

APPLICATION FOR FEDERAL ASSISTANCE  
**SF 424 (R&R)**

		<b>3. DATE RECEIVED BY STATE</b>	<b>State Application Identifier</b>
<b>1. TYPE OF SUBMISSION*</b>		<b>4.a. Federal Identifier</b>	
<input type="radio"/> Pre-application	<input checked="" type="radio"/> Application	<input type="radio"/> Changed/Corrected Application	<b>b. Agency Routing Number</b>
<b>2. DATE SUBMITTED</b>	<b>Application Identifier</b>	<b>c. Previous Grants.gov Tracking Number</b>	
<b>5. APPLICANT INFORMATION</b>		<b>Organizational DUNS*</b> : 004315578	
Legal Name*: University of Georgia Research Foundation Inc.			
Department:			
Division:			
Street1*:	310 East Campus Rd Tucker Hall Room 409		
Street2:			
City*:	Athens		
County:	GA: Georgia		
State*:	GA: Georgia		
Province:			
Country*:	USA: UNITED STATES		
ZIP / Postal Code*:	603020000		
Person to be contacted on matters involving this application			
Prefix:	First Name*: x	Middle Name:	Last Name*: x
Position/Title:	Grants & Contracts Parapro/Pro		
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City*:	Athens		
County:			
State*:	GA: Georgia		
Province:			
Country*:	USA: UNITED STATES		
ZIP / Postal Code*:	306021589		
Phone Number*:	706-542-5946	Fax Number:	Email: hlc19738@uga.edu
<b>6. EMPLOYER IDENTIFICATION NUMBER (EIN) or (TIN)*</b>		581353149	
<b>7. TYPE OF APPLICANT*</b>		M: Nonprofit with 501C3 IRS Status (Other than Institution of Higher Education)	
Other (Specify):			
Small Business Organization Type		<input type="radio"/> Women Owned	<input type="radio"/> Socially and Economically Disadvantaged
<b>8. TYPE OF APPLICATION*</b>		If Revision, mark appropriate box(es).	
<input checked="" type="radio"/> New	<input type="radio"/> Resubmission	<input type="radio"/> A. Increase Award	<input type="radio"/> B. Decrease Award
<input type="radio"/> Renewal	<input type="radio"/> Continuation	<input type="radio"/> C. Increase Duration	<input type="radio"/> D. Decrease Duration
	<input type="radio"/> Revision	<input type="radio"/> E. Other (specify):	
Is this application being submitted to other agencies?*		<input type="radio"/> Yes	<input checked="" type="radio"/> No
What other Agencies?			
<b>9. NAME OF FEDERAL AGENCY*</b> National Institutes of Health		<b>10. CATALOG OF FEDERAL DOMESTIC ASSISTANCE NUMBER</b> TITLE:	
<b>11. DESCRIPTIVE TITLE OF APPLICANT'S PROJECT*</b> Computationally Optimized Dose for Influenza Vaccines (CODIV)			
<b>12. PROPOSED PROJECT</b> Start Date* 04/01/2022		<b>13. CONGRESSIONAL DISTRICTS OF APPLICANT</b> Ending Date* 03/31/2027 GA-010	

**14. PROJECT DIRECTOR/PRINCIPAL INVESTIGATOR CONTACT INFORMATION**

Prefix: First Name\*: Andreas Middle Name: Last Name\*: Handel Suffix:  
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 State\*: GA: Georgia  
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 Country\*: USA: UNITED STATES  
 ZIP / Postal Code\*: 306020000  
 Phone Number\*: 706-542-7480 Fax Number: Email\*: ahandel@uga.edu

**15. ESTIMATED PROJECT FUNDING**

a. Total Federal Funds Requested*	\$3,741,694.00
b. Total Non-Federal Funds*	\$0.00
c. Total Federal & Non-Federal Funds*	\$3,741,694.00
d. Estimated Program Income*	\$0.00

**16. IS APPLICATION SUBJECT TO REVIEW BY STATE EXECUTIVE ORDER 12372 PROCESS?\***

- a. YES  THIS PREAPPLICATION/APPLICATION WAS MADE AVAILABLE TO THE STATE EXECUTIVE ORDER 12372 PROCESS FOR REVIEW ON:  
 DATE:
- b. NO  PROGRAM IS NOT COVERED BY E.O. 12372; OR  
 PROGRAM HAS NOT BEEN SELECTED BY STATE FOR REVIEW

**17. By signing this application, I certify (1) to the statements contained in the list of certifications\* and (2) that the statements herein are true, complete and accurate to the best of my knowledge. I also provide the required assurances \* and agree to comply with any resulting terms if I accept an award. I am aware that any false, fictitious, or fraudulent statements or claims may subject me to criminal, civil, or administrative penalties. (U.S. Code, Title 18, Section 1001)**

I agree\*

\* The list of certifications and assurances, or an Internet site where you may obtain this list, is contained in the announcement or agency specific instructions.

**18. SFLLL or OTHER EXPLANATORY DOCUMENTATION**

File Name:

**19. AUTHORIZED REPRESENTATIVE**

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 Position/Title\*: Grants & Contracts Parapro/Pro  
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**Signature of Authorized Representative\***

Erika.Schwabe

**Date Signed\***

06/04/2021

**20. PRE-APPLICATION** File Name:**21. COVER LETTER ATTACHMENT** File Name:

## 424 R&R and PHS-398 Specific

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## Project/Performance Site Location(s)

### Project/Performance Site Primary Location

I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: University of Georgia  
Duns Number: 619003127  
Street1\*: 310 East Campus Rd Tucker Hall Room 409  
Street2:  
City\*: Athens  
County:  
State\*: GA: Georgia  
Province:  
Country\*: USA: UNITED STATES  
Zip / Postal Code\*: 306021589  
Project/Performance Site Congressional District\*: GA-010

---

### Project/Performance Site Location 1

I am submitting an application as an individual, and not on behalf of a company, state, local or tribal government, academia, or other type of organization.

Organization Name: Emory University  
DUNS Number: 066469933  
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County:  
State\*: GA: Georgia  
Province:  
Country\*: USA: UNITED STATES  
Zip / Postal Code\*: 303220000  
Project/Performance Site Congressional District\*: GA-005

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### Additional Location(s)

File Name:

## RESEARCH & RELATED Other Project Information

**1. Are Human Subjects Involved?\***    Yes    No

1.a. If YES to Human Subjects

Is the Project Exempt from Federal regulations?    Yes    NoIf YES, check appropriate exemption number:   — 1 — 2 — 3 —  4 — 5 — 6 — 7 — 8If NO, is the IRB review Pending?    Yes    No

IRB Approval Date:

Human Subject Assurance Number   FWA0003901

**2. Are Vertebrate Animals Used?\***    Yes    No

2.a. If YES to Vertebrate Animals

Is the IACUC review Pending?    Yes    No

IACUC Approval Date:

Animal Welfare Assurance Number   A3437-01

**3. Is proprietary/privileged information included in the application?\***    Yes    No**4.a. Does this project have an actual or potential impact - positive or negative - on the environment?\***    Yes    No

4.b. If yes, please explain:

4.c. If this project has an actual or potential impact on the environment, has an exemption been authorized or an environmental assessment (EA) or environmental impact statement (EIS) been performed?

4.d. If yes, please explain:

**5. Is the research performance site designated, or eligible to be designated, as a historic place?\***    Yes    No

5.a. If yes, please explain:

**6. Does this project involve activities outside the United States or partnership with international collaborators?\***    Yes    No

6.a. If yes, identify countries:

6.b. Optional Explanation:

Filename

**7. Project Summary/Abstract\***   Project\_Summary.pdf**8. Project Narrative\***   Project\_Narrative.pdf**9. Bibliography & References Cited** References.pdf**10. Facilities & Other Resources**   Facilities.pdf**11. Equipment**

## PROJECT SUMMARY

Vaccination is a highly effective method of protection against viral infections. The inoculum dose, i.e., the amount of antigen or live attenuated pathogen that is used in the vaccine, is an important component of any vaccine. Currently, dose is chosen during pre-clinical, phase I and phase II stages of vaccine development, based on limited data and generally without consideration of host characteristics (e.g., sex or BMI). A more thorough approach to dose optimization could lead to improvements in vaccine efficacy, while minimizing side effects and maximizing vaccine availability.

Our long-term goal is to build a robust framework that combines data and models to predict the impact of dose for current and future vaccines and in specific host populations, and thus, allows dose optimization to become an integral part of the vaccine development process. Such a proposed framework is similar to the pharmacokinetics/pharmacodynamics (PK/PD) approach that is successfully used during drug development but is currently not applied to vaccines.

For this project, we will focus on influenza virus. For existing and especially future universal influenza virus vaccines, immune protection against vaccine strains and other circulating strains should be optimized, while also maximizing safety and availability. *We aim to develop, calibrate, and validate mechanistic computational models to explain the underlying processes and mechanisms by which dose impacts both strength and breadth of the antibody immune response following vaccination.* Our overall objective is to develop and test models that can be used to predict the impact of dose on immunogenicity for current and future influenza vaccines. We will accomplish our objective through three aims: **Aim 1:** Generate longitudinal immune response data from vaccination of ferrets using split-inactivated Fluzone influenza virus vaccine at several different dose levels and for different host characteristics (immunologically naïve, pre-immune, obese, aged). **Aim 2:** Build and fit models to data obtained in aim 1. Elucidate the processes and mechanisms by which dose impacts strength and breadth of the immune response, and how this differs based on host characteristics. Make predictions. **Aim 3:** Use data from a human influenza vaccine cohort to test model predictions. Further refine models. Determine model prediction successes and failures and use models to start informing dose choice during influenza vaccine development.

## **PROJECT NARRATIVE**

Currently, dosing for vaccines is determined based on limited data and generally without regard for host characteristics (e.g., sex, BMI). A more thorough approach to dose optimization could lead to improvements in vaccine efficacy, while minimizing side effects and maximizing vaccine availability. We will develop a framework that combines computational models with data to help optimize dose choice for current and future vaccines.

## **RESOURCES AND RESEARCH ENVIRONMENT**

### **The University of Georgia**

The University of Georgia (UGA), a land-grant and sea-grant university with state-wide commitments and responsibilities, is the state's flagship institution of higher education. The University of Georgia is classified as a Research I university based on its annual incoming external funding awards and the strength and diversity of its graduate degree programs.

On the university level, research support comes from the Office of the Vice President for Research (OVPR) at UGA. These include training, helping to locate funding, internal seed grants, and more. See (<http://www.ovpr.uga.edu/>) for more details.

#### **Handel and Shen groups**

Handel and Shen are both faculty members in the Department of Epidemiology and Biostatistics, College of Public Health at the University of Georgia. Resources available to them are as follows.

**Computing Resources:** The investigators have all-purpose computers as well as a high-performance workstations for their group. They have access to all software and licenses needed for this project. In addition, all investigators have access to the Georgia Advanced Computing Research Center (see below).

**Laboratory & Office:** The investigators have ample office space for themselves and their group members in Miller Hall, the home of the department of Epidemiology and Biostatistics.

**Libraries:** The University of Georgia libraries are well equipped with both physical and online access to all the books, journals, and other research tools needed to perform the work.

**Georgia Advanced Computing Research Center:** The Georgia Advanced Computing Research Center (GACRC) at UGA was established in late 2003 as a partnership between the Office of the Chief Information Officer (CIO) and the Office of the Vice President for Research (OVPR). The GACRC was founded, in large part, because it was apparent that the time and technical expertise required to manage high-performance computing and database platforms, software, storage, physical security, cyber security and telecommunications can be very significant. The GACRC has a fulltime staff of six Systems Administrators and Scientific Computing Consultants, specializing in Linux/UNIX system administration, storage administration, and scientific computing consultation. The primary computational resource is a 2600 compute-core Linux cluster which in addition to conventional compute nodes, has several large memory and GPU specific nodes. High-performance storage for the Linux cluster is provided for users' home directories and temporary scratch space.

The investigators have access to the vast majority of these resources. A multitude of standard scientific software packages, such as Matlab and R, as well as many compilers are installed on the GACRC computers. Ample storage space and backup solutions are also part of the GACRC infrastructure, ensuring that all data is stored safely. More details about the GACRC can be found at <http://gacrc.uga.edu>.

**Software:** The investigators have all the needed software required for the project, such as licenses to standard office software, statistical programs (e.g., SAS) and any other software needed.

### **Ross group**

Dr. Ross' laboratory occupies 3500 square feet of space in the new Center for Vaccines and Immunology (CVI) at the University of Georgia (UGA) and is housed in a newly renovated, 30,000 sq ft footprint in the building (formerly the Small Animal Research Hospital). The facility contains nine modular laboratory work spaces for the individual investigator groups (each module can accommodate 36 scientific staff members), conference rooms, a main lecture hall, dedicated space for core facilities, common laboratory resources space, an SPF vivarium, a BSL- 3 for both animal and non-animal research and administrative spaces.

Dr. Ross has a BSL-2+ tissue culture facility and a BSL2 tissue culture facility independent of his main laboratory. Also available at UGA are a central cold rooms, dark room, freezer rooms, common equipment rooms, glassware processing and autoclaving room. In addition, Dr. Ross has a BSL-3 tissue culture facility in the adjacent building, as well as the new BSL3 suites for animal husbandry. The laboratory is connected to a negative flow air ventilation system and is equipped for research for molecular biology (DNA, RNA, Protein) and tissue and bacterial culture. The main laboratories are fully equipped, including microfuges, RC5C high speed centrifuge, ELISA plate reader and washer, refrigerators, -20°C and -80°C freezers, CO<sub>2</sub> bacterial incubators, water baths, bacterial shakers, and a Helios gene gun system, ELISPOT reader, luminex, luminometer. The adjacent BSL2+ laboratory is equipped with 2-functional HEPA filtered tissue culture hoods, 4-CO<sub>2</sub> incubators, an inverted microscope, a microfuge, a Sorvall Legend RT refrigerated tabletop centrifuge and water baths. The CVI supports the operation of inverted and standard fluorescent microscopes a central warm room, dark room, glassware processing and autoclaving room.

### **Flow Cytometry Core:**

The UGA Flow cytometry core facility provides users with state of the art instrumentation and services. The principal assets of the core consist of 3 analytic instruments (two BD LSR II instruments and one BD FacsArray) and a premiere sorting instrument (FACS ARIA FUSION). The core also provides data analysis support and operates 4 Apple workstations with FacsDiva and FlowJo software.

### **Sorting Facility:**

The BD FACSARIA FUSION is a flexible and highly adaptable sorter. It contains four fixed-aligned, air-cooled lasers: red (640nm), yellow (561nm), blue (488nm) and violet (405nm). In its present configuration, the sorter is capable of evaluating fifteen parameters (forward and side scatter plus eleven fluorescent channels). The FACSARIA FUSION has an increased sensitivity and flexibility due to the octagon and trigon optical arrays. This instrument is equipped with temperature-controlled chambers and has the ability to sort single cells into 96- or 384-well plates. This instrument also has an aerosol management system to eliminate the emission of aerosols generated during operation. Further, the FACSARIA FUSION is designated for sorting of infected samples and will be operated by individuals wearing respirators to further decrease the potential for contact with infectious aerosols. In addition, the entire instrument is contained in a laminar flow biosafety cabinet that is certified annually. This instrument is operated by a qualified, designated operator and the instrument is pre-scheduled with the operator.

### **Analysis Facility:**

The primary analytic facilities of the core are housed in room 318B, which contains 2 BD LSR II analytic instruments. The BD LSR II is a flexible and highly adaptable bench top analyzer. It contains four fixed-aligned, air-cooled lasers: red (635nm), green (532nm), blue (488nm) and violet (405nm). In its present configuration, the analyzer is capable of performing eighteen parameters (forward and side scatter plus sixteen color flow cytometry). The LSR II has an increased sensitivity and flexibility due to the octagon

and trigon optical arrays. It can yield more information from each sample and rare event analysis is more accurate and efficient because of the increased flow rate and the digital acquisition system. These instruments are equipped with HTS units that allow acquisition of samples automatically from 96 and 384 well plates. Additionally, they are also equipped with BD FACS flow supply systems to automate fluid handling. The core provides training to individuals of the institute so they are able to operate these instruments unassisted by core staff. The room 318B also contains a two laser, 6 parameter BD FacsArray. This instrument is dedicated to performing multiplex bead assays and high throughput screening experiments. The core will provide training to individuals so they can operate this instrument without core assistance.

