SLU ID, CVD, Collaborations & Novel T cell Vaccines

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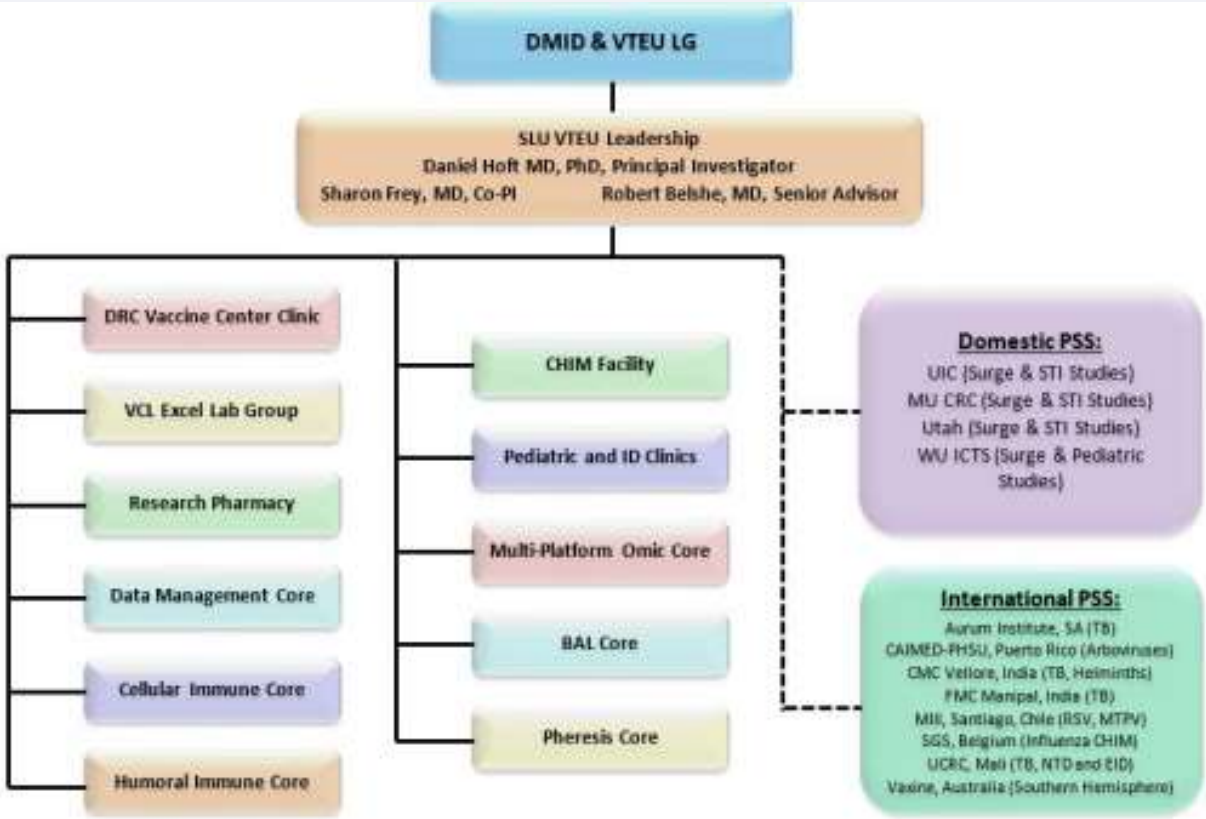
Funding from VTEU, NIH RO1s/R21s, DoD, Gates, Aeras & Industry awards

Overview of SLU CVD/VTEU

IDCRC
Infectious Diseases Clinical Research Consortium

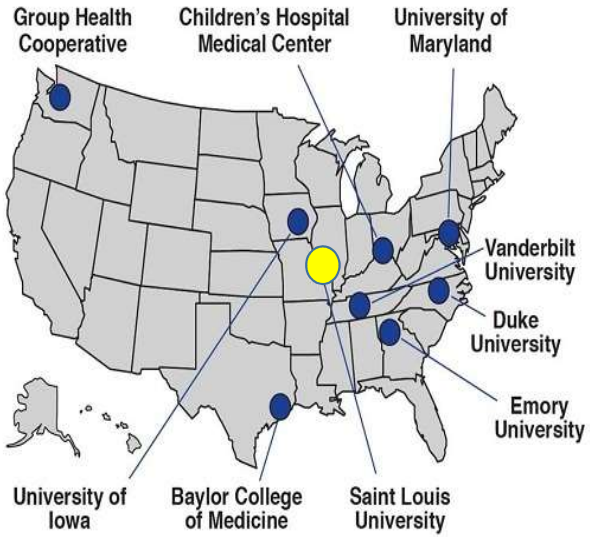
Doisy Research Center

- Vaccine Center Clinic – 1st floor
- Labs & offices – 8th floor
- BSL-3 labs – 8th, 7th & basement
- Challenge Center – walking distance



