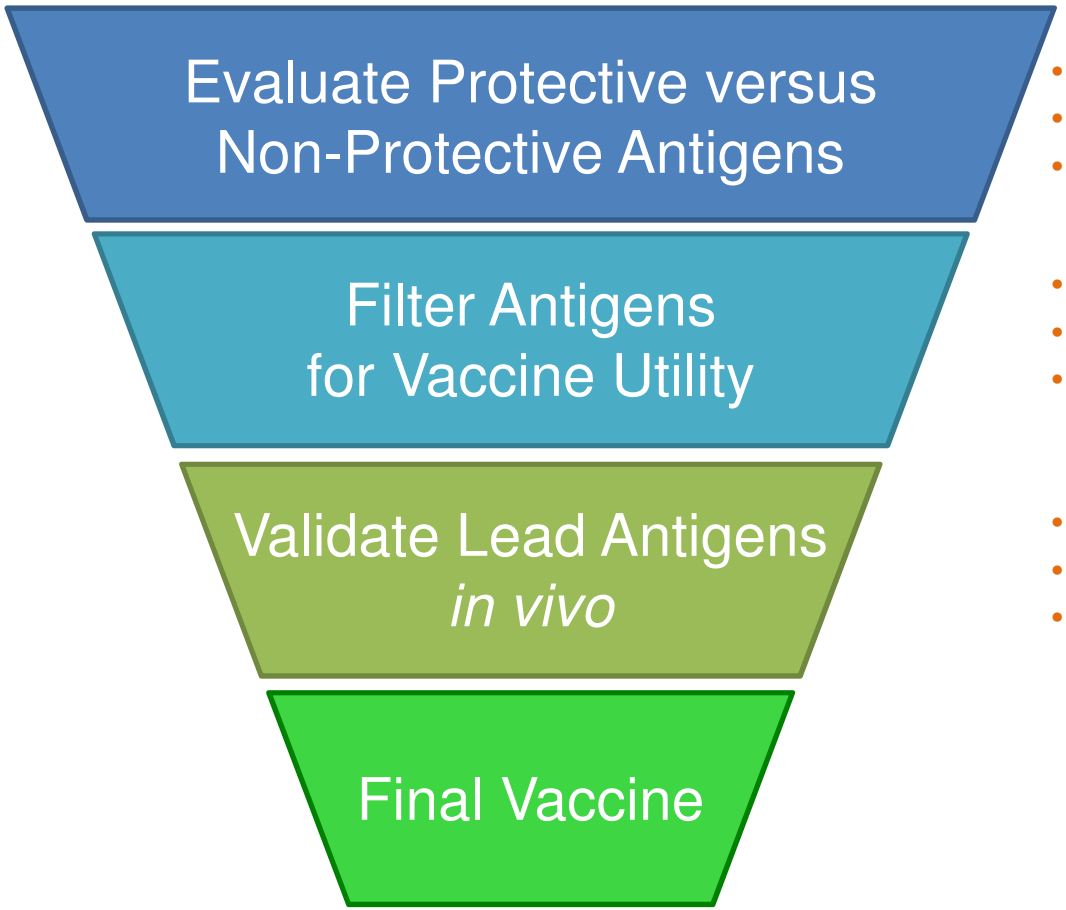
High-Throughput Screening

Screen pathogen proteome through each patient's APCs → Output



CD4+ and CD8+ response per antigen, per subject

in silico and *in vivo* Validation



- Frequency
- Magnitude
- Phenotype

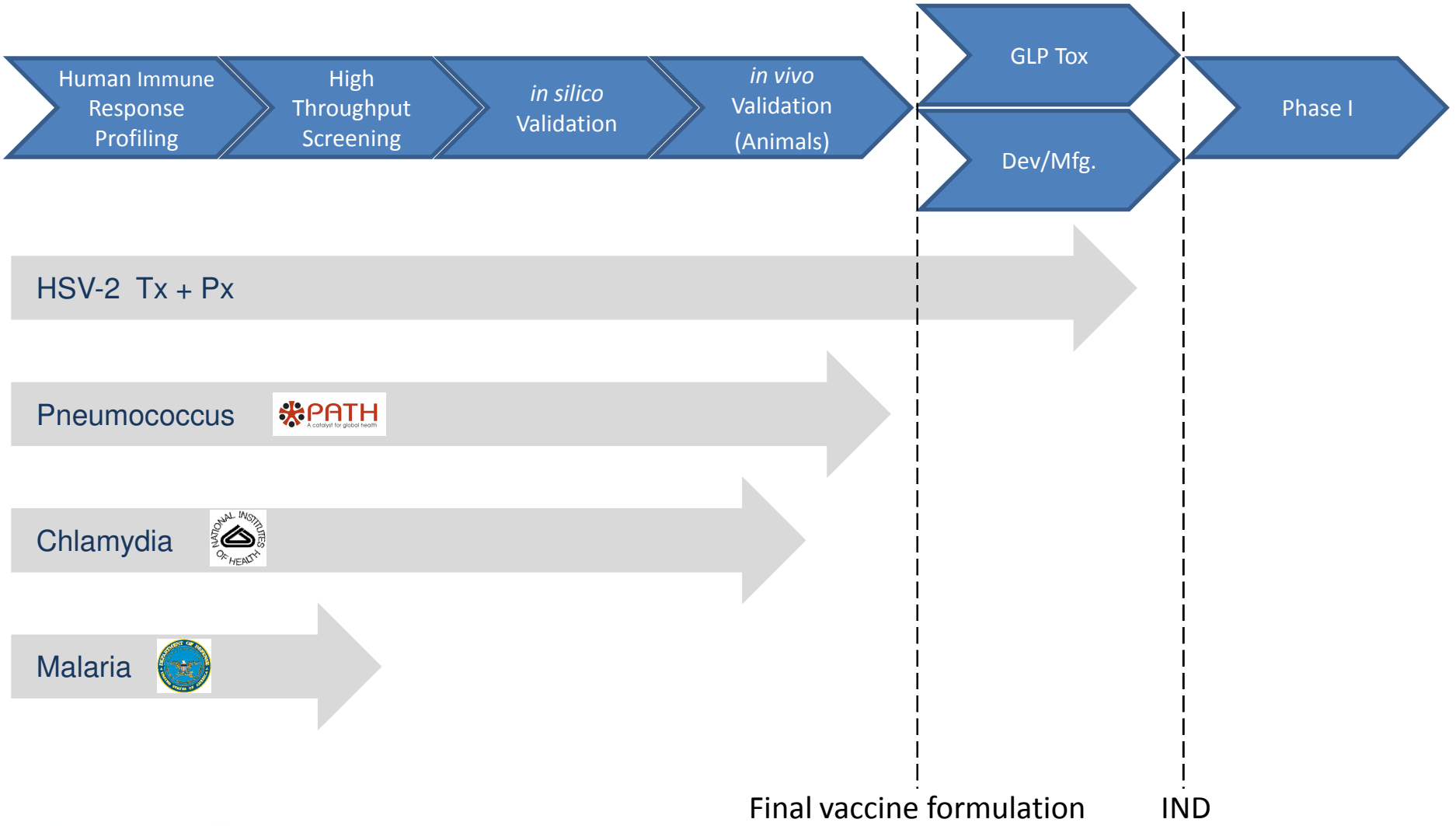
- Low homology to self & commensal organisms
- High homology across strains/species of pathogen
- Ability to produce recombinantly

- Established animal models
- Proof of mechanism
- Proof of concept

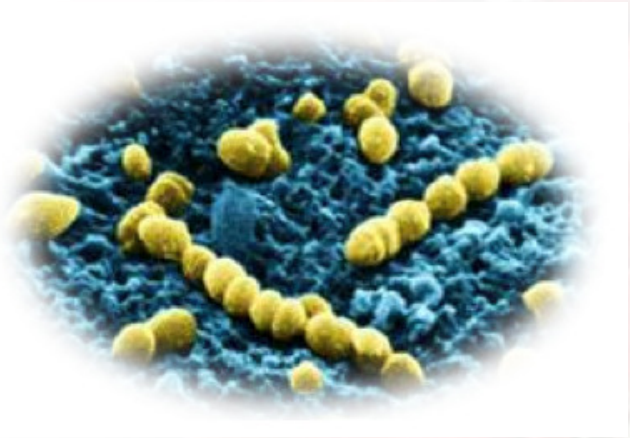
ATLAS™ Advantages

- Comprehensive
  - Full pathogen proteome
  - Broad population coverage
- Validated
  - Antigens discovered in the context of natural human protection
  - Protective antigens discovered in each disease attempted
- Broadly Applicable
  - Multiple pathogen types and proteome sizes
  - Potential applicability outside infectious disease
- Fast
  - Time to first protective antigen discovery < 2 years

The Genocea Pipeline



Streptococcus pneumoniae Vaccine



Next Generation Pneumococcal Vaccine: The Needs

1. Expand serotype coverage; avoid replacement

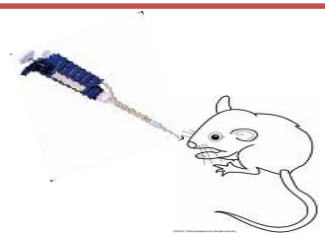
2. Increase and broaden efficacy at mucosal level
   a. Otitis media
   b. Colonization
   c. Indirect immunity

3. Improve efficacy for pneumococcal pneumonia in elderly

4. Simpler and lower cost to manufacture → increase supply and global access

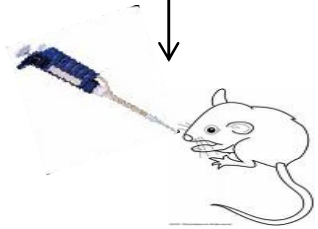
5. Back-up, if PCVs are poorly effective, e.g. type 3