### **Vivarium**

Dr. Ross has access to the BSL2 and BSL3 Vivarium operated by UGA. Dr. Ross houses mice and ferrets in the BSL2 and BSL3 facility. The facilities are the modern masonry construction with animal rooms, support laboratories, cage washing areas, and surgery rooms. Ventilation is by a 100 percent fresh air system that is electronically monitored to maintain optimum temperature and humidity. Animal caging is of stainless steel or plastic depending on the animal species and is sanitized at appropriate intervals by the use of mechanical cage washing equipment. Light cycles are controlled electronically and can be set to provide a cycle appropriate to the study in progress. Animal care is conducted by trained veterinarians, veterinarian technicians and supervised by a doctoral-level animal physiologist. Veterinary care is provided by veterinarians trained and experienced in animal medicine and non-human primate housing, care, and enrichment. This is an AAALAC-accredited facility.

### **Shared Instrumentation suites:**

#### **PCR suite**

Three dedicated rooms for activities related to PCR amplification are housed on the second floor. Rm 229D houses the RNA extraction/Pre-PCR procedure room. This room contains a Qiacube RNA extraction system, 2 thermomixers, 2 PCR preparation cabinets, 3 microfuges, 2 Biorad C1000 thermocyclers, and Eppendorf 5430 centrifuge, 2 -20C freezers and a 4C cooler. Rm 229C houses the Post-PCR room where reactions are prepared and samples are amplified. This room contains 2 PCR prep cabinets, a Qiagility automated PCR prep workstation, 3 BioRad C1000 thermocyclers, a Roche Light Cycler 480II and Rotor Gene for real-time PCR analysis. Rm 229B houses the Gel electrophoresis/DNA analysis room for analysis of amplified samples. This room contains multiple DNA electrophoresis boxes and power supplies, a BioRad C1000 thermocycler, a Nanodrop, a transilluminator and a BioRad Gel Doc gel analysis system.

#### **Glasswash/Autoclave Facility**

Rm 211 houses a common glass wash facility and autoclave suite. This facility has a dedicated technician that serves the needs of the scientific staff of the institute with regards to cleaning and sterilization of glassware and other items.

#### **Bacterial prep suite**

Rm 321 houses the bacterial prep suite for the preparation of large/mid-sized preps of plasmid. This room contains a Sorvall RC-6 and Thermo Legend XTR centrifuge, a 4C cooler, two bacterial incubators, a sonicator a microfuge and heated shakers for bacterial culture.

#### **Recombinant protein prep suite**

Rm 315 houses an AKTA FPLC instrument located in a double sized 4C cooler, a -20C and a -80C freezer.

#### **Fluidigm instrumentation suite**

This equipment suite houses a Fluidigm BioMark HD system that is available for all scientific staff to use for gene expression analysis, SNP analysis, DNA library quantification, single cell gene expression analysis.

#### **Microscopy suite**

Rm 104 contains a common use microscopy suite. There is a shared use Olympus fluorescent microscope in the suite available to all research staff.

#### **Histology/Irradiator**

For irradiation of feeder cell layers, the institute has a Rad Source 2000 X-Ray irradiator housed in Rm 119. For frozen section and histology processing, there is a histology/pathology suite in Rm 122G that contains a fume hood for processing of samples and a Cryostat for preparing sections.

#### **Tissue Culture (BSL2 and BSL3)**

The BSL-2 and BSL-3 suites at UGA are fully equipped to perform standard molecular and cell biology-based studies and have been sanctioned by the CDC and University of Georgia Offices of Biosafety. Specific items in the BSL-2 rooms relevant to this project include -20°C and -80°C freezers, double-door refrigerators, shaking incubators, clinical centrifuges, a high-speed floor centrifuges, microfuges, PCR machines, electrophoresis equipment, gel imaging and documentation system, uv/vis spectrophotometer, a Zeiss Axiovert 200M motorized fluorescent microscope equipped with an Apotome, a Zeiss inverted phase-contrast microscope, and biological safety cabinets. A Luminex Magpix instrument for cytokine analyses and protein concentration determinations is also located in an adjacent BSL2 suite. The BSL-3 suites dedicated to *M. tuberculosis* research contain biological safety cabinets, CO<sub>2</sub> incubators, non- CO<sub>2</sub> incubators, spectrophotometers, tabletop clinical centrifuges with aerosol-containment buckets, Zeiss fluorescent microscope workstations, computers, bacterial cell disruptors, -80°C freezers, waterbath sonicators, and microcentrifuges with aerosol-containment rotors. The BSL- 3 anterooms and common-equipment rooms contain high-speed floor centrifuges with aerosol- containment rotors, double-door refrigerators, backup -80°C freezers, and large-capacity pass-through autoclaves.

The Animal Health Research Center (AHRC) located on the College of Veterinary Medicine campus contains BSL3, ABSL-3 and BSL-3Ag animal containment rooms. It is the only non- federal BSL3Ag facility in the U.S. over 75,000 sq. ft. Large and small animals can be housed and effectively studied simultaneously using a dozen or more bacterial, viral and parasite pathogens. A fully equipped and staffed necropsy center is located within the high containment area of the AHRC, and a highly-trained animal care staff is available around the clock to assist investigators.

#### **Scientific Environment**

The University of Georgia, College of Veterinary Medicine, and Department of Infectious Diseases house a diverse, yet collaborative group of highly productive scientists. Faculty include immunologists, virologists, bacteriologists, and parasitologists. The Department has seen significant growth in the past decade, which continues to enrich the research environment with a mix of new young investigators and senior scholars. Infectious Disease is complemented with departments of Cell Biology, Population Health, Pathology, and others, as well as multiple University Centers. As a member of the UGA Interdisciplinary Life Sciences program, the Department and faculty can recruit from >100 top quality graduate student candidates each year. Moreover, the Infectious Disease program recruits talented postdoctoral fellows and other trainees, as well.

The Department and Centers across campus have active seminar series in addition to journal clubs and cross-disciplinary discussion groups. These, as well as local and regional conferences provide opportunities to regularly present, discuss and enrich research projects.

## **FACILITIES AND RESOURCES: EMORY UNIVERSITY**

### **Rustom Antia (PI) – Department of Biology**

#### **Facilities**

Rustom Antia, Samuel C. Dobbs Professor at Department of Biology at Emory University, has a large renovated laboratory room with two large offices for post-doctoral fellows and ample office space for students (undergraduate, and graduate). In addition to desks, computers, Ethernet, and printers, it includes space for blackboard discussions and coffee.

**Animal:** NA

#### **Computers:**

The Co-Investigator and post-doctoral fellows use high-end multi-processor computers (Apple iMac Desktop Computers or Dell Workstations running Linux). We have access to a computer cluster on which we typically run lengthy simulations which include bootstrap analysis.

**Office:** The Co-I has an office, which is close to the laboratory space.

**Clinical:** NA

#### **Scientific Environment:**

I am part of the Department of Biology at Emory University. We have a common space for discussions, particularly over lunch with a number of groups in the Immunology and Molecular Pathogenesis (IMP) and Population Biology, Ecology and Evolution (PBEE) programs, which have a focus on immunology and disease.

### **Department of Microbiology and Immunology - Veronika Zarnitsyna (Co-Investigator):**

Veronika Zarnitsyna, Assistant Professor at Department of Microbiology and Immunology at Emory University School of Medicine, has an office (room 1017) in the Rollins Research Center. The office is equipped with computers, Ethernet, and printing. It also includes space for blackboard discussions.

**Animal:** NA

**Computer:** Veronika Zarnitsyna and her postdoc have high-end multi-processor computers (Apple iMac Desktop Computers) and several notebooks. She and her postdoc have access to computer cluster to run lengthy simulations.

**Clinical:** NA

**Scientific Environment:** Veronika Zarnitsyna is at the Department of Microbiology and Immunology at Emory University School of Medicine located in the Rollins Research Center. The Rollins Research Center is a 256,250 sq ft multidisciplinary research center that includes the departments of Biology,

Biochemistry, Microbiology and Immunology, Pharmacology, and others. It is also connected to the Rollins School of Public Health that has six Departments including the Department of Biostatistics, Department of Epidemiology, and Department of Global Health. Ongoing invited seminar series in immunology and epidemiology and multiple workshops provide an excellent opportunity to keep abreast of the latest scientific developments in these areas. Emory provides many conference rooms for discussions, including specially designed rooms for discussion over lunch, to foster stimulating discussions and collaborations between established and younger scientists in different programs. The Rollins Research Center is located in a walking distance from the Emory Vaccine Center, the largest and most comprehensive academic vaccine research center in the world and a great collaborative resource. The Department of Microbiology and Immunology has joint seminar series with the Emory Vaccine Center, where professors and postdocs present their current research. This scientific environment provides a unique expertise in immunology and a great opportunity for a regular discussion of the research projects.

Rustom Antia and Veronika Zarnitsyna have many recent joined publications and ongoing collaboration with Andreas Handel.

## RESEARCH & RELATED Senior/Key Person Profile (Expanded)

PROFILE - Project Director/Principal Investigator						
Prefix:	First Name*:	Andreas	Middle Name	Last Name*:	Handel	Suffix:
Position/Title*:	Assoc/Asst Dept Chair/ Dir/ He					
Organization Name*:	University of Georgia					
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County:						
State*:	GA: Georgia					
Province:						
Country*:	USA: UNITED STATES					
Zip / Postal Code*:	306020000					
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Project Role*:	PD/PI		Other Project Role Category:			
Degree Type:	PhD		Degree Year: 2004			
Attach Biographical Sketch*:	File Name:	Biosketch_Handel.pdf				
Attach Current & Pending Support:	File Name:					

PROFILE - Senior/Key Person

Prefix:	First Name*: Ye	Middle Name	Last Name*: Shen	Suffix:
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Division:	Epidemiology & Biostatistics			
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City*:	ATHENS			
County:				
State*:	GA: Georgia			
Province:				
Country*:	USA: UNITED STATES			
Zip / Postal Code*:	306020000			
Phone Number*:	706-542-2754		Fax Number:	
E-Mail*:	yeshen@uga.edu			
Credential, e.g., agency login:	yeshen			
Project Role*:	Co-Investigator		Other Project Role Category:	
Degree Type:	PhD		Degree Year: 2011	
Attach Biographical Sketch*:	File Name:	Shen_biosketch.pdf		
Attach Current & Pending Support:	File Name:			

PROFILE - Senior/Key Person

Prefix:	First Name*: Ted	Middle Name	Last Name*: Ross	Suffix:
Position/Title*:	Professor			
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Department:				
Division:	Veterinary Medicine			
Street1*:	1504 VET MED - 1			
Street2:	501 D. W. BROOKS DR.			
City*:	ATHENS			
County:				
State*:	GA: Georgia			
Province:				
Country*:	USA: UNITED STATES			
Zip / Postal Code*:	306020000			
Phone Number*:	706-542-9708		Fax Number:	
E-Mail*:	tedross@uga.edu			
Credential, e.g., agency login:	TEDROSS			
Project Role*:	Co-Investigator		Other Project Role Category:	
Degree Type:	PhD		Degree Year: 1996	
Attach Biographical Sketch*:	File Name:	Ross_Biosketch.pdf		
Attach Current & Pending Support:	File Name:			

PROFILE - Senior/Key Person

Prefix:	First Name*: Rustom	Middle Name	Last Name*: Antia	Suffix:
Position/Title*:	Professor			
Organization Name*:	Emory University			
Department:	Biology			
Division:	ECAS			
Street1*:	1510 Clifton Road			
Street2:				
City*:	Atlanta			
County:				
State*:	GA: Georgia			
Province:				
Country*:	USA: UNITED STATES			
Zip / Postal Code*:	303224250			
Phone Number*: 404-727-1015		Fax Number:		
E-Mail*: rantia@emory.edu				
Credential, e.g., agency login: rantia				
Project Role*: Co-Investigator		Other Project Role Category:		
Degree Type: PhD		Degree Year: 1991		
Attach Biographical Sketch*:		File Name:	Antia_biosketch.pdf	
Attach Current & Pending Support: File Name:				

PROFILE - Senior/Key Person

Prefix:	First Name*: Veronika	Middle Name	Last Name*: Zarnisyna	Suffix:
Position/Title*:	Assistant Professor			
Organization Name*:	Emory University			
Department:	Microbiology/Immunology			
Division:	SOM			
Street1*:	1510 Clifton Road			
Street2:				
City*:	Atlanta			
County:				
State*:	GA: Georgia			
Province:				
Country*:	USA: UNITED STATES			
Zip / Postal Code*:	303224250			
Phone Number*: 404-727-0817		Fax Number:		
E-Mail*: veronika.i.zarnitsyna@emory.edu				
Credential, e.g., agency login: VZARNITSYNA				
Project Role*: Co-Investigator		Other Project Role Category:		
Degree Type: PhD		Degree Year: 1997		
Attach Biographical Sketch*:		File Name:	Zarnitsyna_Biosketch.pdf	
Attach Current & Pending Support: File Name:				

**BIOGRAPHICAL SKETCH**

NAME: Andreas Handel

eRA COMMONS USER NAME (credential, e.g., agency login): ahandel

POSITION TITLE: Associate Professor &amp; Associate Department Head, Epidemiology and Biostatistics

**EDUCATION/TRAINING**

INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	Completion Date	FIELD OF STUDY
University of Stuttgart, Stuttgart, Germany	B.S. (equivalent)	7/1999	Physics
Georgia Institute of Technology, Atlanta, GA	Ph.D.	7/2004	Physics
Emory University, Atlanta, GA	Postdoc	12/2008	Computational Biology

**A. Personal Statement**

I study the spread and control of infectious diseases using mathematical models, computational simulations, and statistical analysis to understand the dynamics of pathogens on different spatial and temporal scales. One part of my research deals with the infection and immune response dynamics within an infected individual. These within-host studies help understand the mechanisms impacting disease severity, transmission potential and immune protection of individuals, and how those characteristics are altered by drugs and vaccines. The other part of my research concerns the dynamics, control, and evolution of pathogens on the population level. In some of my work, I combine the within-host and between-host scales to obtain an integrated understanding of the complex dynamics of infectious disease spread across scales. The ultimate goal of my work is to help design better intervention and control strategies against infectious diseases, both for individual patients and on the population level. Both vaccines and the role of inoculum dose following infection or vaccination have been a focus of my work for the last several years. The following publications highlight some of my recent work that is most relevant to this project:

- Sung M-H, Shen Y, **Handel A**, Bahl J and Ross TM. Longitudinal Assessment of Immune Responses to Repeated Annual Influenza Vaccination in a Human Cohort of Adults and Teenagers. *Front. Immunol.* (2021) 12:642791. doi: 10.3389/fimmu.2021.642791
- Skarupka AL, **Handel A**, Ross TM. Influenza hemagglutinin antigenic distance measures capture trends in HAI differences and infection outcomes, but are not suitable predictive tools. *Vaccine*. 2020. PMID: 32682618.
- Moore JR, Ahmed H, Manicassamy B, Garcia-Sastre A, **Handel A**, Antia R. Varying Inoculum Dose to Assess the Roles of the Immune Response and Target Cell Depletion by the Pathogen in Control of Acute Viral Infections. *Bull Math Biol.* 2020. doi:10.1007/s11538-020-00711-4
- **Handel A**, Li Y, McKay B, Pawelek KA, Zarnitsyna V, Antia R. Exploring the impact of inoculum dose on host immunity and morbidity to inform model-based vaccine design. *PLoS Comput Biol.* 2018. PMID: 30273336.