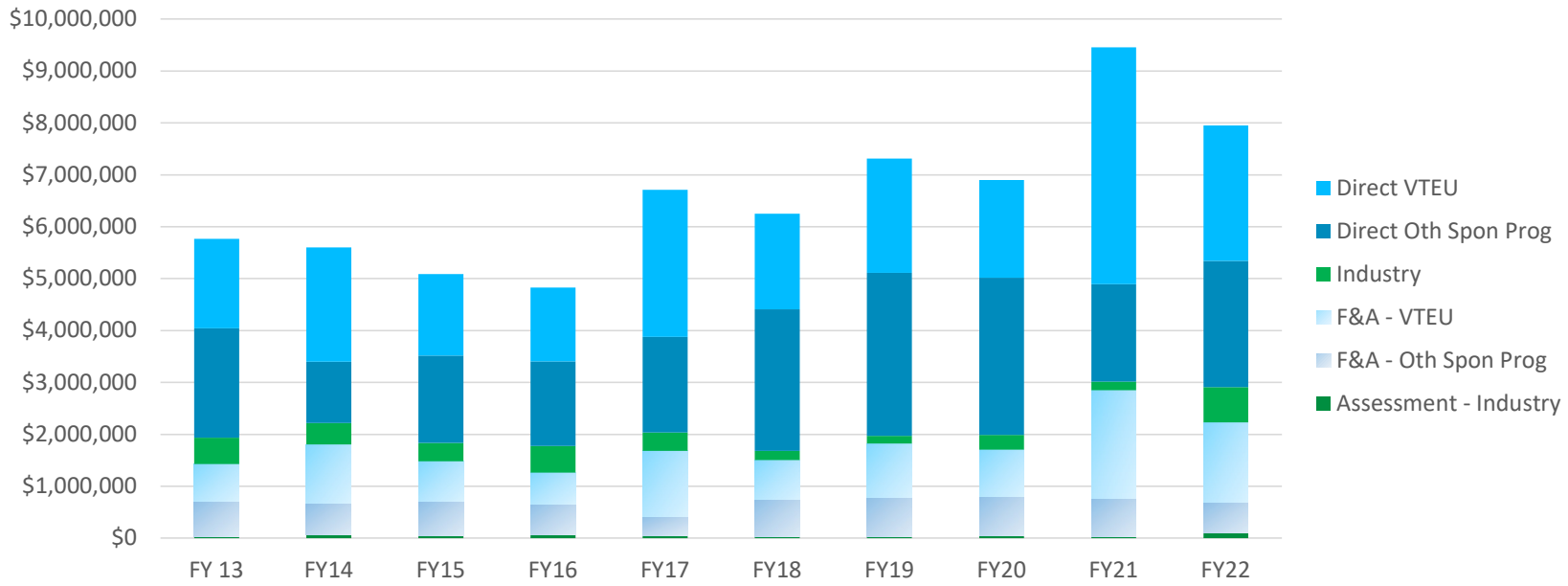
SLU Vaccine & Treatment Evaluation Unit (VTEU)

Hoft, PI; Frey, Co-PI, Belshe, Key Investigator



- SLU funded by NIH/DMID since 1989
- Funds non-HIV clinical vaccine development
- National Preparedness (Smallpox/Flu/Zika/COVID-19)

IDAI-Research Revenue Summary, By Fiscal Year:



- ~$150 million extramural funding awarded last 30 years
- VTEU renewed for 7 year cycle starting in late 2019
- ~$8-9 million annually in Fy21-22 related to CoV pandemic