T cells Prevent Nasopharyngeal Colonization of *S. pneumoniae*

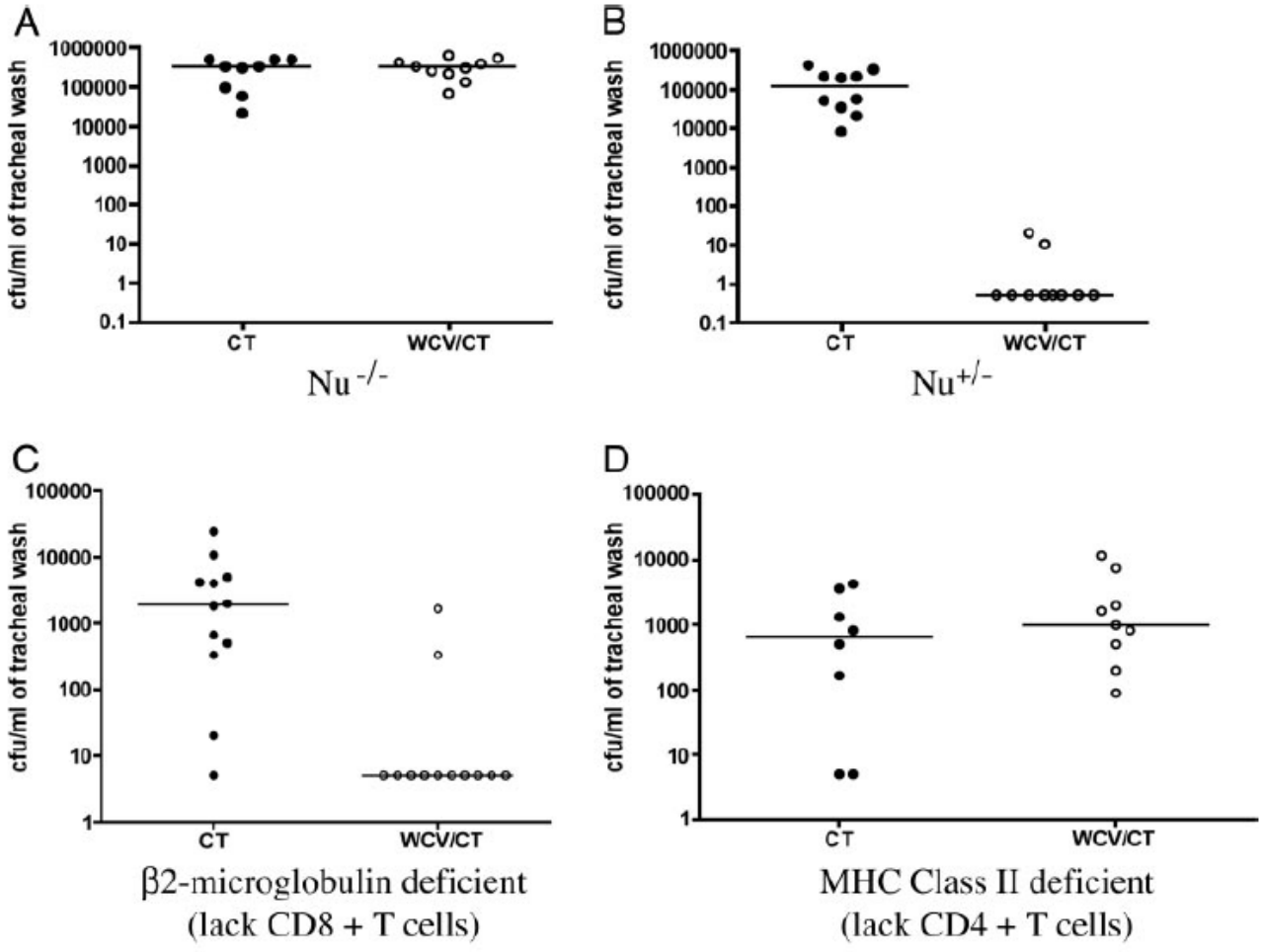


Immunize mice i.n. with unencapsulated, killed *S. pneumoniae* (WCV) plus CT

10 wks



Challenge i.n. with live, encapsulated *S. pneumoniae*



Malley *et al.*, (2005) PNAS 102:13

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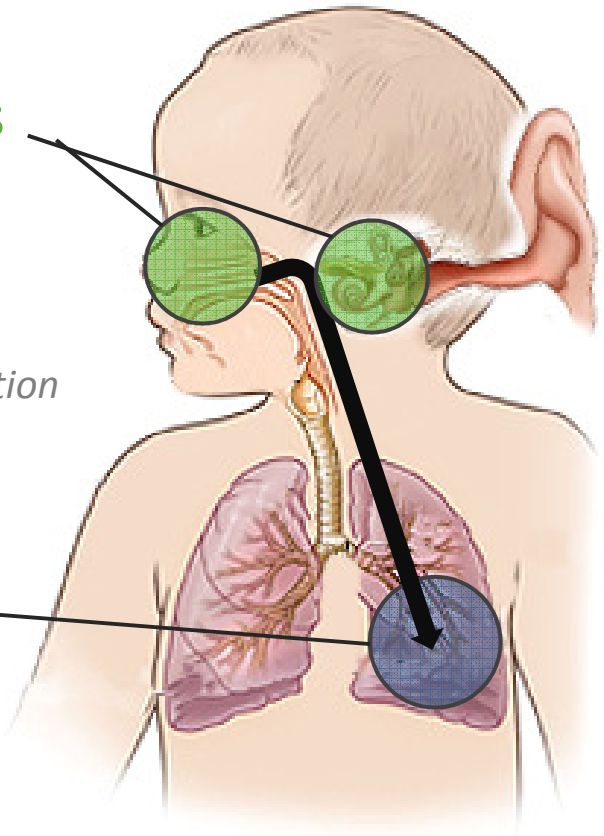
Genocea Can Identify Antigens That Induce IL-17A After Natural Exposure