**B. Positions and Honors**

2004 - 2008 Postdoctoral Researcher, Department of Biology, Emory University, Atlanta, GA

2009 – 2015 Assistant Professor, Department of Epidemiology &amp; Biostatistics, University of Georgia

2010 - Present	Adjunct Assistant/Associate Professor, Department of Infectious Diseases; Member, Faculty of Infectious Diseases; Member, Institute of Bioinformatics, University of Georgia
2011 - Present	Adjunct Assistant/Associate Professor, Department of Epidemiology, Emory University
2015 - Present	Associate Professor, Department of Epidemiology & Biostatistics, University of Georgia
2016 - Present	Associate Department Head, Epidemiology & Biostatistics, University of Georgia

## C. Contributions to Science

### 1. Influenza modeling and analysis

I was among the first to model influenza on the within-host level. I have continued to study different aspects of influenza infection and immune response dynamics on the individual host level. These studies have contributed to an increased understanding of the mechanisms that drive infection and immune response dynamics, and how those are altered by drugs and vaccines. I have also done work on the population level, where some of my studies have provided insights into the impact of different intervention strategies against influenza outbreaks. Representative recent publications in that area are:

- McKay B, Ebelle M, Dale AP, Shen Y, **Handel A**. Virulence-mediated infectiousness and activity trade-offs and their impact on transmission potential of influenza patients. *Proc Biol Sci.* 2020. PMID: 32396798.
- McKay B, Ebelle M, Billings WZ, Dale AP, Shen Y, **Handel A**. Associations Between Relative Viral Load at Diagnosis and Influenza A Symptoms and Recovery. *Open Forum Infect Dis.* 2020. PMCID: PMC7751133.
- **Handel A**, Liao L, Beauchemin C. Progress and trends in mathematical modelling of influenza A virus infections. *Current Opinion in Systems Biology.* 2018. 12:30-36.
- Martinez L, Cheng W, Wang X, Ling F, Mu L, Li C, Huo X, Ebelle MH, Huang H, Zhu L, Li C, Chen E, **Handel, A.**, Shen Y. A Risk Classification Model to Predict Mortality Among Laboratory-Confirmed Avian Influenza A H7N9 Patients: A Population-Based Observational Cohort Study. *J Infect Dis.* 2019. PMID: 31622983.

### 2. Multiscale modeling

I realized early on in my within-host and between-host modeling work that it is important to connect the scales if one wants to understand the overall pathogen dynamics more fully. My work has shown how details of viral binding and release kinetics affect transmission fitness and how fitness trade-offs on different scales can affect avian influenza virus dynamics. Representative publications are:

- **Handel A**, Rohani P. Crossing the scale from within-host infection dynamics to between-host transmission fitness: a discussion of current assumptions and knowledge. *Philos Trans R Soc Lond B Biol Sci.* 2015 Aug 19;370(1675). doi: 10.1098/rstb.2014.0302. Review. PubMed PMID: 26150668.
- **Handel A**, Lebarbenchon C, Stallknecht D, Rohani P. Trade-offs between and within scales: environmental persistence and within-host fitness of avian influenza viruses. *Proc Biol Sci.* 2014 Jul 22;281(1787). doi: 10.1098/rspb.2013.3051. PubMed PMID: 24898369.
- **Handel A**, Akin V<sup>A</sup>, Pilyugin SS, Zarnitsyna V, Antia R. How sticky should a virus be? The impact of virus binding and release on transmission fitness using influenza as an example. *J R Soc Interface.* 2014 Mar 6;11(92):20131083. doi: 10.1098/rsif.2013.1083. Print 2014 Mar 6. PubMed PMID: 24430126.
- **Handel A**, Brown J, Stallknecht D, Rohani P. A multi-scale analysis of influenza A virus fitness trade-offs due to temperature-dependent virus persistence. *PLoS Comput Biol.* 2013;9(3):e1002989. doi: 10.1371/journal.pcbi.1002989. Epub 2013 Mar 21. PubMed PMID: 23555223.

### 3. CD8 T-cell modeling and analysis

A focus of my within-host studies, often in the context of influenza, has been the T-cell response. This work is done in close collaboration with experimentalists. Our studies have shed light on how age affects T-cell dynamics, the role of T-cells in autoimmunity, and the mechanisms leading to immunodominance patterns observed following primary and subsequent infections. Representative recent publications are:

- Wu T, Guan J, **Handel A**, Tscharke DC, Sidney J, Sette A, Wakim LM, Sng XYX, Thomas PG, Croft NP, Purcell AW, La Gruta NL. Quantification of epitope abundance reveals the effect of direct and cross-presentation on influenza CTL responses. *Nat Commun.* 2019. PMID: 31253788.
- Ooi JD, Petersen J, Tan YH, Huynh M, Willett ZJ, Ramarathinam SH, Eggenhuizen PJ, Loh KL, Watson KA, Gan PY, Alikhan MA, Dudek NL, **Handel A**, Hudson BG, Fugger L, Power DA, Holt SG, Coates PT, Gregersen JW, Purcell AW, Holdsworth SR, La Gruta NL, Reid HH, Rossjohn J, Kitching AR. Dominant protection from HLA-linked autoimmunity by antigen-specific regulatory T cells. *Nature* 2017. PMID: 28467828.
- Quinn KM, Zaloumis SG, Cukalac T, Kan WT, Sng XY, Mirams M, Watson KA, McCaw JM, Doherty PC, Thomas PG, **Handel A**, La Gruta NL. Heightened self-reactivity associated with selective survival, but not expansion, of naïve virus-specific CD8+ T cells in aged mice. *Proc Natl Acad Sci.* 2016. PMID: 26787864.
- Zarnitsyna VI, **Handel A**, McMaster SR, Hayward SL, Kohlmeier JE, Antia R. Mathematical Model Reveals the Role of Memory CD8 T Cell Populations in Recall Responses to Influenza. *Front Immunol.* 2016. PMID: 27242779.

### 4. Evolutionary studies

While my work generally is informed by an evolutionary perspective, several of my past studies have explicitly considered evolutionary questions. I have investigated the interaction between population size and fitness landscape topology and the impacts on pathogen evolution. In other work, I have considered the evolutionary consequences of latency to tuberculosis fitness. Representative publications are:

- McKay B<sup>†</sup>, Ebell M, Dale AP, Shen Y, **Handel A**. Virulence-mediated infectiousness and activity trade-offs and their impact on transmission potential of influenza patients. *Proc Biol Sci.* 2020. PMID: 32396798.
- Zheng N<sup>†</sup>, Whalen CC, **Handel A**. Modeling the potential impact of host population survival on the evolution of *M. tuberculosis* latency. *PLoS One.* 2014;9(8):e105721. doi: 10.1371/journal.pone.0105721. PubMed PMID: 25157958.
- **Handel A**, Rozen DE. The impact of population size on the evolution of asexual microbes on smooth versus rugged fitness landscapes. *BMC Evol Biol.* 2009 Sep 18;9:236. doi: 10.1186/1471-2148-9-236. PubMed PMID: 19765292.
- **Handel A**, Bennett MR. Surviving the bottleneck: transmission mutants and the evolution of microbial populations. *Genetics.* 2008 Dec;180(4):2193-200. doi: 10.1534/genetics.108.093013. PubMed PMID: 18854584.

### 5. Teaching and Research tool development and dissemination

Recently, I have placed an increasing emphasis on developing tools and materials that help individuals learn aspects of infectious disease dynamics. To that end, I have developed 3 R software packages and written several tutorials and reviews on infectious disease modeling. Representative recent publications are:

- **Handel, A.\*** A software package for immunologists to learn simulation modeling. *BMC Immunology* 2020, 21 (1). <https://doi.org/10.1186/s12865-019-0321-0>.
- **Handel, A.\***, La Gruta NL, Thomas PG. Simulation modelling for immunologists. *Nat Rev Immunol.* 2020. PMID: 31804613.
- **Handel A\*.** Learning infectious disease epidemiology in a modern framework. *PLoS Comput Biol.* 2017. PubMed PMID: 29049284.

**Complete List of Published Work (currently 77 peer-reviewed publications) in MyBibliography:**  
<http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40154260/?sort=date&direction=descending>

#### D. Additional Information: Research Support and/or Scholastic Performance

##### CURRENT

- 75N93021C00018, NIH/NIAID (Tompkins PI). Project period: 4/2021 – 3/2028  
*Center for Influenza Disease and Emergence Research (CIDER)*  
 Role: Co-I.  
 CIDER integrates human cohort studies with state-of-the-art fundamental research to examine susceptibility, immunity, infection, and disease severity, inform public and agricultural health, and engage with national and international pandemic response efforts.
- BAA 75D301-20-R-67837, CDC (Ottesen PI). Project period: 10/2020 – 9/2022  
*Prevalence of and risk factors for community-associated carriage of antimicrobial resistant Enterobacteriaceae and antimicrobial resistance genes*  
 Role: Co-I.  
 The goal of this project is to study the incidence and prevalence patterns of antimicrobial resistant genes in several distinct human populations.
- U01AI150747, NIH/NIAID (Antia PI) Project period: 6/2020 – 5/2025  
*Dynamics and evolution of immune responses to influenza*  
 Role: PI on UGA sub-contract  
 The goal of this project is to continue our combined experimental and modeling approach to deepen our understanding how the pre-existing humoral and cellular immunity alters the dynamics of virus and immunity following vaccination and infection.
- Supplement to R01GM124280, NIH/NIAID (Lopman PI) Project period: 6/2020 – 5/2021  
*Preparing for the SARS-CoV2 vaccine: Modeling of transmission pathways, viral evolution, and vaccination strategies.*  
 Role: PI on UGA sub-contract  
 The goal of this project is to use modeling to understand transmission and evolution of SARS-CoV-2 in preparation for a future COVID vaccine.
- 75N93019C00060, NIH (Ross PI) Project period: 9/2019 – 8/2026  
*Center for Influenza Vaccine Research for High Risk Populations (CIVR-HRP)*  
 Role: Co-Investigator  
 The goal of this project is to develop a universal influenza vaccine with a focus on high risk populations.
- R01GM124280, NIH/NIAID (Lopman PI) Project period: 6/2018 – 5/2023  
*Integrating data streams with multi-scale modeling to guide norovirus vaccine decision-making*  
 Role: PI on UGA sub-contract

The goal of this project is to use a combination of diverse data streams and models to better understand norovirus transmission dynamics with the goal of supporting development of a future norovirus vaccine.

### COMPLETED (SELECTED)

U19AI117891, NIH/NIAID (Antia PI)

Project period: 4/2015 – 3/2020

*Dynamics and evolution of immune responses to influenza*

Role: PI on UGA sub-contract

The goal of this project is to use a combination of models and experiments to develop a quantitative framework for how the pre-existing humoral and cellular immunity alters the dynamics of virus and immunity following vaccination and infection.

NSF Award #1545433 (Ezenwa PI)

Project period: 9/2015 – 8/2020

*Interdisciplinary Disease Ecology across Scales: from Byte to Benchtop to Biosphere*

Role: Senior Personnel/Mentor

The goal of this project is to provide doctoral students with data-enabled science and engineering training to solve complex, interdisciplinary problems related to diseases and the environment.

R01AI093856, NIH/NIAID (Whalen PI)

Project period: 7/2012 – 6/2017

*Community Transmission of M. tuberculosis in Urban Africa*

Role: Co-investigator

The goal of this project is to fill gaps in our knowledge about the spread of tuberculosis in African cities using a contact and transmission network approach.

1R56AI091938, NIH/NIAID (Thomas PI)

Project period: 9/2011 - 8/2013

*Quantifying and modeling influenza viral dynamics and host responses*

Role: PI on UGA sub-contract

The goal of this project was to understand the dynamical interactions between virus and host response to influenza using a combination of experiments and mathematical modeling.

Faculty Research Grant, University of Georgia (Handel PI)

Project Period 7/2011 – 6/2012

*Developing an agent-based model to study tuberculosis transmission and vaccination*

Role: PI

The goal of this project was to develop a detailed, agent-based model of tuberculosis transmission and simulation of clinical vaccine trials.

5K25AI072193, NIH/NIAID (Handel PI)

Project period: 5/2007 - 4/2012

*Quantitative studies of CD8 T-cell dynamics*

Role: PI

The goal of this project was to obtain a quantitative understanding of the dynamics of CD8 T-cells after viral infections and to understand how these dynamics depend on antigen and other stimuli.

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Shen, Ye

eRA COMMONS USER NAME: yeshen

POSITION TITLE: Associate Professor, Department of Epidemiology and Biostatistics

**EDUCATION/TRAINING**

INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	Completion Date MM/YYYY	FIELD OF STUDY
Fudan University, Shanghai, China	B.S.	06/2003	Statistics
Yale University, New Haven, CT	Ph.D.	12/2011	Biostatistics

**A. Personal Statement**

The primary work of the proposed study is to start the development of a model+data framework that can be used to predict the impact of dose for current and future influenza vaccines and thus allows optimization of dose. I am delighted to serve as study Co-I and Biostatistician on this project. My current research focuses on statistical/epidemiological analyses of public health and biomedical data, with major application areas in various infectious diseases including influenza, HIV, TB, schistosomiasis, and other neglected tropical diseases (NTDs). I am formally trained in many contemporary statistical methods, and have been involved in multiple projects funded by NIH and Bill Melinda Gates Foundation (BMGF), etc. I recently served as a subcontract PI for the statistics core of a large-scale BMGF operational research project in five countries, and am currently serving as a senior statistical consultant for an NIH ICEMR U19 grant executing multi-disciplinary research programs in west Africa. My experience of working on infectious disease data was furthered through recent collaborations on several NIH R01 studies examining interventions for HIV-positive rural persons. More recently, I also served as the biostatistician for a NIH large-scale center grant to develop universal influenza vaccines targeting the high-risk population. I have been collaborating with the study PI, Dr. Andreas Handel, on several epidemiological and modeling studies of human seasonal influenza, avian influenza H7N9, and COVID-19 and published findings along the line. For this project, I will provide statistical support to the proposed research through conduct of statistical analyses to be reported to the study's core members, and the report generation for various descriptive, predictive, and outcome analyses. I will also contribute to the preparation of manuscripts that result from the study data. In summary, I have a demonstrated record of successful and productive research projects in an area of high relevance for the proposed study, and my expertise and experience have prepared me to contribute to the project.

Relevant NIH/BMGF funded projects:

HHS-NIH-NIAID-BAA2018_003 NIAID Center for Influenza Vaccine Research for High Risk Populations (CIVR-HRP) The center proposes the integration of comprehensive assessment of broadly-protective or universal influenza vaccine candidates with fundamental research that will provide insight into the mechanisms that foster vaccine effectiveness against co-circulating influenza strains from the major subtypes of influenza virus. Role: Co-Investigator	Ross (PI)	09/16/19 – 09/15/26
R01 AG053081 NIA Reducing HIV Risk Behavior in Depressed and Non-Depressed Older Adults with HIV The goal of this study is to test the efficacy of a telephone-delivered intervention to reduce condomless sex in older adults with HIV. Role: Co-Investigator/Biostatistician	Lovejoy (PI)	03/15/16 – 02/29/21

1021RR374053 - Bill and Melinda Gates Foundation Colley (PI) 12/01/08 – 06/30/20  
The Schistosomiasis Consortium for Operational Research and Evaluation (SCORE)  
SCORE's vision is to inform efforts to gain control of schistosomiasis in high-prevalence areas, sustain control and move towards elimination in areas of moderate prevalence, and ultimately eliminate schistosomiasis.  
Role: Principal Investigator (Sub-contract)

Attached below is a list of peer reviewed publications to highlight my experience and qualifications for this project:

1. Sung, M. H., **Shen, Y.**, Handel, A., Bahl, J., & Ross, T. M. (2021). Longitudinal assessment of immune responses to repeated annual influenza vaccination in a human cohort of adults and teenagers. *Frontiers in immunology*, 12, 472.
2. Martinez, L., Cheng, W., Wang, X., Ling, F., Mu, L., Li, C., ... & **Shen, Y.** (2019). A risk classification model to predict mortality among laboratory-confirmed avian influenza A H7N9 patients: a population-based observational cohort study. *The Journal of Infectious Diseases*, 220(11), 1780-1789.
3. **Shen, Y.**, Li, C., Dong, H., Wang, Z., Martinez, L., Sun, Z., ... & Xu, G. (2020). Community outbreak investigation of SARS-CoV-2 transmission among bus riders in eastern China. *JAMA internal medicine*, 180(12), 1665-1671.
4. Cheng, W., Pan, A., Rathbun, S. L., Ge, Y., Xiao, Q., Martinez, L., ... & **Shen, Y.** (2021). Effectiveness of neuraminidase inhibitors to prevent mortality in patients with laboratory-confirmed avian influenza A H7N9. *International Journal of Infectious Diseases*, 103, 573-578.