Significant SLU CVD Accomplishments

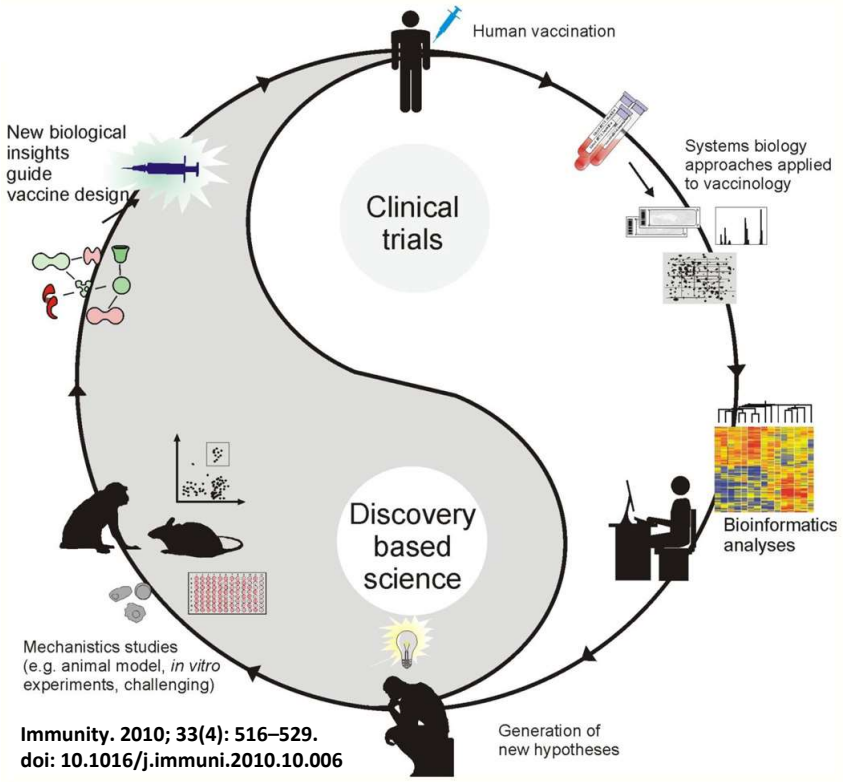
- Clinical development of FluMist (Belshe)
- Pandemic H5 vaccine national stockpile (Frey)
- 1st wave H7 vaccine national stockpile (Frey)
- Novel T cell targeting universal flu vaccines (Hoft)
- FIH next generation TB vaccines (Hoft, rBCG/rAd)
- Development $\gamma\delta$ T cell-targeting TB vaccines (Hoft)
- Mucosal BCG induces human sIgA/BAL T cells (Hoft)
- Dose-sparing vaccinia (smallpox) strategy (Frey)
- FIH Dengue/Yellow Fever vaccine (George)
- FIH Zika vaccine trials (ZPIV, George)

SLU CVD Contributions to Vaccine Licensure

- Flumist – LAIV vaccine
- Rotavirus vaccine
- Hepatitis A vaccine
- Pneumococcal vaccines
- *Hemophilus influenza* type B vaccines
- DTaP acellular pertussis vaccine
- Human Papilloma Virus/cervical cancer vaccine
- 2005 H5N1 pandemic vaccine national stockpile
- 2009 H1N1 pandemic vaccine
- 2013 H7N9 pandemic vaccine national stockpile

Systems Vaccinology Omic Work

(Transcriptomics, Proteomics, Lipidomics & Metabolomics)



Immunity. 2010; 33(4): 516–529.
doi: 10.1016/j.immuni.2010.10.006

- **VTEU Omic Core**
  - -Tularemia pilot
  - -Malaria Vaccine/CHMI
  - -HT transcriptomics (WU GTAC)
- **Investigator-initiated NIH**
  - -Murine Th1 vs Th17 cells
  - -hGzmA inhibition of Mtb
  - -Human PO vs ID BCG
  - -Human BCG challenges

CVD Pandemic Flu Vaccine Development

- Clinical Vaccine development

  -H5/N8 + ASO3 or MF59 (Frey site PI, DMID-15-0064)
  -H5/N8 CMI studies (Frey site PI, DMID-15-0066)
  -FluGen M2SR vaccine (Hoft PI, DMID-17-0012)

- Pre-clinical Vaccine Development

  -Multimeric-001/H7HA, stem Abs (Frey, DMID-14-0112)
  -H5 VN/IN prime/boost, stem Abs (Frey, DMID-16-0051)
  -Universal T cell based vaccine (Hoft, NIH/DoD funded)

- Development of Influenza Human Challenge Facility

  -SLU invested ~$400K in renovation of old hotel floor
  -Capacity for up to 23 subjects/airborne containment
  -Cooperative agreements/funding for specific trials pending