Locus/ Mechanism of Action

Genocea Antigens
(T_H17 $CD4^+$ T cell-mediated)

- *Conserved*
- *Protect against colonization*

PCVs and PPSVs (antibody-mediated)



Consequences of Pneumococcal Disease

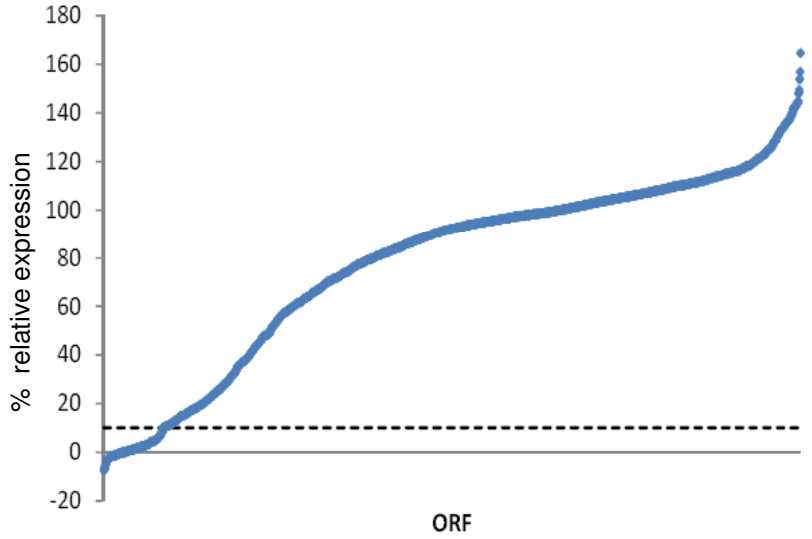
- Nasopharyngeal colonization
- Otitis media

- Pneumonia
- Bacteremia
- Meningitis

http://www.ohiohealth.com/
http://www.childrenscentralcal.org/HealthE/P02948/Pages/P02950.aspx

Built a Pneumococcal Expression Library That Covers 96% of Proteome

- Expression library constructed containing >99% of the predicted genes in pneumococcus (2,242 clones)
  - Base library provided by Pathogen Functional Genomic Resource Center (PFGRC)
- Full length protein expression detected for 96% of the proteome by assaying for an epitope tag on the C-terminus of each clone



% relative expression = response in the test sample divided by the response to the minimal epitope-pulsed positive control

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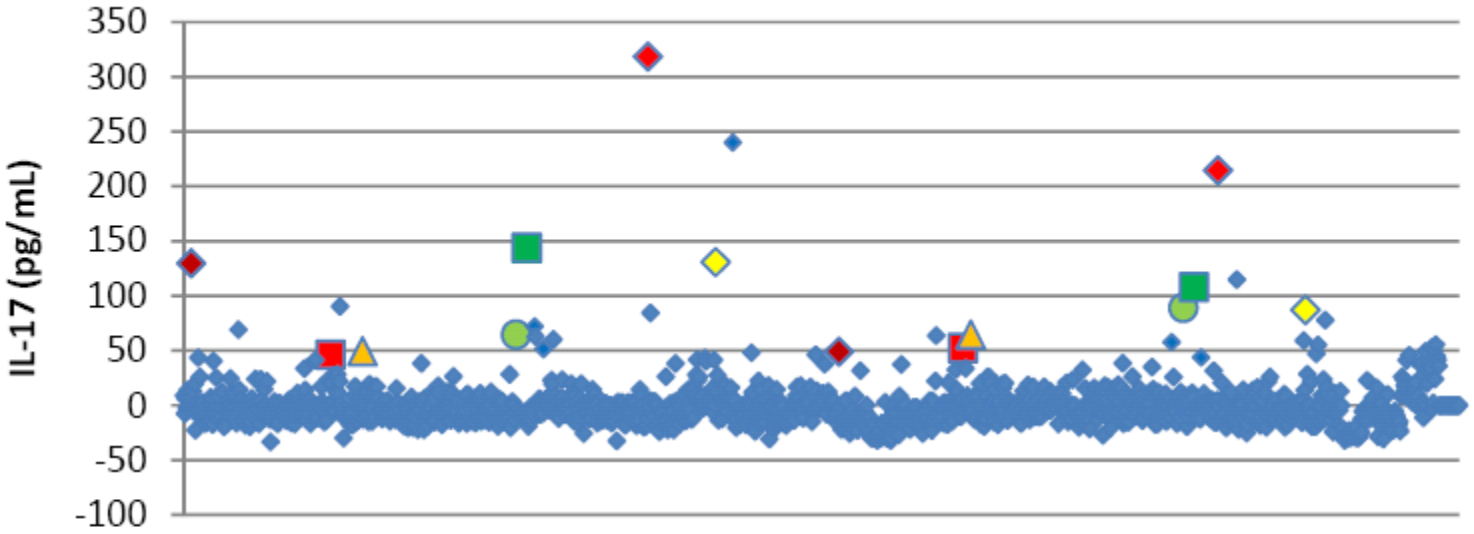
Pneumococcus T_H17 Antigen Discovery