## B. Positions and Honors

### Positions and Employment

- 2017-current Associate Professor, Department of Epidemiology and Biostatistics, College of Public Health, University of Georgia, Athens, GA  
2011-2017 Assistant Professor, Department of Epidemiology and Biostatistics, College of Public Health, University of Georgia, Athens, GA  
2007-2010 Research Assistant, School of Public Health, Yale University, New Haven, CT

### Other Experience and Professional Memberships

- 2020- Journal Reviewer: *Annals of Internal Medicine*  
2019 Scientific Program Committee Member, ICSA 2020 Applied Statistics Symposium  
2018- Journal Reviewer: *Statistical Methods in Medical Research*  
2017- Grant Proposal Reviewer: Deutsche Forschungsgemeinschaft (German Research Foundation)  
2016- Grant Proposal Reviewer: Research Grants Council (RGC) of Hong Kong  
2016- Journal Reviewer: *Statistics and its Interface*  
2016- Journal Reviewer: *Journal of Multivariate Analysis*  
2016- Journal Reviewer: *Biostatistics*  
2015- Associate Editor, *Frontiers in Pharmacology*  
2015- Journal Reviewer: *Statistics in Medicine*  
2013- Journal Reviewer: *The Scandinavian Journal of Statistics*  
2012 Review Panelist, The CDC/CSTE Applied Epidemiology Fellowship program  
2012 Reviewer, the Academic Public Health Caucus program, 140th APHA Annual Meeting  
2012- Journal Reviewer: *Journal of Applied Statistics*  
2010- Member, Institute of Mathematical Statistics (IMS)  
2009- Member, American Statistical Association (ASA)

### Honors

- 2019 GRCG Award, University of Georgia, Athens, GA  
2010 Yale Graduate School of Arts and Sciences CTF Award, New Haven, CT  
2006-2011 Yale Fellowship, Yale University, New Haven, CT

## C. Contribution to Science

1. My methodological research interest focused on repeatedly measured outcome analysis. I studied joint modeling problems in clinical trials, in which both longitudinal outcomes and time to progression data were collected. Analyzing these data requires skills in both longitudinal data modeling and survival analysis. I am familiar with both methodologies and currently developing joint modeling approaches to combine the two types of information, which can often enhance efficiencies in handling missing data. In addition, I have also extended traditional estimation equation approaches to incorporate weights for inhomogeneous spatial point processes. We showed that the proposed weights can incorporate information on both inhomogeneity and dependence of the process, and significant efficiency gains can be achieved for non-Poisson processes, compared to the Poisson maximum likelihood estimator. More recently, I have also developed a functional data analysis approach to model repeatedly measured outcomes so that the statistical power of the study can be improved. I hope to incorporate these methods into dynamic predictive models proposed in the current studies.

- ❖ Guan, Y. & **Shen, Y.** (2010). A Weighted Estimating Estimation Approach for Inhomogeneous Spatial Point Processes. *Biometrika*, 97(4), 867-880.
- ❖ **Shen, Y.**, Aparna, A., Sinha, R., and Li, Y. (2014) Joint Modeling Tumor Burden and Time to Event Data in Oncology Trials. *Pharmaceutical Statistics*, 13(5), 286-293.
- ❖ **Shen, Y.**, Huang, H., and Guan Y. (2016) A Conditional Estimating Equation Approach for Recurrent Event Data with Additional Longitudinal Information. *Statistics in Medicine*, 35(24), 4306-4319.
- ❖ Woldu, H., Heckman, T., Handel, A., and **Shen, Y.** (2019). Applying Functional Data Analysis to Assess Tele-Interpersonal Psychotherapy's Efficacy to Reduce Depression. *Journal of Applied Statistics*, 46(2), 203-216.

2. I have made contributions to the understanding of human immune responses after influenza vaccination through the recent collaboration with the Center for Influenza Vaccine Research for High-Risk Populations (CIVR-HRP) at UGA, aiming to develop universal influenza vaccines targeting the high-risk population. I have also studied the epidemiology of human infections with avian influenza A/H7N9, which remains a big threat and has a great potential to cause a pandemic in the foreseeable future. Understanding the contributing factors to the extremely high mortality of laboratory-confirmed A/H7N9 cases is critical to the prevention and treatment of the life-threatening diseases. To address the challenge, I have previously led the effort in developing and validating a prognostic risk classification model for A/H7N9 patients.

- ❖ Sung, M. H., **Shen, Y.**, Handel, A., Bahl, J., & Ross, T. M. (2021). Longitudinal assessment of immune responses to repeated annual influenza vaccination in a human cohort of adults and teenagers. *Frontiers in immunology*, 12, 472.
- ❖ Cheng, W., Wang, X., **Shen, Y.**, Yu, Z., Liu, S., Cai, J., & Chen, E. (2018). Comparison of the three waves of avian influenza A (H7N9) virus circulation since live poultry markets were permanently closed in the main urban areas in Zhejiang Province, July 2014-June 2017. *Influenza and Other Respiratory Viruses*, 12(2), 259-266.
- ❖ Martinez, L., Cheng, W., Wang, X., Ling, F., Mu, L., Li, C., ... & **Shen, Y.** (2019). A risk classification model to predict mortality among laboratory-confirmed avian influenza A H7N9 patients: a population-based observational cohort study. *The Journal of Infectious Diseases*, 220(11), 1780-1789.
- ❖ Cheng, W., Pan, A., Rathbun, S. L., Ge, Y., Xiao, Q., Martinez, L., ... & **Shen, Y.** (2021). Effectiveness of neuraminidase inhibitors to prevent mortality in patients with laboratory-confirmed avian influenza A H7N9. *International Journal of Infectious Diseases*, 103, 573-578.

3. During my role as a subcontract PI for the statistics core of the BMGF funded SCORE project for over 8 years, I led multiple research studies mainly focusing on the nested human cohorts in countries including Kenya, Tanzania, Niger, and Mozambique. We published epidemiological findings on subjects infected with schistosomiasis in communities undergoing mass drug administrations. In addition, we also conducted modeling studies to predict persistent hotspots in SCORE studies for gaining control of *S. mansoni* in Kenya and Tanzania, which built the foundation of the proposed studies in our proposal.

- ❖ Ezeamama, A. E., He, C. L., **Shen, Y.**, Yin, X. P., Binder, S. C., Campbell, C. H., ... & Olsen, A. (2016). Gaining and sustaining schistosomiasis control: study protocol and baseline data prior to different treatment strategies in five African countries. *BMC Infectious Diseases*, 16(1), 229.
- ❖ **Shen, Y.**, King, C. H., Binder, S., Zhang, F., Whalen, C. C., Secor, W. E., ... & Kinung'hi, S. (2017). Protocol and baseline data for a multi-year cohort study of the effects of different mass drug treatment

approaches on functional morbidities from schistosomiasis in four African countries. *BMC Infectious Diseases*, 17(1), 652.

- ❖ **Shen, Y.**, Wiegand, R. E., Olsen, A., King, C. H., Kittur, N., Binder, S., ... & Mwinzi, P. N. (2019). Five-Year Impact of Different Multi-Year Mass Drug Administration Strategies on Childhood Schistosoma mansoni–Associated Morbidity: A Combined Analysis from the Schistosomiasis Consortium for Operational Research and Evaluation Cohort Studies in the Lake Victoria Regions of Kenya and Tanzania. *The American Journal of Tropical Medicine and Hygiene*, 101(6), 1336-1344.

4. While developing biostatistical methodologies, I also applied my knowledge of statistics to different research areas (mainly public health and biomedical studies) to enhance the methodological development in those fields. Working with my colleagues, I helped with the development and validation of the Good Outcome Following Attempted Resuscitation (GO-FAR) score, which aims to inform patients and providers of the likelihood of survival after in-hospital cardiac arrest (IHCA), neurologically intact or with minimal deficits. We hope this newly developed tool can be useful when discussing do-not-attempt-resuscitation orders. Another application was a direct extension of my expertise in joint modelling of longitudinal and survival data. We proposed to analyze the treatment effect on tumor growth kinetics using a joint modeling framework accounting for the informative missing mechanism, which was new in phase-II oncology trials. More recently, we also applied our expertise in statistics and machine learning to validate WHO screening algorithms algorithm for child contacts of tuberculosis cases in resource-constrained areas and to predict hotspots of non-responding villages undergoing mass drug administration for schistosomiasis control. These works were published on high quality journals such as *Lancet Respiratory Medicine* and *Journal of Infectious Diseases*.

- ❖ Ebelle, M., Jang, W., **Shen, Y.**, and Geocadin, R. (2013). Development and validation of the Good Outcome Following Attempted Resuscitation (GO-FAR) score to predict neurologically intact survival following in-hospital cardiopulmonary resuscitation. *JAMA Internal Medicine*, 173(20): 1872-8.
- ❖ **Shen, Y.**, Aparna, A., Sinha, R., and Li, Y. (2014). Joint Modeling Tumor Burden and Time to Event Data in Oncology Trials. *Pharmaceutical Statistics*, 13(5): 286-293.
- ❖ Martinez, L., **Shen, Y.**, Handel, A., Chakraburty, S., Stein, C., Malone, L., Boom, H.W., Quinn, F.D., Joloba, M.L., Whalen, C., and Zalwango, S. (2018). Effectiveness of WHO's Screening Algorithm for Child Contacts of Tuberculosis Cases in Resource-constrained Areas: A Prospective Cohort Study in Uganda. *Lancet Respiratory Medicine*, 6: 276–286.
- ❖ **Shen, Y.**, Sung, M., King, C., Binder, S., Kittur, N., Whalen, C., and Colley, D. (2020). Modeling approaches to predicting persistent hotspots in SCORE studies for gaining control of schistosomiasis *mansonii* in Kenya and Tanzania. *Journal of Infectious Diseases*, 221(5), 796-803.

5. As a biostatistician, I also frequently collaborated with researchers in many fields to contribute my expertise in study design and data analysis. These collaborations have resulted in many high impact publications. So far, I've been involved in applications covering a broad range of medical and public health research areas such as: cardiovascular risk evaluation, spinal disorder research, infectious disease modeling, ageing research, patient satisfaction assessment, and environmental science studies.

- ❖ Janket, S.J., **Shen, Y.**, and Baird, A.E. (2008). Why must new cardiovascular risk factors be carefully re-assessed prior to clinical application? *European Heart Journal*, 29(10), 1336.
- ❖ Zhang, X., Davidson, E., Searchinger, T., Mauzerall, D., Dumas, P., and **Shen, Y.** (2015). Managing nitrogen for sustainable development. *Nature*, 528, 51-59.
- ❖ **Shen Y.**, King C.H., Binder S., Zhang F., Whalen C., Secor W.E., et al. (2017) Protocol and baseline data for a multi-year cohort study of the effects of different mass drug treatment approaches on functional morbidities from schistosomiasis in four African countries. *BMC Infectious Diseases*. 17(1): 652.
- ❖ **Shen, Y.**, Li, C., Dong, H., Wang, Z., Martinez, L., Sun, Z., ... & Xu, G. (2020). Community outbreak investigation of SARS-CoV-2 transmission among bus riders in eastern China. *JAMA internal medicine*, 180(12), 1665-1671.

#### Complete List of Published Work in MyBibliography:

<http://www.ncbi.nlm.nih.gov/sites/myncbi/1rU6wTubl6wAw/bibliography/47885319/public/?sort=date&direction=ascending>

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Ted M. Ross

ERA COMMONS USER NAME (credential, e.g., agency login): TEDROSS

POSITION TITLE: Professor and Director

**EDUCATION/TRAINING** (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	Completion Date MM/YYYY	FIELD OF STUDY
University of Arkansas, Fayetteville, AR	B.S., M.S.	1986, 1989	Zoology, Microbiology
Vanderbilt University, Nashville, TN	Ph.D.	1996	Microbiology
Duke University, Durham, NC	Post-Doc	1996-1998	Genetics-HIV Biology
Emory University, Atlanta, GA	Sr. Res Assoc.	1998-2000	Emory Vaccine Center

**A. Personal Statement**

Dr. Ross is a highly motivated, creative, and skilled scientist with experience in the fields of virology, vaccines, immunology, and microbiology. Dr. Ross is the senior investigator that developed computationally-optimized broadly reactive antigen (COBRA) technology for the rational design of vaccine candidates for influenza viruses (1-4). He is the Project Director for NIAID/NIH CIVIC Contract, where he leads a 35 member investigator team at 15 institutions for one of the Vaccine Centers. He is also the lead developer of COBRA based vaccine design for SARS-2 Coronavirus Spike Protein currently being tested in high risk animal models for immunogenicity and protective efficacy against the SARS-2 virus. He was the lead investigator for development of DNA, recombinant protein and virus-like particle (VLP) vaccines for pandemic (1) and seasonal influenza (2-4), as well as several vaccine candidates under investigation. Dr. Ross has a long track record of using ferrets for seasonal (1-3) and high path avian influenza strains (H5N1, H7N9, H9N2) (1). He and his laboratory have performed numerous studies in ferrets at ABSL2 and ABSL3 using seasonal (H1N1, H3N2, B influenza) and H5N1 select agent influenza viruses. He has developed pre-immune models for testing vaccines in ferret models (2) using both commercial vaccines (TIV; FluZone Sanofi-Pasteur) and experimental universal vaccine strategies (VLPs, DNA, live-attenuated, viral vectors). He studies human immune responses to influenza vaccination to determine antibody and B cell responses in people of different ages and pre-immune history. His work possesses a unique vision and he is passionate about utilizing novel vaccine designs to elicit high-titer protective immune responses for adult, elderly, and juvenile ferrets. He has multiple high impact publications in pre-clinical vaccine assessment in mice, ferrets, and non-human primates (1), is the primary investigator on externally funded research projects, and has project management skills in multi-investigator UO1 and PO1 projects.

1. Carter DM, Darby CA, Johnson SK, Carlock MA, Kirchenbaum GA, Allen, JD, Vogel TU, Delagrave S, DiNapoli J, Alefantis T, Kleanthous H, **Ross TM**. Elicitation of protective antibodies against a broad panel of H1N1 viruses in ferrets pre-immune to historical H1N1 influenza viruses. 2017. *J Virol.* 91(24). 4720-4734.
2. Wong TM, Bebin-Blackwell A-G., Allen JD, Park B, Carter DM, Kleanthous H, Alefantis, T, **Ross TM**. H3 COBRA hemagglutinin vaccines elicit antibodies with hemagglutinin-inhibition (HAI) activity against a diverse panel of H3N2 influenza viruses. 2017. *J Virol.* 91:24. e01581-17.
3. Nuñez IA, Carlock MA, Allen JD, Owino SO, Moehling K, Nowalk MP, Diagle K, Sweeney K, Mundle S, Vogel TU, Delagrave S, Ramagopan M, Zimmerman RK, Kleanthous H, **Ross TM**. Impact of age and pre-existing influenza immunity in humans on the elicitation of anti-hemagglutinin antibodies receiving split inactivated influenza vaccines. 2017. *PLoS One.* 12(11). E0185666.

4. Allen JD, Jang H, **Ross TM**. Elicitation of protective antibodies against 20 years of future H3N2 co-circulating influenza virus variants in ferrets pre-immune to historical H3N2 influenza viruses. 2019. *J. Virol.* pii.009346-18.