Molecular strategy to develop "universal[2]" T cell vaccines

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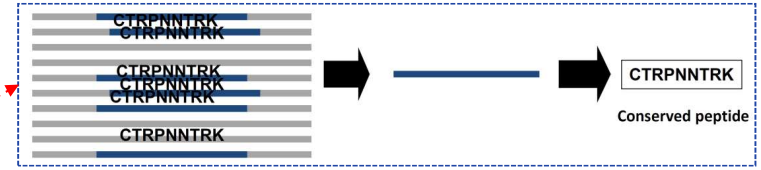
Identification of diverse influenza M1, M2, & NP sequences

Conservation analyses



Epitope prediction

Designed for population coverage
- Prediction for 6 class I supertypes
- Prediction of promiscuous DR-binders (8 common class II alleles)

Triage of human cross-reactive sequences

Eliminates sequences with high human homology

Epitope selection

Proof of Concept
- 31 conserved influenza HLA-A2 predicted epitopes
- 25 conserved influenza Pan-DR epitopes

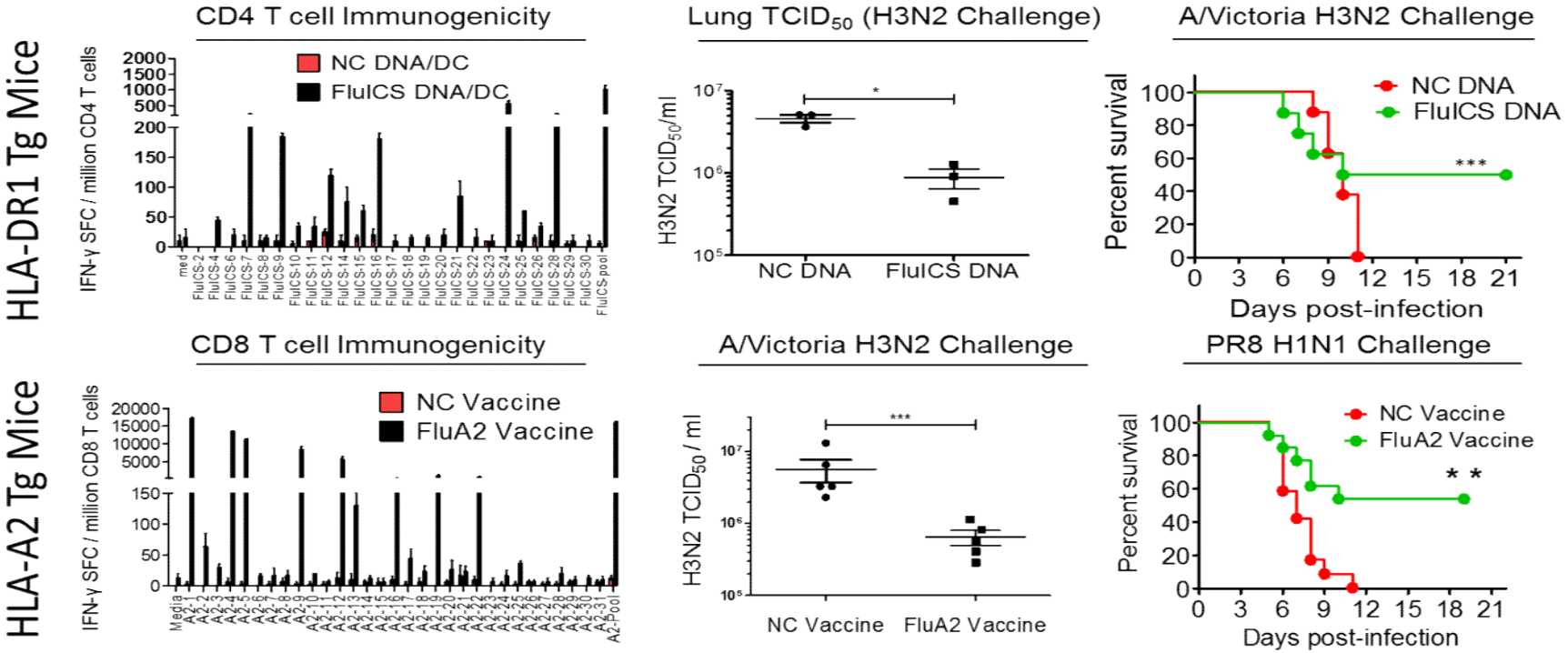
Vaccine design

String-of-beads DNA vaccines encoding predicted epitopes

Immunogenicity/Efficacy

Protection against H1N1 and H3N2

Proof of Concept Data



- Both CD4 & CD8 epitope vaccinations induced heterotypic protection against H1N1 & H3N2
- CD4 epitopes predicted to induce heterotypic protection in >95% of world's population
- CD8 epitopes predicted to induce heterotypic protection in ~50% of world's population