- Screened full expression library with T cells derived from:
  - WCV-immunized mice
  - Healthy adult human donors
- Developed method for enriching Pneumococcus-specific T_H17 cells from human peripheral blood
- Developed a robust pooling strategy to limit number of required human cells
- Identified antigens by measuring specific IL-17A secretion from $CD4^+$ T cells

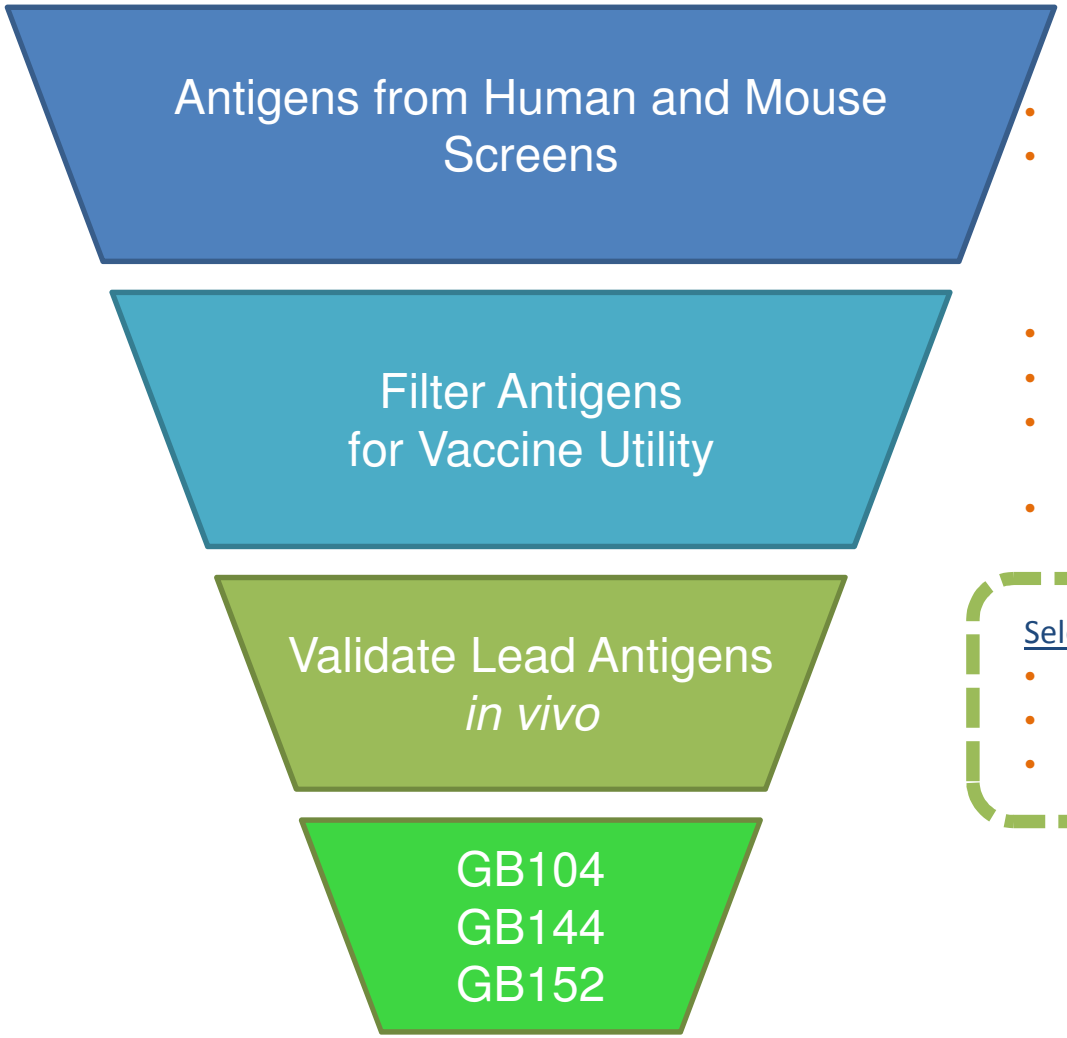
Dual pooled screening method enables screening of large proteomes



Pools with the same colored symbol contain the same library clone

- Each clone present in two unique pools of four clones in the library
- Both pools must be above the threshold for a positive response
- Reduces the number of human cells needed for the screen
- Increases the statistical power of each screen