## B. Positions and Honors

2000-2003	Assistant Professor, East Carolina University, Dept. of Microbiology and Immunology.
2003-2009	Assistant Professor, Univ. of Pittsburgh, Div. of Infectious Diseases.
2006-present	Investigator, University of Pittsburgh, Center for Vaccine Research.
2009-2013	Associate Professor (w/Tenure), Univ. of Pittsburgh, Molecular Genetics & Biochemistry
2013-2015	Professor (Full Member), VGTI of Florida, Director-Vaccine & Infectious Diseases Division
2015-Present	Eminent Scholar, Georgia Research Alliance
2015-present	Professor Department of Infectious Diseases (w/Tenure), University of Georgia
2015-present	Director Center for Vaccines and Immunology, University of Georgia

## Honors/Awards

1996	Sidney P. Colowick Award - Outstanding Graduate Achievement, Vanderbilt University
2013-present	Fellow, International Society for Vaccines
2020-2021	President, International Society for Vaccines

## Patents

Ross has 16 influenza patents.

## C. Contributions to Science

**Dr. Ross has contributed to science in several important ways.**

**1. COBRA H5N1 influenza VLP vaccine development. The development of a broadly-reactive antigen to stimulate immune responses against a panel of influenza strains that lead to a Universal influenza vaccine is critical for the future of influenza vaccine development. COBRA elicits responses against panels of H5N1 influenza viruses. This technology has been applied for H1N1, H3N2, H7N9, H2N2, and B influenza strains.**

Giles BM and **Ross TM**. Development of a computationally optimized broadly reactive (COBRA) hemagglutinin for elicitation of protective antibodies against multiple clades of H5N1. 2011. *Vaccine*. 29:3043-54.

Giles BM, Bissel SJ, DeAlmeida DR, Wiley CA, and **Ross TM**. Antibody Breadth and protective efficacy is Increased by Vaccination with Computationally Optimized Hemagglutinin but not with Polyvalent Hemagglutinin base H5N1 VLP Vaccines. 2012. *Clin Vacc Immunol*. 19:128-39. PMCID: PMC3272934.

Carter DM, Darby CA, Lefoley BC, Crevar CJ, Alefantis T, Oomen R, Anderson SF, Strugnell T, Cortés-Garcia G, Vogel TU, Parrington M, Kleanthous H, **Ross TM**. Design and Characterization of a Computationally Optimized Broadly Reactive Hemagglutinin vaccine for H1N1 influenza viruses. COBRA HA vaccine. 2016. *J Virol.* 90(9):4720-4723.

Allen JD, Owino SO, Carter DM, Crevar CJ, Evers T, Fox CB, Coler RN, Reed SG, Baldwin SL, **Ross, TM**. Broadened immunity and protective responses with an emulsion-adjuvanted H5 COBRA VLP vaccine. 2017. *Vaccine*. 35(38):5209-5216

**2. Sequential infection of seasonal influenza viruses elicit antibodies to pandemic influenza strains. Understanding why older, middle-aged, and younger individuals are protected against emerging influenza virus strains is a fundamental question in the influenza field and for influenza vaccine development. Pre-existing immunity is critical of the effective function of a seasonal or universal influenza vaccine.**

Carter DM, Bloom CE, Nascimento EJ, Marques ETA, Craig JK, Cherry JL, Lipman DJ, **Ross TM**. Sequential Ferret H1N1 influenza infection elicits neutralizing Abs to emerging H1N1 isolates. 2013. *J Virol.* 87:1400-1410.

Kirchenbaum GA, Carter DM, **Ross TM**. Sequential Infection in Ferrets with Seasonal H1N1 Influenza Boost Hemagglutinin Stalk Specific Antibodies. 2016. *J. Virol.* 90:1116-1128.

Kirchenbaum GA, **Ross TM**. Generation of Monoclonal Antibodies against Immunoglobulin Proteins of the Domestic Ferret (*Mustela putorius furo*). J Immunol Res. 2017. 5874572. doi: 10.1155/2017/5874572.

Nuñez IA, Carlock MA, Allen JD, Owino SO, Moehling K, Nowalk MP, Diagle K, Sweeney K, Mundle S, Vogel TU, Delagrange S, Ramgopal M, Zimmerman RK, Kleanthous H, **Ross TM**. Impact of age and pre-existing influenza immunity in humans on the elicitation of anti-hemagglutinin antibodies receiving split inactivated influenza vaccines. 2017. PLoS One. 12(11). E0185666.

**3. Understanding antibody and B cell responses in people with pre-existing immunity to influenza following consecutive seasonal vaccination with split-inactivated influenza vaccines. The multi-year, coordinated, serologic assessment of reactivity against a panel of H1N1 and H3N2 viral isolates will educate subject selection and will enable evaluation of the central hypothesis that individuals with serological breadth against an array of seasonal influenza A and B strains will possess a larger and more broadly reactive HA-specific memory B cell and/or plasmablasts in subjects with limited Ab reactivity.**

Abreu RB, Kirchenbaum GA, Clutter EF, **Ross TM**. Memory B cell recall following vaccination with split inactivated influenza vaccine in children, teens, adults, and the elderly. 2020. J. Clin. Invest. Insight. In press.

Sautto GA, Kirchenbaum GA, Abreu RB, Ecker JW, Pierce SR, Kleanthous H, **Ross TM**. Characterization of H1 HA COBRA induced Ab epitope mapping by monoclonal antibodies. 2020. J. Immunol. 204(2):375-385.

Carlock MA, Ingram JG, Clutter EF, Cecil NC, Ramgopal M, Zimmerman RK, Kleanthous K, **Ross TM**. Impact of age and pre-existing influenza on the induction of human antibody responses against influenza B viruses. Hum Vacc Immunother. 2019. 15(9):2030-2043.

Moehling KK, Nowalk MP, Lin CJ, Bertolet M, **Ross TM**, Carter CE, Susick M, Saul SG, Kaynar AM, Bromberger JT, Zimmerman RK. The Effect of frailty on HAI response to influenza vaccine among community-dwelling adults  $\geq$ 50 years of age. Hum Vaccin Immunother. 2018. 14(2):361-367.

#### D. Additional Information: Research Support and/or Scholastic Performance

##### Ongoing Research Support

**NIH/NIAID 1R01AI132205 Partnership Award (PI: DeGroot) Period Covered: 08/17-7/22**

**Title: Structure-Guided Design of CD4 T cell Memory-Enhanced rHA H7N9 Influenza.**

In this program, we will produce and test novel rH7-HA vaccines designed to broaden the memory CD4+ T cell repertoire recruited upon vaccination for enhanced immunity. Then identify the most immunogenic and protective design with fewest epitopes introduced to serve as the platform molecule for design refinement. Both B cell and T cell responses will be assessed in seasonal influenza pre-immune HLA transgenic mice and (ii) CD4+ T cell and B cell antigenicity using peripheral blood leukocytes from seasonal influenza human vaccinees. The lead candidate will be identified with minimum mutational load and maximal immunogenicity and protective efficacy that is ready for IND enabling studies by the end of the award period.

**NIH/NIAID CERIS Option 15 (PI: Orenstein)**

**Period Covered: 09/17-9/21**

While pre-existing influenza immunity influences the recall response to seasonal vaccination, it remains unclear *how the composition of serum antibody and B cell memory is shaped by annual vaccination over the course of multiple seasons*. Addressing this fundamental question will further develop our understanding of how individuals respond to vaccination and advance efforts toward development of broadly protective influenza vaccines with improved efficacy in all populations. To address this question, serum antibody, memory B cells, and vaccine-elicited plasmablasts from young and elderly subjects receiving annual influenza vaccination in multiple seasons as compared to one season will be profiled. The multi-year, coordinated, serologic assessment of reactivity against a panel of IAV and IBV isolates will enable evaluation of the central hypothesis that individuals with serological breadth against an array of seasonal influenza A and B strains will possess a larger and more broadly reactive HA-specific memory B cell and/or plasmablasts relative to subjects with limited antibody reactivity.

**NIH/NIAID Collaborative Influenza Vaccine Innovation Centers (CIVIC). (PI: Ross) Period: 09/19-09/26**

The Contract uses an integration of comprehensive vaccine development, design, optimization and testing with assessment of immunological and non-immunological host parameters, statistical modeling of vaccine and infection-induced responses to determine profiles and biomarkers that predict which vaccine candidates and formulations will be most effective in humans including high-risk populations.

ACTIVE

(UO1, Shacker) 04/1/2020 – 03/31/2025 0.24 calendar months  
NIH/NIAID \$1,000,000 (DC:\$666,667 / IDC:\$333,333)

**The effect of inflammation and damage to lymph node structures on durable protective immunity following vaccination**

*Yellow Fever vaccination in people.*

Role: co-I

Assessment of serum samples from YFV vaccinated subjects.

ACTIVE

(Contract, Guzman) 04/1/2020 – 03/31/2025 2.4 calendar months  
European Union (EU) \$1,000,000 (DC:\$666,667 / IDC:\$333,333)

**Indo-European Consortium for Next Generation Influenza Vaccine Innovation (INCENTIVE)**

*Developing HA and NA vaccines in preclinical and clinical studies.*

Role: Project co-PI

The Contract uses an integration of comprehensive vaccine development, design, optimization and testing in mice, ferrets, and non-human primates followed by clinical trials in Europe and India subjects with assessment of immunological parameters to determine profiles and biomarkers that predict which vaccine candidates.

ACTIVE

(RO1, Ainslie) 01/15/2020 – 01/14/2025 1.2 calendar months  
NIH/NIAID \$375,000 Influenza (DC:\$250,00 / IDC:\$125,000)

**Development of a Microparticles expressing universal NA and HA antigens**

Role: co-I

Design and testing microparticle based vaccines for immune response in mice and ferrets.

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Rustom Antia

ERA COMMONS USER NAME (credential, e.g., agency login): rantia

POSITION TITLE: Professor of Biology

**EDUCATION/TRAINING** (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE <i>(if applicable)</i>	Completion Date MM/YYYY	FIELD OF STUDY
Indian Institute of Technology, Bombay	MSc	06/1983	Physics
University of Massachusetts, Amherst	PhD	02/1991	Molecular & Cellular Biology
Imperial College, London	Post-doc	09/1994	Mathematical Biology

**A. Personal Statement**

My research interests span a range of problems on host-pathogen interactions, and involves modeling across scales. At the within-host scale, I study fundamental aspects of the immune system, such as the generation of a diverse repertoire of antigen-specific lymphocytes, how the immune system discriminates between self and pathogens, and the differentiation of cells during responses and immunological memory. I apply this basic understanding of the immune system to explore the dynamics of human infections with a focus on influenza, but also malaria and HIV. We link these models at the within host scale with epidemiological models for the transmission of pathogens in a population of hosts. This allows us to address basic questions on the evolution of pathogens and their virulence, as well as applied questions on the design of vaccines.

A current focus of my research is the dynamics of responses to influenza and coronaviruses. We are particularly interested in how the waning of immunity and strain variation affect the dynamics of infection and boosting of immunity following exposure to new strains of the virus. We are particularly interested in responses to conserved regions of the influenza that could be the targets for a universal influenza vaccine. The current collaborative project with Dr. Handel serves to extend these studies focusing on the effect of inoculum size on the dynamics of responses to influenza.

My group is relatively small, consisting of a couple of post-docs and graduate students. Most of the post-doctoral fellows have prior training in quantitative fields such as mathematics and physics. Almost all have moved directly to faculty positions at major universities worldwide. I have played a role in advising graduate students in more experimental areas and fostering the integration of quantitative approaches with their experimental studies.

Ongoing and recently completed projects that I would like to highlight include:

U19 AI 117891 (Antia/Ahmed MPI)            04/01/2015 – 03/31/2020 (NCE 2021)  
Modeling the dynamics and evolution of immune responses to influenza viruses

U01AI117891, NIH/NIAID (Antia/Ahmed MPI)            4/2020 – 3/2025  
Dynamics and evolution of immune responses to influenza

Citations:

1. Moore JR, Ahmed H, Manicassamy B, Garcia-Sastre A, Handel A, and Antia R. (2020) Varying Inoculum Dose to Assess the Roles of the Immune Response and Target Cell Depletion by the Pathogen in Control of Acute Viral Infections. *Bulletin of Mathematical Biology* 82:35.
2. Lavine JS, Bjornstad ON, Antia R (2021) Immunological characteristics govern the transition of COVID-19 to endemicity. *Science* 371, 741-745.
3. Bull JJ, Nuismer S and Antia R (2019) Recombinant vector vaccine evolution. *PLoS Computational Biology*. 15: e1006857.

## B. Positions, Scientific Appointments, and Honors

2009 - : Samuel Candler Dobbs Professor of Biology, Emory University  
 2007 - : Professor, Department of Biology, Emory University  
 2000 - 2007 : Associate Professor, Department of Biology, Emory University  
 1994 - 2000 : Assistant Professor, Department of Biology, Emory University

## C. Contributions to Science

### I. Basic rules for the dynamics of immune responses and immunological memory

We have used models to explore the *differentiation and dynamics of CD8 T responses*, and in particular the 'programmed' nature of immune responses (i.e., continued division of CD8 T cells after stimulation independent of the presence of the pathogen), which is an energetically costly strategy that may have evolved to provide a robust defense against pathogens that are trying to subvert the generation of immune responses. Following resolution of an infection, the immune system maintains long-term *memory* that confers protection against subsequent infections by the same pathogen. We have analyzed the longevity of humoral (antibody) responses in both humans and in the mouse model system. We are currently interested in why antibody responses to protein antigens decay faster than those elicited by infections with live viruses.

- a. Antia A, Ahmed H, Handel A, Carlson NE, Amanna IJ, Antia R, Slifka M (2018) Heterogeneity and longevity of antibody memory to viruses and vaccines. *PLOS Biology* 16 e2006601.
- b. Youngblood B, Hale JS, Kissick HT, Ahn E, Xu X, Wieland, Araki K, West EE, Ghoneim HE, Fan Y, Dogra P, Davis CW, Konieczny BT, Antia R, Cheng X, & Ahmed R. (2017) *Nature* **552**: 404-409.
- c. Vezys V, Yates A, Casey KA, Lanier G, Ahmed R, Antia R & Masopust D. (2009) Memory CD8 T-cell compartment grows in size with immunological experience. *Nature*. **457**:196-199.

## 2. Dynamics of infections

We are interested in the dynamics of both acute infections that exhibit strain variation such as influenza, as well as persistent infections such as malaria and HIV.

We are interested in how the influenza virus uses strain variation to escape immunity. We are addressing this question by developing a quantitative framework for how pre-existing immunity affects the dynamics of subsequent responses. Our current models for the dynamics of antibody responses suggest that interference between antibodies to different epitopes plays a key role in regulating the dynamics of recall responses to influenza and other viruses that exhibit strain variation. We plan to apply this framework to design strategies that will allow boosting of responses to conserved epitopes shared by different influenza strains.

Persistent infections such as malaria and HIV are probably the biggest ongoing threat to human health. We know surprisingly little about what regulates the dynamics of the pathogen and what causes pathology during these infections. Antigenic variation is a common strategy used to escape immunity and generate infections of a long duration.

- a. Bharal S, PL, Antia R, and Dixit N. (2019) A dynamical motif comprising the interactions between antigens and CD8 T cells may underlie the outcomes of viral infections. *Proc.Natl.Acad.Sci.* **116**: 17393-17398.
- b. Zarnitsyna VI, Lavine J, Ellebedy A, Ahmed R, Antia R (2016) Multi-epitope models explain how pre-existing antibodies affect the generation of broadly protective responses to influenza. *PLOS Pathogens* **12(6)**:e1005692.
- c. Handel, A., Longini, I.M. & Antia, R. (2010) Towards a quantitative understanding of the within-host dynamics of influenza A infections. *J R Soc Interface*. **7**: 35-47.

### **3. Cross-scale models linking the dynamics and evolution of infections within and between hosts**

To cite Dobzyanski, nothing in biology makes sense except in the light of evolution. We are interested in a number of evolutionary questions such as why do pathogens harm their hosts and to what extent can we predict changes in the virulence of pathogens, and how does the interplay between ecological and evolutionary factors affect the emergence of novel pathogens. We have developed a quantitative framework that links the magnitude of the components of the immune response (viz. antibodies, CD4 and CD8 T cells, etc.) with different measures of a vaccine's efficacy at preventing infection ( $VE_S$ ), reducing pathology ( $VE_P$ ) and reducing transmission ( $VE_I$ ), and are applying this to infections such as influenza, CoV-2 and malaria.