Eickhoff…Hoft, Vaccine, 2020

Progress & Potential Rapid Development Pathway

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Universal Influenza Vaccine Preclinical Development

Rapid PoC Testing in Human Volunteers at SLU Center for Vaccine Development

Preclinical Development → Clinical Development

EpiVax Immunoinformatics→ T cell-targeted vaccine

- New R01 awarded to Hoft Lab in 2020
- Confirm >95% population coverage of CD4 epitopes
- Identify CD8 epitopes for 5 other Class I supertypes
- Human PBMC confirmation of immunogenicity
- Develop optimal delivery systems (mRNA/VLP/rAd)
- Confirming induction of protection in HLA Tg mice

Interested in industry, government and academic partners to further pursue this **universal influenza vaccine strategy**

Clinical Vaccine Center & Human Influenza Challenge Unit

- VTEU for 30 years; Extensive phase I–III experience
- Increasing pre-clinical to clinical translation ~15 years
- SLU investment of ~$600,000 in challenge unit
- Upgraded HVAC system → aerosol containment
- Negative pressure / Double-door entrances
- Capacity for quarantine of 23 subjects at once

Interested in conducting **human influenza challenge studies** with government, industry, and foundation support

SLU Challenge Unit

CVD Tuberculosis Research

- Vaccine development

  -Mucosal BCG vaccination (DMID-01-351; Hoft)

  -Vaccines targeting γδ T cells (VTEU/Gates/R01s; Hoft)

  -Human BCG challenge model (DMID-11-0033; Hoft)

- TB drug development

  -Efflux pump inhibitors (Abate/CWHM)

  -RNase H inhibitors (Abate/Tavis/CWHM)

- Epidemiology, Natural history & LTBI Tx

  -Retrospective NTM studies (Abate/DMID-16-0037)

$\gamma_9\delta_2$ T cell Relevance for Human TB Immunity

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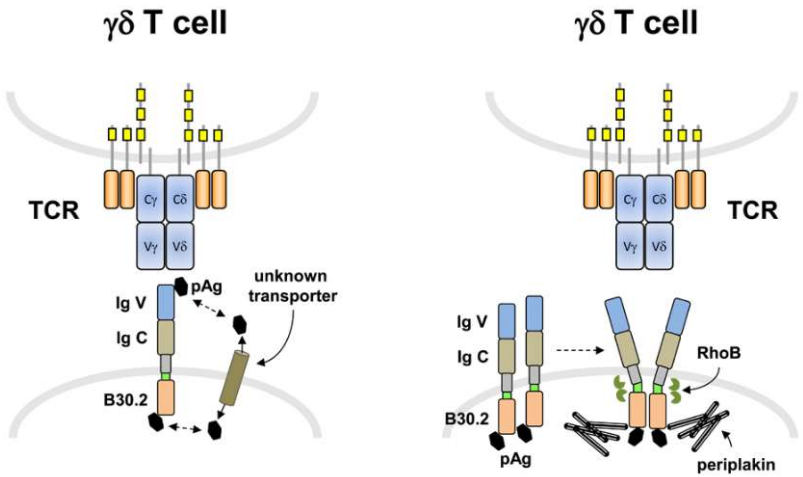
- Accumulate in infected lung mucosa
- Develop memory effector responses
- Restricted by BTN3A1 not MHC (DURT)
- Activated by lipids & phosphoAg
- Potent inhibition of intracellular Mtb
- No homologue in the mouse model