Hit to Lead Selection Approach for Pneumococcus Antigens



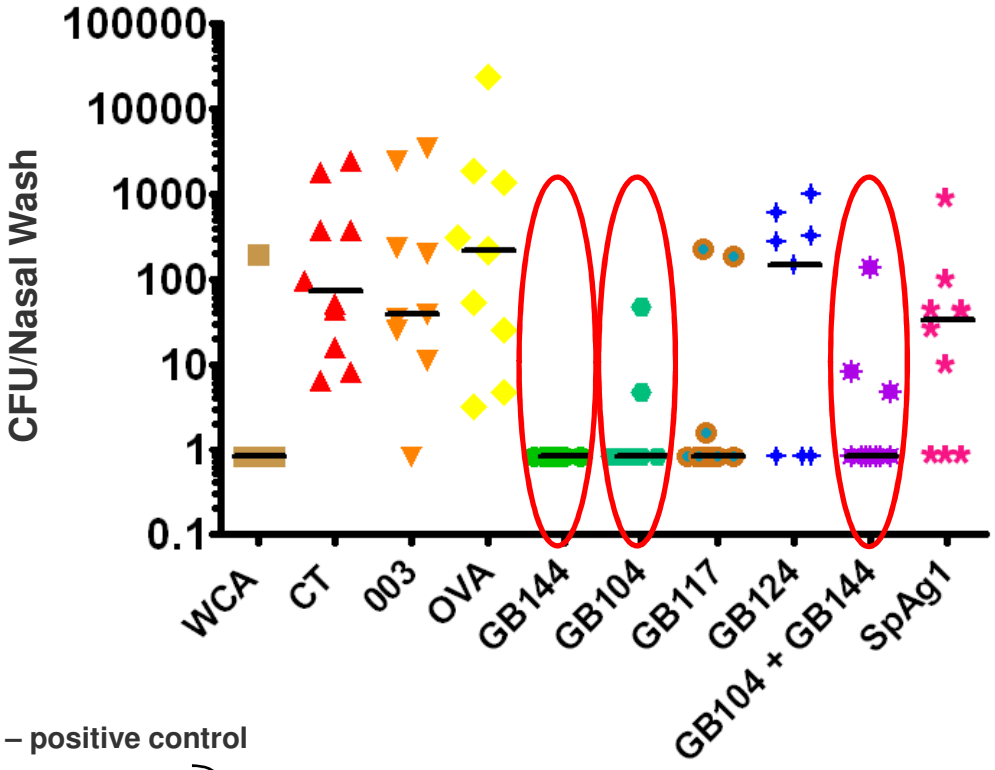
- Frequency
- Phenotype

- Low homology to self antigens
- < 30% seq. identity to sequenced gut flora
- > 95% seq. identity among sequenced SPN strains
- Ability to recombinantly produce antigen

Select priority antigens based on:

- Ability to induce T_H17 in mice
- Ability to protect in colonization models
- Ability to protect in sepsis models

Lead Antigens Demonstrate Protection & Prevent Colonization



WCA = whole cell vaccine – positive control
CT = adjuvant alone
003 = irrelevant HIS-tagged antigen
OVA = irrelevant antigen
} negative controls

SPAg1 in an antigen chosen from the literature that was NOT identified as an antigen in Genocea library screens

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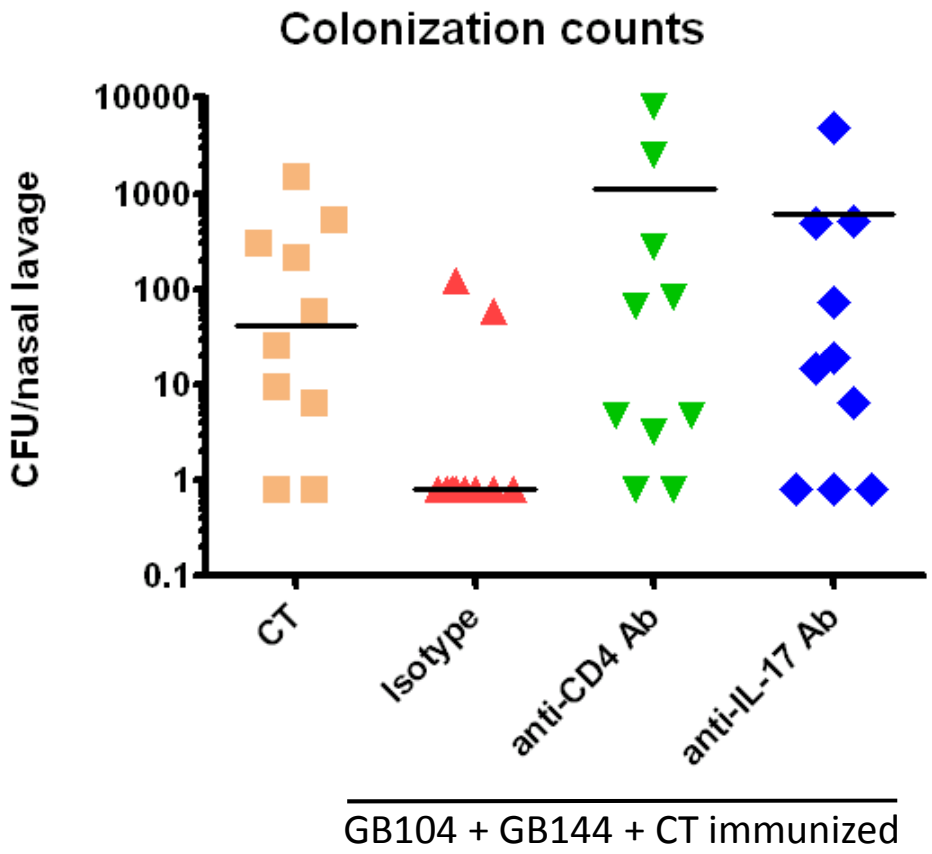
IL-17 and CD4+ T cells are essential for protection