- a. Lavine JS, Bjornstad ON, Antia R (2021) Immunological characteristics govern the transition of COVID-19 to endemicity. *Science* 371, 741-745.
- b. Zarnitsyna VI, Bulusheva I, Handel A, Longini IM, Halloran ME, and Antia R (2018) Intermediate levels of vaccination coverage may minimize seasonal influenza outbreaks. *PLOS one* **13**:e0199674.
- c. Antia R, Regoes RR, Koella JC, & Bergstrom CT, (2003) The role of evolution in the emergence of infectious diseases. *Nature* **26**:658-661.

#### **Complete List of Published Work in My Bibliography:**

<http://www.ncbi.nlm.nih.gov/pubmed/?term=%22antia+r%22%5BAU%5D>

**BIOGRAPHICAL SKETCH**

Provide the following information for the Senior/key personnel and other significant contributors.  
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

---

NAME: Zarnitsyna, Veronika I.

---

ERA COMMONS USER NAME (credential, e.g., agency login): VZARNITSYNA

---

POSITION TITLE: Assistant Professor, Department of Microbiology and Immunology

---

EDUCATION/TRAINING (*Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.*)

INSTITUTION AND LOCATION	DEGREE (if applicable)	Completion Date MM/YYYY	FIELD OF STUDY
Moscow Institute of Physics and Technology	MS	06/1994	Physics
Institute of Theoretical and Experimental Biophysics, Puschino, Russia	PhD	12/1997	Biophysics
Georgia Institute of Technology, Atlanta, GA	Postdoctoral	06/2007	Biophysics
Emory University, Atlanta, GA	Postdoctoral	07/2014	Immunology

#### A. Personal Statement

During my PhD training, I developed my love of using mathematical models to enhance our understanding of biological processes. I studied a blood coagulation enzymatic cascade and predictions of my model of spatial thrombus growth resulted in creating a clinical hemophilia test. That experience led to my appreciation of the importance of integrative approach with experiments and modeling complementing and enhancing each other.

To seek greater scientific opportunities and have the chance to develop cutting edge new approaches on a world-class stage, I moved from Russia to US, where I became a Research Scientist in the laboratory of Professor Cheng Zhu at Georgia Institute of Technology. I enriched my modeling toolbox by many state-of-the-art experimental techniques and focused on study of T cell receptor interaction with peptide-MHC (TCR-pMHC affinity, T cell discrimination between different peptides, T cell receptor repertoire and cross-reactivity). My key contributions to that topic were published in *Nature*, *PNAS* and other journals.

Since joining Emory University, I am doing integrative work with data from human studies and mouse immunity experiments, modeling humoral and cellular adaptive immunity to viral infections and vaccination. This proposal aims to develop a robust framework for prediction of the impact of vaccine dose on immunogenicity and safety for current and future influenza vaccines. I have expertise in developing the mathematical models of adaptive immune response to influenza viral infection and vaccination and in statistical analysis of longitudinal immune response (for both antibody and CD8 T cell data) in human studies using mixed effects models. This proposal integrates modeling with experiments using ferret animal model data and longitudinal human data after influenza infection and vaccination and builds on strong established collaborations between myself, Andreas Handel, and Rustom Antia groups as confirmed by track record of many of our joint publications. I believe we have a very strong team of experimentalists and modelers to apply the best available techniques and expertise to address the question of optimizing vaccine dose and to successfully complete the proposed research.

Ongoing and recently completed projects that I would like to highlight include:

U01 HL139483  
Zarnitsyna (MPI with Dr. Jacob E. Kohlmeier)  
09/01/18-05/31/23

## Multi-scale modeling of influenza vaccination for optimal T cell immunity

U01 AI150747

Antia (PI), Role: Co-Investigator

06/29/2020-05/31/2025

Dynamics and evolution of immune responses to influenza viruses

U19 AI057266-17S1

Ahmed (PI), Role: Co-Investigator

06/01/2020 -05/31/2022

Immunological memory to COVID-19

### Citations:

1. A. Handel, V. Akin, S.S. Pilyugin, V. Zarnitsyna, R. Antia. How sticky should a virus be? The impact of virus binding and release on transmission fitness using influenza as an example. *Journal of The Royal Society Interface*, 11 (92), 20131083, 2014.
2. V.I. Zarnitsyna, A. Handel, S.R. McMaster, S.L. Hayward, J.E. Kohlmeier, R. Antia. Mathematical Model Reveals the Role of Memory CD8 T Cell Populations in Recall Responses to Influenza. *Frontiers in Immunology*. May 9; 7:165, PMID: 27242779, 2016.
3. V. I. Zarnitsyna, I. Bulusheva, A. Handel, I. M. Longini, M. E. Halloran, R. Antia. Intermediate Levels of Vaccination Coverage May Minimize Seasonal Influenza Outbreaks. *PLOS ONE* 13 (6), e0199674, 2018.
4. A. Handel, Y. Li, B. McKay, K. Pawelek, V. Zarnitsyna, R. Antia. Exploring the impact of inoculum dose on host immunity and morbidity to inform model-based vaccine design. *PLOS Computational Biology*, 14(10): e1006505, PMID: 30273336, 2018.

## B. Positions, Scientific Appointments, and Honors

04/2021-current	Review Editor, <i>Frontiers in Immunology</i> (System Immunology)
12/2019-current	Member, The American Association of Immunologists (AAI)
09/2015-current	Assistant Professor, Microbiology and Immunology Department, Emory University
07/2015-09/2015	Research Associate, Biology Department, Emory University
01/2013-06/2014	Postdoctoral fellow, Biology Department, Emory University
07/2007-12/2012	Research Scientist II, Joint Georgia Tech/Emory Department of Biomedical Engineering
11/2001-06/2007	Postdoctoral fellow, Woodruff School of Mechanical Engineering, Georgia Institute of Technology
12/1997-10/2001	Research Scientist/Senior Research Scientist, National Research Center for Hematology, Laboratory of Physical Biochemistry of Blood, Moscow, Russia

## Honors

2011	Sigma Xi Best Paper Award, Georgia Tech Chapter
2008	Sigma Xi Best Paper Award, Georgia Tech Chapter
2003	Catherine Filene Shouse Grant for attending summer course "Physiology" in MBL
2003	David Wolf award "Best biophysics in Analytical and Quantitative Microscopy"
2001	Travel Grant to attend the Gordon Research Conference on Nonlinear Science, South Hadley, MA, June 17-22, 2001
2001	Winner of Federal Russian President Program "Integracia" competition for scientists

## C. Contributions to Science

1. Spatio-temporal dynamics of blood clotting. Analysis of the blood coagulation cascade pathway allowed us to dissect the roles of individual reactions in the different phases of thrombus formation (such as activation, propagation and termination) and to predict the existence of novel reactions playing a key role in the final phase of clotting (the termination of propagation). Intrinsic coagulation pathway was thought to be

a “metabolic atavism” without any significant role in the thrombus formation, but our study has been shown that it is essential and determines the second phase of clotting – its propagation. Additionally, our theoretical analysis of thrombus growth has revealed that blood can be viewed as a first experimental example of double-active medium and it has led to a novel branch in the theory of active media and synergetics.

- a. **V.I. Zarnitsina**, A.V. Pokhilko and F.I. Ataullakhanov. A mathematical model for the spatio-temporal dynamics of intrinsic pathway of blood coagulation. I. The model description. *Thrombosis Research*, 84 (4): 225-236, 1996.
  - b. **V.I. Zarnitsina**, A.V. Pokhilko and F.I. Ataullakhanov. A mathematical model for the spatio-temporal dynamics of intrinsic pathway of blood coagulation. II. Results. *Thrombosis Research*, 84 (5): 333-344, 1996.
  - c. M.A. Panteleev, **V.I. Zarnitsina**, F.I. Ataullakhanov. Tissue Factor Pathway Inhibitor: a Possible Mechanism of Action. *Eur.J. Biochem*, 269 (8): 2016-2031, 2002.
  - d. **V.I. Zarnitsina**, F.I. Ataullakhanov, A.I. Lobanov, and O.L. Morozova. Dynamics of spatially nonuniform patterning in the model of blood coagulation. *Chaos: An Interdisciplinary Journal of Nonlinear Science*, 11 (1): 57-70, 2001.
  - e. F.I. Ataullakhanov, **V.I. Zarnitsina**, A.V. Pokhilko, A.I. Lobanov, O.L. Morozova. Spatio-temporal dynamics of blood coagulation and pattern formation: a theoretical approach. *International Journal of Bifurcation and Chaos*, 12 (09), 1985-2002, 2002.
2. T cell receptor interaction with peptide-MHC (TCR-pMHC affinity and discrimination between different peptides). I have used Micropipette Adhesion Frequency assay and Bio-membrane Force Probe assay to measure the two-dimensional affinity for T cell receptor-pMHC interaction. The results have shown that these measurements correlate better with T cell functional responses in comparison to three-dimensional affinity traditionally measured by surface plasmon resonance (SPR) technique. These studies suggest the important role of T cell receptor organization and the effect of its microenvironment on the cell surface.
- a. **V.I. Zarnitsyna**, J. Huang, F. Zhang, Y.-H. Chien, D.E. Leckband, and C. Zhu. Memory in receptor-ligand mediated cell adhesion. *Proceedings of the National Academy of Sciences of the United States of America*, 104: 18037-18042, PMID: 17991779, 2007.
  - b. J. Huang, **V.I. Zarnitsyna**, B. Liu, L.J. Edwards, N. Jiang, B.D. Evavold, and C. Zhu. The kinetics of two dimensional TCR and pMHC interactions determine T cell responsiveness. *Nature*, 464: 932-936, PMID: 20357766, 2010
  - c. **V.I. Zarnitsyna** and C. Zhu. T cell triggering: insights from 2D kinetics analysis of molecular interactions. *Physical Biology*, 9: 045005, PMID: 22871794, 2012.
  - d. S. Pryshchep, **V.I. Zarnitsyna**, J. Hong, B.D. Evavold, C. Zhu. Accumulation of serial forces on TCR and CD8 frequently applied by agonist pMHC triggers calcium in T cell, *The Journal of Immunology*, 193(1): 68-76, PMID: 24890718, 2014.
3. T cell repertoire and cross-reactivity. One of the immunological puzzles is why mice and humans have similar repertoires even though humans have over 1000-fold more T cells. We proposed how the idea of the “protecon,” the smallest unit of protection, might explain this discrepancy and estimated the size of “protecon” based on available precursor frequencies data. We also extended existing calculations to estimate the extent of expected T cell cross-reactivity between the responses to different pathogens. Our results are consistent with two observations: a low probability of observing cross-reactivity between the immune responses to two randomly chosen pathogens; and the ensemble of memory cells being sufficiently diverse to generate cross-reactive responses to new pathogens. One of the way to quantify the T cell functional diversity is by measuring the spread of T cell two-dimensional affinities for a given pathogen. Using this unique approach, we compared the distributions of regulatory and T effector cells affinities for self-peptides in demyelinating disease.
- a. **V.I. Zarnitsyna**, B. D. Evavold, L. N. Schoettle, J. N. Blattman, R. Antia. Estimating the diversity, completeness, and cross-reactivity of the T cell repertoire. *Frontiers in Immunology*, 4: 485. eCollection, PMID: 24421780, 2013.
  - b. J.D. Hood, **V.I. Zarnitsyna**, C. Zhu, B.D. Evavold. Regulatory and T Effector Cells Have Overlapping Low to High Ranges in TCR Affinities for Self during Demyelinating Disease. *The Journal of Immunology*, 195 (9), 4162-4170, PMID: 26385521, 2015.

4. Modeling the adaptive immune response to influenza virus. We have used mathematical models of the humoral immune response to explore how pre-existing immunity affects the ability of vaccines to boost antibodies to the head and stem of HA in humans, and, in particular, how it leads to the lack of boosting of broadly cross-reactive antibodies to the stem epitopes. We also analyzed a mathematical model to study in detail the impact of attachment and detachment rates on virus fitness. We applied our model to influenza, where stickiness is determined by a balance of the hemagglutinin (HA) and neuraminidase (NA) proteins, and investigated how drugs, the adaptive immune response and vaccines may impact influenza stickiness and fitness. We also explored how different subsets of memory T cells can contribute to protection from following influenza infections.
- a. A. Handel, V. Akin, S.S. Pilyugin, **V. Zarnitsyna**, R. Antia. How sticky should a virus be? The impact of virus binding and release on transmission fitness using influenza as an example. *Journal of The Royal Society Interface*, 11 (92), 20131083, 2014
  - b. **V.I. Zarnitsyna**, J. Lavine, A.H. Ellebedy, R. Ahmed, R. Antia. Multi-epitope Models Explain How Pre-existing Antibodies Affect the Generation of Broadly Protective Responses to Influenza. *PLoS Pathogens*. Jun 23;12(6):e1005692. PMID: 27336297, 2016.
  - c. **V.I. Zarnitsyna**, A. Handel, S.R. McMaster, S.L. Hayward, J.E. Kohlmeier, R. Antia. Mathematical Model Reveals the Role of Memory CD8 T Cell Populations in Recall Responses to Influenza. *Front Immunol*. May 9;7:165, PMID: 27242779, 2016.
  - d. A.H. Ellebedy, R. Nachbagauer, K. J.L. Jackson, Y.-N. Dai, J. Han, C.W. Davis, D. Stadlbauer, N. Rouphael, V. Chromikova, M. McCausland, C. Chang, M. Cortese, M. Bower, C. Chennareddy, A.J. Schmitz, **V.I. Zarnitsyna**, L. Lai, A. Rajabhathor, C. Kazemian, R. Antia, M. Mulligan, A.B. Ward, D. Fremont, S.D. Boyd, B. Pulendran, F. Krammer, R. Ahmed. S03 adjuvant enhances both HA head and stem specific antibody responses in humans after H5N1 influenza vaccination. *Proceedings of the National Academy of Sciences of the United States of America*, 117(30): 17957-17964, 2020
  - e. N. Doria-Rose, M.S. Suthar, M. Makowski, S. O'Connell, A. B. McDermott, B. Flach, J.E. Ledgerwood, J. R. Mascola, B. S. Graham, B. C. Lin, S. O'Dell, S. D. Schmidt, A. T. Widge, V.-V. Edara, E. J. Anderson, L. Lai, K. Floyd, N. G. Rouphael, **V. Zarnitsyna**, P. C. Roberts, M. Makhene, W. Buchanan, C. J. Luke, J. H. Beigel, L. A. Jackson, K. M. Neuzil, H. Bennett, B. Leav, J. Albert, P. Kunwar. Antibody Persistence through 6 Months after the Second Dose of mRNA-1273 Vaccine for Covid-19. *The New England Journal of Medicine*, April 6, 2021, DOI: 10.1056/NEJMc2103916

Please, note that spelling of my name on publications slightly changed from “Zarnitsina” to “Zarnitsyna” as Russian transliteration rules changed when I received my foreign passport in 2001.

Link to the complete list of publications:

[https://pubmed.ncbi.nlm.nih.gov/?term=\(Zarnitsina%5BAuthor%5D\)%20OR%20\(Zarnitsyna%5BAuthor%5D\)&sort=](https://pubmed.ncbi.nlm.nih.gov/?term=(Zarnitsina%5BAuthor%5D)%20OR%20(Zarnitsyna%5BAuthor%5D)&sort=)

## RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

ORGANIZATIONAL DUNS\*: 004315578

**Budget Type\***:   ● Project   ○ Subaward/Consortium

**Enter name of Organization:** University of Georgia Research Foundation Inc.

**Start Date\***: 04-01-2022

**End Date\***: 03-31-2023

**Budget Period:** 1

### A. Senior/Key Person

	Prefix First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1.	Andreas		Handel		PD/PI	107,048.00	0	2	0	23,788.00	8,564.00	32,352.00
2.	Andreas		Handel		PD/PI	35,683.00	0	0	2	23,788.00	5,471.00	29,259.00
3.	Ye		Shen		Co-Investigator	93,759.00	0	0.5	0	5,209.00	1,875.00	7,084.00
4.	Ye		Shen		Co-Investigator	31,253.00	0	0	1	10,418.00	2,396.00	12,814.00
5.	Ted		Ross		Co-Investigator	149,475.00	0	0	0.45	7,474.00	2,691.00	10,165.00

**Total Funds Requested for all Senior Key Persons in the attached file**

**0.00**

<b>Additional Senior Key Persons:</b>	File Name:	<b>Total Senior/Key Person</b>	<b>91,674.00</b>
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### B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
1	Post Doctoral Associates	12	0	0	60,000.00	27,600.00	87,600.00
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Coordinator	9	0	0	28,125.00	12,938.00	41,063.00
1	Research Technician	9	0	0	26,250.00	12,075.00	38,325.00
<b>3</b>	<b>Total Number Other Personnel</b>					<b>Total Other Personnel</b>	<b>166,988.00</b>
						<b>Total Salary, Wages and Fringe Benefits (A+B)</b>	<b>258,662.00</b>

RESEARCH & RELATED Budget {A-B} (Funds Requested)

## RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1

ORGANIZATIONAL DUNS\*: 004315578

Budget Type\*: ● Project ○ Subaward/Consortium

Organization: University of Georgia Research Foundation Inc.