γδ T cells Produce GzmA Key for Inhibiting Mtb

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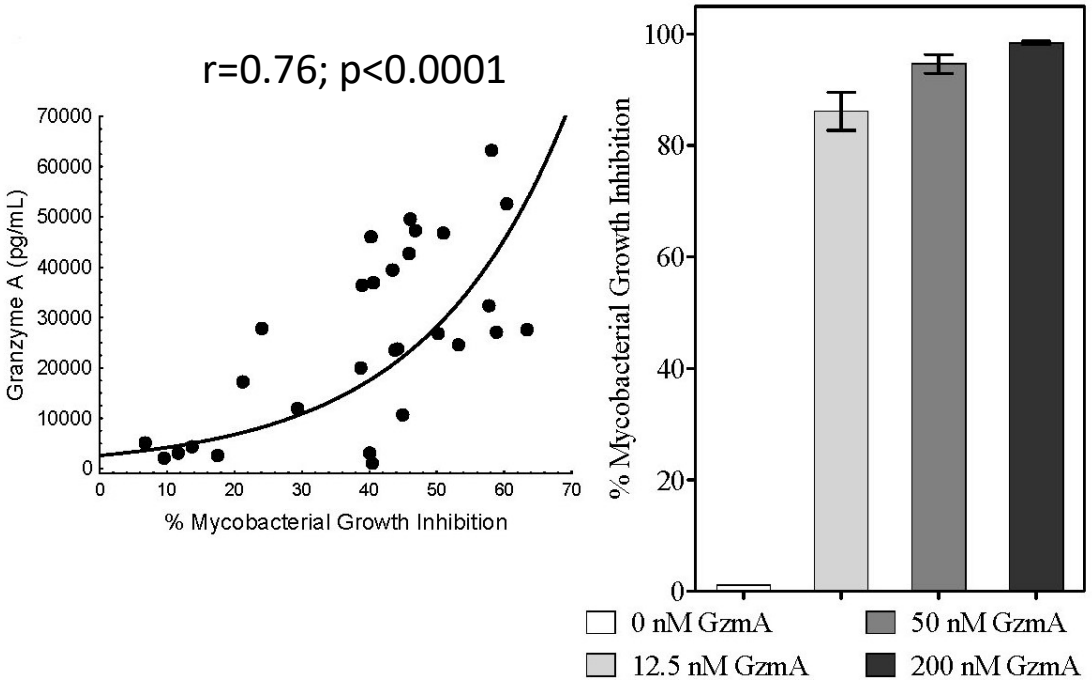
- γδ T cell GzmA production highly correlated with inhibitory effect
- Highly purified GzmA alone induces BCG intracellular inhibition
- GzmA knockdown reverses γδ T cell protective effects (not shown)



Spencer et al, PloS Pathogens, 2013

Mtb Methyl Glucose Lipopolysaccharides (mGLP) Induce Mtb-Inhibitory $\gamma_9\delta_2$ T cells

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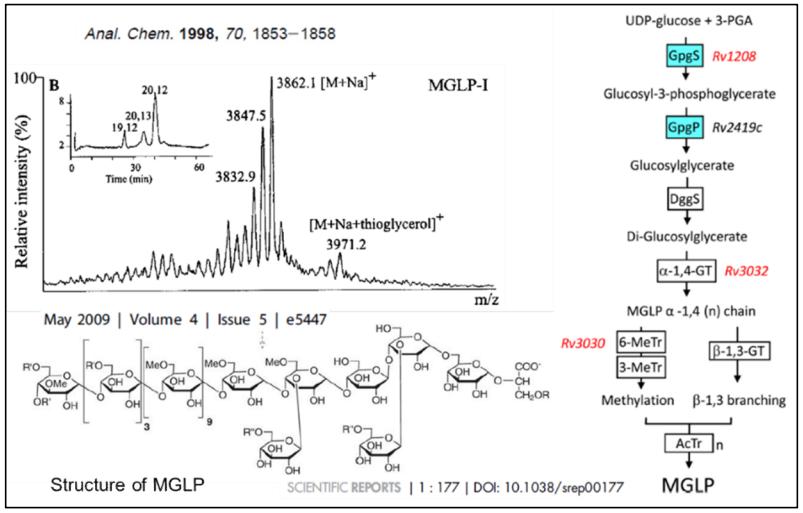
AMERICAN SOCIETY FOR MICROBIOLOGY | Infection and Immunity

A Subset of Protective $\gamma_9\delta_2$ T Cells Is Activated by Novel Mycobacterial Glycolipid Components

Mei Xia,[a] Danny C. Hesser,[b] Prithwiraj De,[b] Isaac G. Sakala,[a*] Charles T. Spencer,[a*] Jay S. Kirkwood,[c] Getahun Abate,[a] Delphi Chatterjee,[b] Karen M. Dobos,[b] Daniel F. Hoft[a]