- Mice immunized with a combination of GB104, GB144 and CT
- Anti-CD4, anti-IL-17 or isotype control antibodies administered prior to challenge
- CD4 depletion or neutralization of IL-17 abrogates immunity to colonization



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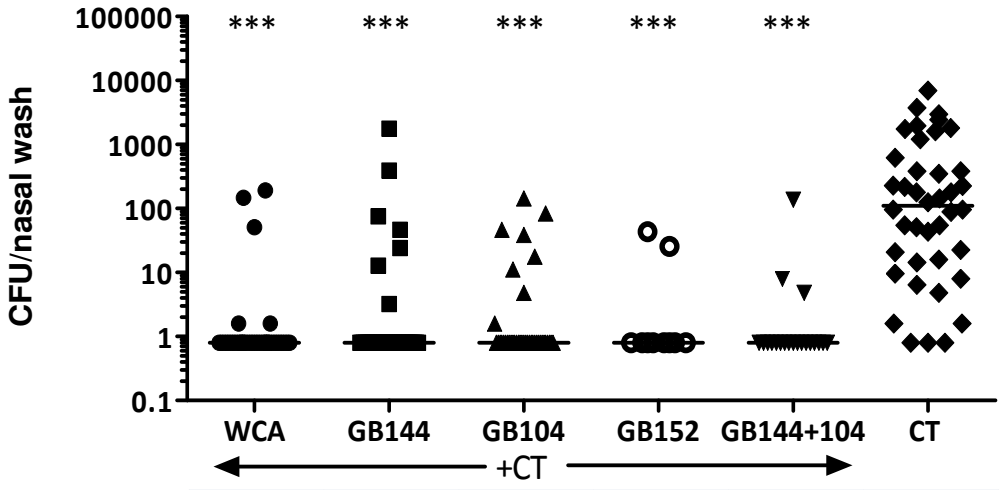
Top Antigens – Nomination Based on i.n. Vaccination Data

- Antigens were first chosen based on human and mouse screening data
- Final vaccine candidates nominated after repeatable protection in colonization model after i.n. administration with CT
- Goal is parenteral administration – alum chosen:
  - Induced systemic IL-17A
  - Induced robust IgG



Percent of mice protected from colonization

2 i.n. immunizations, 2 weeks apart; studies 857, 870, 901, 912

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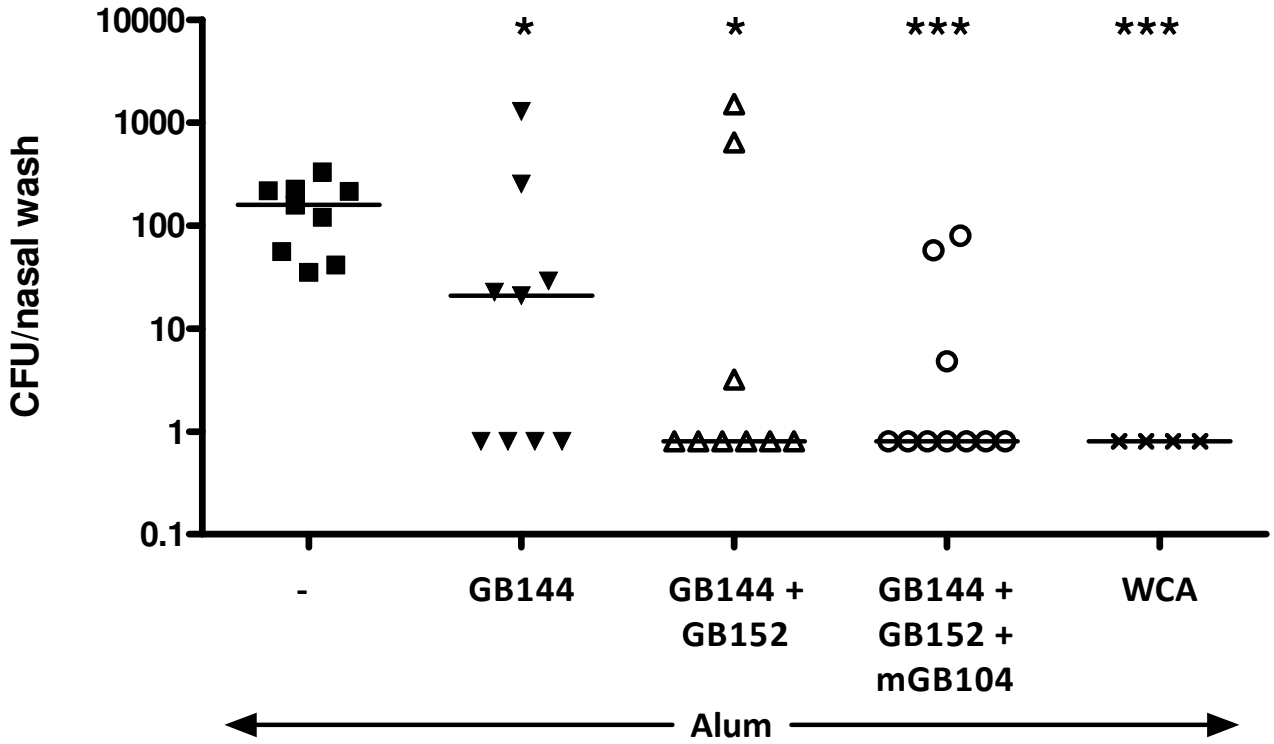
Antigen Combination with Alum Protects against Colonization