Start Date\*: 04-01-2022

End Date\*: 03-31-2023

Budget Period: 1

C. Equipment Description	
List items and dollar amount for each item exceeding \$5,000	
Equipment Item	Funds Requested (\$)*
Total funds requested for all equipment listed in the attached file	0.00
Total Equipment	0.00
Additional Equipment: File Name:	

D. Travel	
1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)	8,000.00
2. Foreign Travel Costs	4,000.00
Total Travel Cost	12,000.00

E. Participant/Trainee Support Costs	
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees	Total Participant Trainee Support Costs

RESEARCH & RELATED Budget {C-E} (Funds Requested)

# RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1

**ORGANIZATIONAL DUNS\*:** 004315578

**Budget Type\*:** ● Project ○ Subaward/Consortium

**Organization:** University of Georgia Research Foundation Inc.

**Start Date\*:** 04-01-2022

**End Date\*:** 03-31-2023

**Budget Period:** 1

<b>F. Other Direct Costs</b>		<b>Funds Requested (\$)*</b>
1. Materials and Supplies		67,000.00
2. Publication Costs		0.00
3. Consultant Services		0.00
4. ADP/Computer Services		0.00
5. Subawards/Consortium/Contractual Costs		148,675.00
6. Equipment or Facility Rental/User Fees		0.00
7. Alterations and Renovations		0.00
8 . Animal Related Costs		66,200.00
<b>Total Other Direct Costs</b>		<b>281,875.00</b>

<b>G. Direct Costs</b>		<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>		<b>552,537.00</b>

<b>H. Indirect Costs</b>			
<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
1 . Research/Fed/OnCampus (MTDC)	51	428,862.00	218,719.00
<b>Total Indirect Costs</b>			<b>218,719.00</b>
<b>Cognizant Federal Agency</b>			DHHS, Steve Zuraf, 202-401-2808
(Agency Name, POC Name, and POC Phone Number)			

<b>I. Total Direct and Indirect Costs</b>		<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>		<b>771,256.00</b>

<b>J. Fee</b>		<b>Funds Requested (\$)*</b>
0.00		

<b>K. Total Costs and Fee</b>		<b>Funds Requested (\$)*</b>
771,256.00		

<b>L. Budget Justification*</b>	File Name: UGA_Budget_Justification.pdf (Only attach one file.)
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RESEARCH & RELATED Budget {F-K} (Funds Requested)

## RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

ORGANIZATIONAL DUNS\*: 004315578

**Budget Type\***:   ● Project   ○ Subaward/Consortium

**Enter name of Organization:** University of Georgia Research Foundation Inc.

**Start Date\***: 04-01-2023

**End Date\***: 03-31-2024

**Budget Period:** 2

### A. Senior/Key Person

	Prefix First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1.	Andreas		Handel		PD/PI	0.00	0	2	0	24,502.00	8,821.00	33,323.00
2.	Andreas		Handel		PD/PI	0.00	0	2	0	24,502.00	5,635.00	30,137.00
3.	Ye		Shen		Co-Investigator	0.00	0	0.5	0	5,365.00	1,931.00	7,296.00
4.	Ye		Shen		Co-Investigator	0.00	0	0	1	10,730.00	2,468.00	13,198.00
5.	Ted		Ross		Co-Investigator	0.00	0	0.45	0	7,474.00	2,771.00	10,245.00

**Total Funds Requested for all Senior Key Persons in the attached file**

**0.00**

<b>Additional Senior Key Persons:</b>	File Name:	<b>Total Senior/Key Person</b>	<b>94,199.00</b>
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### B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
1	Post Doctoral Associates	12	0	0	61,800.00	28,428.00	90,228.00
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Coordinator	9	0	0	28,969.00	13,326.00	42,295.00
1	Research Technician	9	0	0	27,038.00	12,437.00	39,475.00
<b>3</b>	<b>Total Number Other Personnel</b>					<b>Total Other Personnel</b>	<b>171,998.00</b>
					<b>Total Salary, Wages and Fringe Benefits (A+B)</b>		<b>266,197.00</b>

RESEARCH & RELATED Budget {A-B} (Funds Requested)

## RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2

ORGANIZATIONAL DUNS\*: 004315578

Budget Type\*: ● Project ○ Subaward/Consortium

Organization: University of Georgia Research Foundation Inc.

Start Date\*: 04-01-2023

End Date\*: 03-31-2024

Budget Period: 2

<b>C. Equipment Description</b>	
List items and dollar amount for each item exceeding \$5,000	
Equipment Item	Funds Requested (\$)*
Total funds requested for all equipment listed in the attached file	0.00
Total Equipment	0.00
Additional Equipment: File Name:	

<b>D. Travel</b>	
1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)	8,000.00
2. Foreign Travel Costs	4,000.00
Total Travel Cost	12,000.00

<b>E. Participant/Trainee Support Costs</b>	
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees	Total Participant Trainee Support Costs

RESEARCH & RELATED Budget {C-E} (Funds Requested)

## RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2

**ORGANIZATIONAL DUNS\*:** 004315578

**Budget Type\*:**  Project  Subaward/Consortium

**Organization:** University of Georgia Research Foundation Inc.

**Start Date\*:** 04-01-2023

**End Date\*:** 03-31-2024

**Budget Period:** 2

<b>F. Other Direct Costs</b>		<b>Funds Requested (\$)*</b>
1. Materials and Supplies		48,500.00
2. Publication Costs		0.00
3. Consultant Services		0.00
4. ADP/Computer Services		0.00
5. Subawards/Consortium/Contractual Costs		148,675.00
6. Equipment or Facility Rental/User Fees		0.00
7. Alterations and Renovations		0.00
8 . Animal Related Costs		61,600.00
<b>Total Other Direct Costs</b>		<b>258,775.00</b>

<b>G. Direct Costs</b>		<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>		<b>536,972.00</b>

<b>H. Indirect Costs</b>			
<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
1 . Research/Fed/OnCampus (MTDC)	51	388,297.00	198,032.00
<b>Total Indirect Costs</b>			<b>198,032.00</b>
<b>Cognizant Federal Agency</b>			DHHS, Steve Zuraf, 202-401-2808
(Agency Name, POC Name, and POC Phone Number)			

<b>I. Total Direct and Indirect Costs</b>		<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>		<b>735,004.00</b>

<b>J. Fee</b>		<b>Funds Requested (\$)*</b>
		<b>0.00</b>

<b>K. Total Costs and Fee</b>		<b>Funds Requested (\$)*</b>
		<b>735,004.00</b>

<b>L. Budget Justification*</b>	File Name: UGA_Budget_Justification.pdf (Only attach one file.)
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RESEARCH & RELATED Budget {F-K} (Funds Requested)

## RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 3

ORGANIZATIONAL DUNS\*: 004315578

**Budget Type\***:   ● Project   ○ Subaward/Consortium

**Enter name of Organization:** University of Georgia Research Foundation Inc.

Start Date\*: 04-01-2024

End Date\*: 03-31-2025

Budget Period: 3

### A. Senior/Key Person

	Prefix First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1 .	Andreas		Handel		PD/PI	0.00	0	2	0	25,237.00	9,085.00	34,322.00
2 .	Andreas		Handel		PD/PI	0.00	0	0	2	25,237.00	5,805.00	31,042.00
3 .	Ye		Shen		Co-Investigator	0.00	0	0.5	0	5,526.00	1,989.00	7,515.00
4 .	Ye		Shen		Co-Investigator	0.00	0	0	1	11,052.00	2,542.00	13,594.00
5 .	Ted		Ross		Co-Investigator	0.00	0	0.45	0	7,474.00	2,771.00	10,245.00

Total Funds Requested for all Senior Key Persons in the attached file

0.00

Additional Senior Key Persons:	File Name:	Total Senior/Key Person	96,718.00
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### B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
1	Post Doctoral Associates	12	0	0	63,654.00	29,281.00	92,935.00
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Coordinator	9	0	0	29,838.00	13,725.00	43,563.00
1	Research Technician	9	0	0	27,849.00	12,810.00	40,659.00
3	<b>Total Number Other Personnel</b>					<b>Total Other Personnel</b>	<b>177,157.00</b>
					<b>Total Salary, Wages and Fringe Benefits (A+B)</b>		<b>273,875.00</b>

RESEARCH & RELATED Budget {A-B} (Funds Requested)

## RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3

ORGANIZATIONAL DUNS\*: 004315578

Budget Type\*: ● Project ○ Subaward/Consortium

Organization: University of Georgia Research Foundation Inc.

Start Date\*: 04-01-2024

End Date\*: 03-31-2025

Budget Period: 3

C. Equipment Description	
List items and dollar amount for each item exceeding \$5,000	
Equipment Item	Funds Requested (\$)*
Total funds requested for all equipment listed in the attached file	0.00
Total Equipment	0.00
Additional Equipment: File Name:	

D. Travel	
1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)	8,000.00
2. Foreign Travel Costs	4,000.00
Total Travel Cost	12,000.00

E. Participant/Trainee Support Costs	
1. Tuition/Fees/Health Insurance	
2. Stipends	
3. Travel	
4. Subsistence	
5. Other:	
Number of Participants/Trainees	Total Participant Trainee Support Costs

RESEARCH & RELATED Budget {C-E} (Funds Requested)

## RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 3

**ORGANIZATIONAL DUNS\*:** 004315578

**Budget Type\*:** ● Project ○ Subaward/Consortium

**Organization:** University of Georgia Research Foundation Inc.

**Start Date\*:** 04-01-2024

**End Date\*:** 03-31-2025

**Budget Period:** 3

<b>F. Other Direct Costs</b>		<b>Funds Requested (\$)*</b>
1. Materials and Supplies		49,955.00
2. Publication Costs		8,000.00
3. Consultant Services		0.00
4. ADP/Computer Services		0.00
5. Subawards/Consortium/Contractual Costs		148,675.00
6. Equipment or Facility Rental/User Fees		0.00
7. Alterations and Renovations		0.00
8 . Animal Related Costs		53,600.00
<b>Total Other Direct Costs</b>		<b>260,230.00</b>

<b>G. Direct Costs</b>		<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>		<b>546,105.00</b>

<b>H. Indirect Costs</b>			
<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
1 . Research/Fed/OnCampus (MTDC)	51	397,431.00	202,690.00
<b>Total Indirect Costs</b>			<b>202,690.00</b>
<b>Cognizant Federal Agency</b>			DHHS, Steve Zuraf, 202-401-2808
(Agency Name, POC Name, and POC Phone Number)			

<b>I. Total Direct and Indirect Costs</b>		<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>		<b>748,795.00</b>

<b>J. Fee</b>		<b>Funds Requested (\$)*</b>
0.00		

<b>K. Total Costs and Fee</b>		<b>Funds Requested (\$)*</b>
748,795.00		

<b>L. Budget Justification*</b>	File Name: UGA_Budget_Justification.pdf (Only attach one file.)
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RESEARCH & RELATED Budget {F-K} (Funds Requested)

## RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 4

ORGANIZATIONAL DUNS\*: 004315578

**Budget Type\***:   ● Project   ○ Subaward/Consortium

**Enter name of Organization:** University of Georgia Research Foundation Inc.

**Start Date\***: 04-01-2025

**End Date\***: 03-31-2026

**Budget Period:** 4

### A. Senior/Key Person

	Prefix First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1 .	Andreas		Handel		PD/PI	0.00	0	2	0	25,994.00	9,358.00	35,352.00
2 .	Andreas		Handel		PD/PI	0.00	0	0	2	25,994.00	5,975.00	31,969.00
3 .	Ye		Shen		Co-Investigator	0.00	0	0.5	0	5,692.00	2,049.00	7,741.00
4 .	Ye		Shen		Co-Investigator	0.00	0	0	1	11,384.00	2,618.00	14,002.00
5 .	Ted		Ross		Co-Investigator	0.00	0	0.45	0	7,474.00	2,771.00	10,245.00

**Total Funds Requested for all Senior Key Persons in the attached file**

**0.00**

<b>Additional Senior Key Persons:</b>	File Name:	<b>Total Senior/Key Person</b>	<b>99,309.00</b>
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### B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
1	Post Doctoral Associates	12	0	0	65,564.00	30,159.00	95,723.00
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Coordinator	9	0	0	30,733.00	14,137.00	44,870.00
1	Research Technician	9	0	0	28,684.00	13,195.00	41,879.00
<b>3</b>	<b>Total Number Other Personnel</b>				<b>Total Other Personnel</b>		<b>182,472.00</b>
					<b>Total Salary, Wages and Fringe Benefits (A+B)</b>		<b>281,781.00</b>

RESEARCH & RELATED Budget {A-B} (Funds Requested)

## RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 4

ORGANIZATIONAL DUNS\*: 004315578

Budget Type\*: ● Project ○ Subaward/Consortium

Organization: University of Georgia Research Foundation Inc.

Start Date\*: 04-01-2025

End Date\*: 03-31-2026

Budget Period: 4

### C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item

Funds Requested (\$)\*

Total funds requested for all equipment listed in the attached file

0.00

Total Equipment

0.00

Additional Equipment: File Name:

### D. Travel

Funds Requested (\$)\*

1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)

8,000.00

2. Foreign Travel Costs

4,000.00

Total Travel Cost

12,000.00

### E. Participant/Trainee Support Costs

Funds Requested (\$)\*

1. Tuition/Fees/Health Insurance

2. Stipends

3. Travel

4. Subsistence

5. Other:

Number of Participants/Trainees

Total Participant Trainee Support Costs

RESEARCH & RELATED Budget {C-E} (Funds Requested)

## RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 4

**ORGANIZATIONAL DUNS\*:** 004315578

**Budget Type\*:** ● Project ○ Subaward/Consortium

**Organization:** University of Georgia Research Foundation Inc.

**Start Date\*:** 04-01-2025

**End Date\*:** 03-31-2026

**Budget Period:** 4

<b>F. Other Direct Costs</b>		<b>Funds Requested (\$)*</b>
1. Materials and Supplies		48,500.00
2. Publication Costs		8,000.00
3. Consultant Services		0.00
4. ADP/Computer Services		0.00
5. Subawards/Consortium/Contractual Costs		148,675.00
6. Equipment or Facility Rental/User Fees		0.00
7. Alterations and Renovations		0.00
8 . Animal Related Costs		53,600.00
<b>Total Other Direct Costs</b>		<b>258,775.00</b>

<b>G. Direct Costs</b>		<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>		<b>552,556.00</b>

<b>H. Indirect Costs</b>			
<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
1 . Research/Fed/OnCampus (MTDC)	51	403,885.00	205,981.00
<b>Total Indirect Costs</b>			<b>205,981.00</b>
<b>Cognizant Federal Agency</b>			DHHS, Steve Zuraf, 202-401-2808
(Agency Name, POC Name, and POC Phone Number)			

<b>I. Total Direct and Indirect Costs</b>		<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>		<b>758,537.00</b>

<b>J. Fee</b>		<b>Funds Requested (\$)*</b>
		<b>0.00</b>

<b>K. Total Costs and Fee</b>		<b>Funds Requested (\$)*</b>
		<b>758,537.00</b>

<b>L. Budget Justification*</b>	File Name: UGA_Budget_Justification.pdf (Only attach one file.)
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RESEARCH & RELATED Budget {F-K} (Funds Requested)

## RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 5

ORGANIZATIONAL DUNS\*: 004315578

**Budget Type\***:   ● Project   ○ Subaward/Consortium

**Enter name of Organization:** University of Georgia Research Foundation Inc.

Start Date\*: 04-01-2026

End Date\*: 03-31-2027

Budget Period: 5

### A. Senior/Key Person

	Prefix First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1 .	Andreas		Handel		PD/PI	0.00	0	2	0	26,774.00	9,639.00	36,413.00
2 .	Andreas		Handel		PD/PI	0.00	0	0	2	26,774.00	6,158.00	32,932.00
3 .	Ye		Shen		Co-Investigator	0.00	0	0.5	0	5,863.00	2,111.00	7,974.00
4 .	Ye		Shen		Co-Investigator	0.00	0	0	1	11,725.00	2,697.00	14,422.00
5 .	Ted		Ross		Co-Investigator	0.00	0	0.45	0	7,474.00	2,771.00	10,245.00

Total Funds Requested for all Senior Key Persons in the attached file

0.00

Additional Senior Key Persons: File Name: Total Senior/Key Person 101,986.00

### B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
1	Post Doctoral Associates	12	0	0	67,531.00	31,064.00	98,595.00
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	Research Coordinator	9	0	0	31,655.00	14,561.00	46,216.00
1	Research Technician	9	0	0	29,545.00	13,591.00	43,136.00
<b>3</b>	<b>Total Number Other Personnel</b>					<b>Total Other Personnel</b>	<b>187,947.00</b>
					<b>Total Salary, Wages and Fringe Benefits (A+B)</b>		<b>289,933.00</b>

RESEARCH & RELATED Budget {A-B} (Funds Requested)

## RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 5

ORGANIZATIONAL DUNS\*: 004315578

Budget Type\*:  Project  Subaward/Consortium

Organization: University of Georgia Research Foundation Inc.