Division of Infectious Diseases, Allergy & Immunology, Edward A. Doisy Research Center, Saint Louis University School of Medicine, St. Louis, Missouri, USA[a]; Department of Microbiology, Immunology, and Pathology, Colorado State University, Fort Collins, Colorado, USA[b]; Proteomics and Metabolomics Facility, Colorado State University, Fort Collins, Colorado, USA[c]

IAI, 2016



Structural determinants in a glucose-containing lipopolysaccharide from *Mycobacterium tuberculosis* critical for inducing a subset of protective T cells

Prithwiraj De[1], Michael McNeil[2], Mei Xia[3], Claudia M. Boot[1], Danny C. Hesser[1], Karolien Denef[1], Christopher Rithner[1], Tyler Sours[1], Karen M. Dobos[4], Daniel Hoft[3] and Delphi Chatterjee[2*]

JBC, 2018

- Acylations of saccharides required for biologic activity
- Acylated glucosyl residues on nonreducing terminus required

γδ T cell Targeting Vaccine Translational Development

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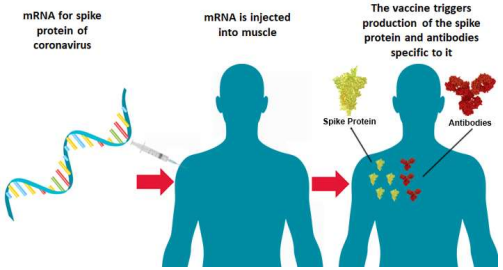
- Conduct NHP mGLP vaccination & challenge experiments
- Development of synthesis pathway for active mGLP core
- Development of novel adjuvants for γδ T cell vaccines
- Basic molecular detail of how mGLP activates γδ T cells
- GMP production, phase I testing, immunization/BCG challenge

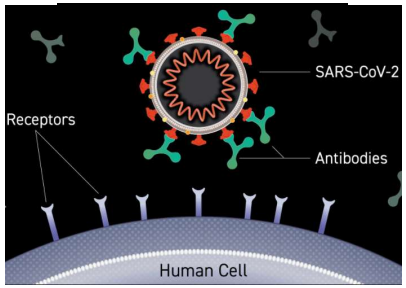
COVID Prevention Network (CoVPN)

- Mega-network combining VTEU, HPTN & HVTN (~50 sites)
- Phase 3 COVID-19 vaccine trials & mAb treatment trials
- Greater than 90 sites involved in each phase 3
- Required >60% efficacy (lower limit CI >30%)
- Enriched for exposure and disease severity risks (25-40%)
- 30,000 volunteers/trial randomized/blinded 1:1
- Unprecedented Private-Public collaboration

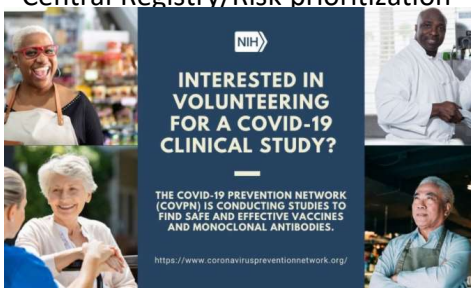
Vaccines



Monoclonal Antibodies



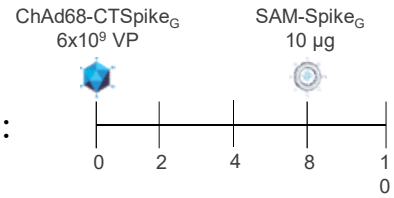
Central Registry/Risk prioritization



Vaccine Booster Concepts to Enhance COVID-19 Immunity

- Give 3rd/4th doses of EUA vaccine to increase nAb titers
- Bivalent boosters with updated Omicron spike sequence(s)
- Heterologous vector prime/boosts (eg-rAd/mRNA & IM/IN)
- Boost with vaccines designed to induce broader T cell immunity

DMID-20-0034Gritstone Phase 1:



Now boosting EUA immunity at SLU CVD
(slu.vaccine.edu; call 14-977-6333)

- Hoft Lab working on universal pathogenic CoV T cell vaccines

Conclusions & Future Work

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- Academia, government & industry collaborations key
- Novel T cell targeting vaccine strategies are being developed
- May allow enhanced protection against intracellular pathogens
- Molecular approaches can generate universal vaccine strategies
- Targeting DURT cells also has significant potential
- Need further collaborative research to capitalize on this potential

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The SLU Center for Vaccine Development is actively recruiting for physician scientists and a computational biology leader.