- Results
  - GB144 alone was protective against colonization with 45% efficacy
  - Trivalent formulation showed maximum efficacy

*p<0.05; ***p<0.005

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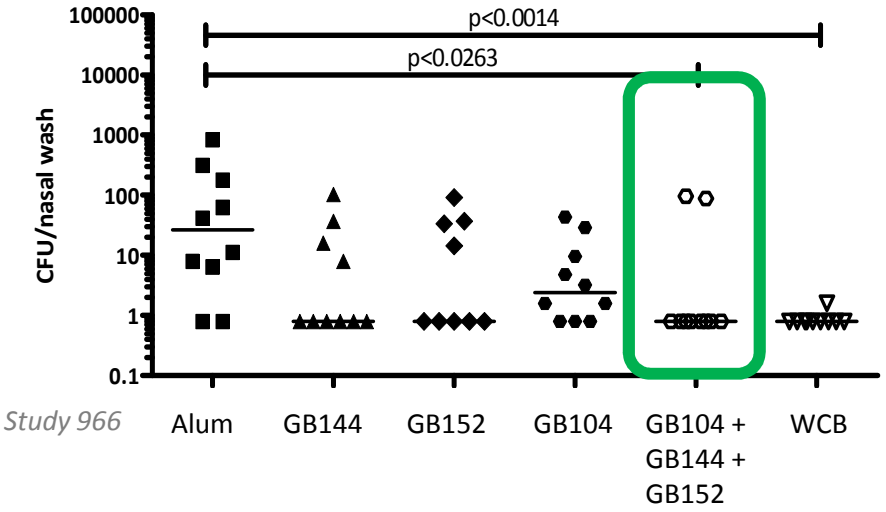
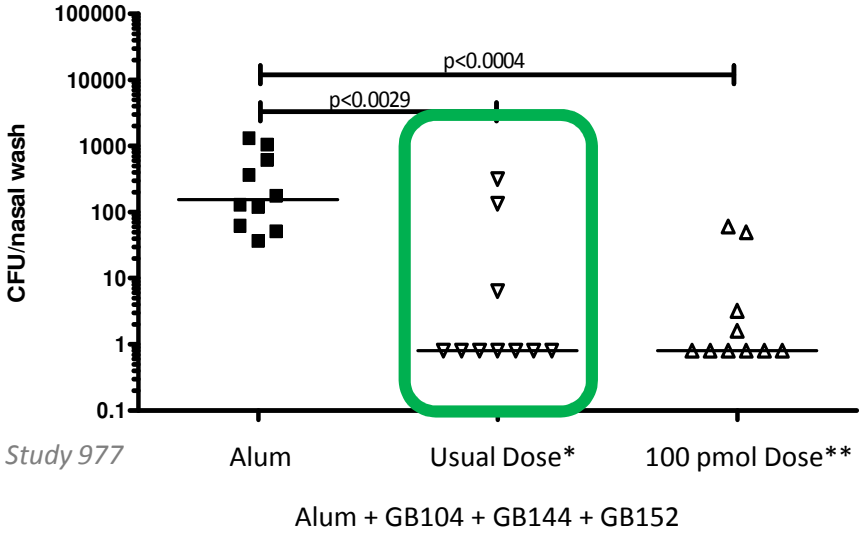
Triple Combination Results Repeated in Several Studies





Alum + GB104 + GB144 + GB152

Study	Median Alum CFU	Median Test Group CFU	Log Reduction	% Protected
957	71.3	0.8	2.0	89
966	26.5	0.8	1.5	80
967	20.0	0.8	1.4	60
972	38.5	0.8	1.7	80
973	74.5	2.4	1.5	40
977	153.9	0.8	2.3	70
977 (low dose)	153.9	0.8	2.3	60

** Usual Dose: 1µg GB144, 10µg each GB104 & GB152*

*** 100pmol: 2µg GB144, 3µg GB104, 8µg GB152*

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Pre-clinical Development Summary

- Three novel antigens that are protective
  - Intranasally with cholera toxin
  - Parenterally with alum
- One antigen adsorbed to alum is protective against sepsis when administered parenterally (data not shown)
- Combination antigen studies are underway to
  - Demonstrate efficacy with optimal combination of antigens against IPD
  - Identify appropriate B cell antigens for possible inclusion in final formulation
  - Titrate appropriate doses of each antigen alone and in combination
- Protein characterization and purification methods are in development

Genocea Pneumococcus Vaccine is Unique

Features	Genocea Program	Potential Benefit
Proteins conserved across all sequenced variants	✓	• Protect against all Pneumococcus strains
Colonization protection	✓	• Work upstream of, or together with, existing vaccines
Sepsis protection	(✓)	• Protect like current vaccines
Works with approved adjuvant	✓	• Simpler regulatory path • Lower downstream costs
Intramuscular route of administration	✓	• Ease of administration

Acknowledgements

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