Start Date\*: 04-01-2026

End Date\*: 03-31-2027

Budget Period: 5

### C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
<b>Total funds requested for all equipment listed in the attached file</b>	<b>0.00</b>
<b>Total Equipment</b>	<b>0.00</b>
Additional Equipment: File Name:	

### D. Travel

	Funds Requested (\$)*
1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)	8,000.00
2. Foreign Travel Costs	4,000.00
<b>Total Travel Cost</b>	<b>12,000.00</b>

### E. Participant/Trainee Support Costs

1. Tuition/Fees/Health Insurance
2. Stipends
3. Travel
4. Subsistence
5. Other:

Number of Participants/Trainees

Total Participant Trainee Support Costs

RESEARCH & RELATED Budget {C-E} (Funds Requested)

## RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 5

**ORGANIZATIONAL DUNS\*:** 004315578

**Budget Type\*:** ● Project ○ Subaward/Consortium

**Organization:** University of Georgia Research Foundation Inc.

**Start Date\*:** 04-01-2026

**End Date\*:** 03-31-2027

**Budget Period:** 5

<b>F. Other Direct Costs</b>		<b>Funds Requested (\$)*</b>
1. Materials and Supplies		41,500.00
2. Publication Costs		8,000.00
3. Consultant Services		0.00
4. ADP/Computer Services		0.00
5. Subawards/Consortium/Contractual Costs		148,675.00
6. Equipment or Facility Rental/User Fees		0.00
7. Alterations and Renovations		0.00
8 . Animal Related Costs		47,300.00
<b>Total Other Direct Costs</b>		<b>245,475.00</b>

<b>G. Direct Costs</b>		<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>		<b>547,408.00</b>

<b>H. Indirect Costs</b>			
<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
1 . Research/Fed/OnCampus (MTDC)	51	398,731.00	203,353.00
<b>Total Indirect Costs</b>			<b>203,353.00</b>
<b>Cognizant Federal Agency</b>			DHHS, Steve Zuraf, 202-401-2808
(Agency Name, POC Name, and POC Phone Number)			

<b>I. Total Direct and Indirect Costs</b>		<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>		<b>750,761.00</b>

<b>J. Fee</b>		<b>Funds Requested (\$)*</b>
0.00		

<b>K. Total Costs and Fee</b>		<b>Funds Requested (\$)*</b>
750,761.00		

<b>L. Budget Justification*</b>	File Name: UGA_Budget_Justification.pdf (Only attach one file.)
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RESEARCH & RELATED Budget {F-K} (Funds Requested)

## UGA BUDGET JUSTIFICATION

### **SENIOR/KEY PERSONNEL**

#### **Andreas Handel, Principal Investigator** (2 Academic and 2 Summer months EFT/YR).

Dr. Handel will be leading the project. He will be coordinating all parts of the project. Jointly with Dr. Shen, he will be overseeing and mentoring the UGA-based postdoc. He will also be directly involved in the model building and analysis.

#### **Ye Shen, Co- Investigator** (.5 Academic and 1 Summer months ETF/YR)

Dr. Shen will be part of the modeling and data analysis group. He will focus on statistical analysis and help oversee those aspects of the project, co-mentoring the UGA based postdoc with Dr. Handel.

#### **Ted M. Ross, PhD, Principal Investigator** (.45 academic months EFT/yr.),

Dr. Ross has published many articles in peer review journals regarding influenza infection and vaccine development. Dr. Ross has expertise in virology and immunology. Dr. Ross has significant experience with influenza modeling in both animal models and human vaccine trials, analyzing antibody responses, and determining breadth of vaccine elicited responses. He will oversee and direct the animal trials.

### **Other Personnel**

**Spencer Pierce, Research Professional** (9 calendar months EFT/yr.): Mr. Pierce is under the direction of Dr. Ross. He will assist with animal trials and analyze data as needed.

**Hua Shi, Research Technician** (9 calendar months EFT/yr.): Mr. Shi is under the direction of Dr. Ross and will assist with the animal trials.

### **TDB, Post Doc, (100% 12 month effort/YR)**

A Post Doc will be the main individual responsible for coding and implementing the models and fitting procedures. He will be mentored by and will work alongside Dr. Handel and Dr. Shen.

### **Travel:** \$10,000 per year for five years.

We request \$8,000 each year to cover 1 domestic trip each for Dr. Handel, Dr. Shen, Dr. Ross and the postdoc to present their work at conferences and scientific meetings.

Each trip may cost \$2000 with airfare (\$1000); three days of hotel (\$600), and meals and incidentals (\$400).

An additional \$4,000 each year is requested for 1 international trip to present work at international conferences for one of the UGA team members.

### **Supplies:**

\$4,500 is requested in year 1 for purchasing a high-performance computer workstation (Dual Processor, 20 Core Dell Precision T7920 or equivalent). This machine will be used to perform most of the data fitting.

A total of 260 ferrets (4 groups with 60 each, 20 animals for dose-finding and ancillary studies) will be purchased, at a cost of \$700/ferret.

Lab supplies will be purchased to perform the necessary assays (HAI, Fluidigm and flow cytometry) as described in the research plan.

Shipping costs for animals and supplies are budgeted.

#### **Other Direct Costs:**

Animal per diem housing costs and flow cytometry facility use charges are budgeted.

#### **FRINGE BENEFITS**

Fringe benefits are calculated at the following rates:

Annual Salaries above \$75,000 have a fringe rate of 36%

Annual Salaries between \$50,000-\$74,999 have a fringe rate of 38%

Annual Salaries between \$35,000-49,999 have a fringe rate of 46%

Annual Salaries below \$35,000 have a fringe rate of 23%

Summer Salaries have a fringe rate of 23%

Graduate students have a 5% fringe rate.

#### **INDIRECT COSTS**

University's federally negotiated indirect costs are charged at 51% of the modified total direct costs per DHHS Agreement.

## RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals (\$)
Section A, Senior/Key Person	483,886.00
Section B, Other Personnel	886,562.00
Total Number Other Personnel	15
Total Salary, Wages and Fringe Benefits (A+B)	1,370,448.00
Section C, Equipment	0.00
Section D, Travel	60,000.00
1. Domestic	40,000.00
2. Foreign	20,000.00
Section E, Participant/Trainee Support Costs	0.00
1. Tuition/Fees/Health Insurance	0.00
2. Stipends	0.00
3. Travel	0.00
4. Subsistence	0.00
5. Other	0.00
6. Number of Participants/Trainees	0
Section F, Other Direct Costs	1,305,130.00
1. Materials and Supplies	255,455.00
2. Publication Costs	24,000.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	743,375.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Other 1	282,300.00
9. Other 2	0.00
10. Other 3	0.00
Section G, Direct Costs (A thru F)	2,735,578.00
Section H, Indirect Costs	1,028,775.00
Section I, Total Direct and Indirect Costs (G + H)	3,764,353.00
Section J, Fee	0.00
Section K, Total Costs and Fee (I + J)	3,764,353.00

## RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 1

ORGANIZATIONAL DUNS\*: 6646993300000

**Budget Type\***:  Project  Subaward/Consortium

**Enter name of Organization:** Emory University

**Start Date\***: 04-01-2022

**End Date\***: 03-31-2023

**Budget Period:** 1

### A. Senior/Key Person

	Prefix First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1.	Rustom		Antia		Co-Investigator	199,300.00	0.5	0	0	8,305.00	2,467.00	10,772.00
2.	Veronika		Zarnitsyna		Co-Investigator	90,000.00	2	0	0	15,000.00	4,455.00	19,455.00

**Total Funds Requested for all Senior Key Persons in the attached file**

<b>Additional Senior Key Persons:</b>	File Name:	<b>Total Senior/Key Person</b>	<b>30,227.00</b>
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### B. Other Personnel

Number of Personnel*	Project Role*	Calendar Months	Academic Months	Summer Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*
1	Post Doctoral Associates	9.76	0	0	44,723.00	13,283.00	58,006.00
	Graduate Students						
	Undergraduate Students						
	Secretarial/Clerical						
1	<b>Total Number Other Personnel</b>				<b>Total Other Personnel</b>	<b>58,006.00</b>	
					<b>Total Salary, Wages and Fringe Benefits (A+B)</b>	<b>88,233.00</b>	

RESEARCH & RELATED Budget {A-B} (Funds Requested)

## RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 1

ORGANIZATIONAL DUNS\*: 6646993300000

Budget Type\*:  Project  Subaward/Consortium

Organization: Emory University

Start Date\*: 04-01-2022

End Date\*: 03-31-2023

Budget Period: 1

### C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
<b>Total funds requested for all equipment listed in the attached file</b>	<b>0.00</b>
<b>Total Equipment</b>	<b>0.00</b>
Additional Equipment: File Name:	

### D. Travel

	Funds Requested (\$)*
1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)	5,000.00
2. Foreign Travel Costs	0.00
<b>Total Travel Cost</b>	<b>5,000.00</b>

### E. Participant/Trainee Support Costs

1. Tuition/Fees/Health Insurance
2. Stipends
3. Travel
4. Subsistence
5. Other:

**Total Participant Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

# RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 1

**ORGANIZATIONAL DUNS\*:** 6646993300000

**Budget Type\*:**  Project  Subaward/Consortium

**Organization:** Emory University

**Start Date\*:** 04-01-2022

**End Date\*:** 03-31-2023

**Budget Period:** 1

<b>F. Other Direct Costs</b>		<b>Funds Requested (\$)*</b>
1. Materials and Supplies		1,767.00
2. Publication Costs		0.00
3. Consultant Services		0.00
4. ADP/Computer Services		0.00
5. Subawards/Consortium/Contractual Costs		0.00
6. Equipment or Facility Rental/User Fees		0.00
7. Alterations and Renovations		0.00
<b>Total Other Direct Costs</b>		<b>1,767.00</b>

<b>G. Direct Costs</b>		<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>		<b>95,000.00</b>

<b>H. Indirect Costs</b>		<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
1 . MTDC			56.5	95,000.00	53,675.00
<b>Total Indirect Costs</b>					<b>53,675.00</b>
<b>Cognizant Federal Agency</b>					DHHS, Steve Zuraf, 301-492-4855
(Agency Name, POC Name, and POC Phone Number)					

<b>I. Total Direct and Indirect Costs</b>		<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>		<b>148,675.00</b>

<b>J. Fee</b>		<b>Funds Requested (\$)*</b>
		<b>0.00</b>

<b>K. Total Costs and Fee</b>		<b>Funds Requested (\$)*</b>
		<b>148,675.00</b>

<b>L. Budget Justification*</b>	File Name: Emory_Budget_Justification.pdf (Only attach one file.)
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RESEARCH & RELATED Budget {F-K} (Funds Requested)

## RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 2

ORGANIZATIONAL DUNS\*: 6646993300000

**Budget Type\***:  Project  Subaward/Consortium

**Enter name of Organization:** Emory University

**Start Date\***: 04-01-2023

**End Date\***: 03-31-2024

**Budget Period:** 2

### A. Senior/Key Person

	Prefix First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1.	Rustom		Antia		Co-Investigator	199,300.00	0	0.5	0	8,305.00	2,467.00	10,772.00
2.	Veronika		Zarnitsyna		Co-Investigator	90,000.00	2	0	0	15,450.00	4,588.00	20,038.00
<b>Total Funds Requested for all Senior Key Persons in the attached file</b>												<b>0.00</b>
<b>Additional Senior Key Persons:</b> File Name:										<b>Total Senior/Key Person</b>		<b>30,810.00</b>

### B. Other Personnel

Number of Personnel*	Project Role*	Calendar	Months	Academic	Months	Summer	Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*	
1	Post Doctoral Associates		9.76		0		0		44,723.00		13,284.00
	Graduate Students										
	Undergraduate Students										
	Secretarial/Clerical										
<b>1</b>	<b>Total Number Other Personnel</b>								<b>Total Other Personnel</b>		<b>58,007.00</b>
									<b>Total Salary, Wages and Fringe Benefits (A+B)</b>		<b>88,817.00</b>

RESEARCH & RELATED Budget {A-B} (Funds Requested)

## RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 2

ORGANIZATIONAL DUNS\*: 6646993300000

Budget Type\*:  Project  Subaward/Consortium

Organization: Emory University

Start Date\*: 04-01-2023

End Date\*: 03-31-2024

Budget Period: 2

### C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
<b>Total funds requested for all equipment listed in the attached file</b>	<b>0.00</b>
<b>Total Equipment</b>	<b>0.00</b>
Additional Equipment: File Name:	

### D. Travel

	Funds Requested (\$)*
1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)	5,000.00
2. Foreign Travel Costs	0.00
<b>Total Travel Cost</b>	<b>5,000.00</b>

### E. Participant/Trainee Support Costs

1. Tuition/Fees/Health Insurance
2. Stipends
3. Travel
4. Subsistence
5. Other:

**Total Participant Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

## RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 2

**ORGANIZATIONAL DUNS\*:** 6646993300000

**Budget Type\*:**  Project  Subaward/Consortium

**Organization:** Emory University

**Start Date\*:** 04-01-2023

**End Date\*:** 03-31-2024

**Budget Period:** 2

<b>F. Other Direct Costs</b>		<b>Funds Requested (\$)*</b>
1. Materials and Supplies		1,183.00
2. Publication Costs		0.00
3. Consultant Services		0.00
4. ADP/Computer Services		0.00
5. Subawards/Consortium/Contractual Costs		0.00
6. Equipment or Facility Rental/User Fees		0.00
7. Alterations and Renovations		0.00
<b>Total Other Direct Costs</b>		<b>1,183.00</b>

<b>G. Direct Costs</b>		<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>		<b>95,000.00</b>

<b>H. Indirect Costs</b>		<b>Indirect Cost Type</b>	<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
1 . MTDC			56.5	95,000.00	53,675.00
<b>Total Indirect Costs</b>					<b>53,675.00</b>
<b>Cognizant Federal Agency</b>					DHHS, Steve ZUraf, 301-492.4855
(Agency Name, POC Name, and POC Phone Number)					

<b>I. Total Direct and Indirect Costs</b>		<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>		<b>148,675.00</b>

<b>J. Fee</b>		<b>Funds Requested (\$)*</b>
		<b>0.00</b>

<b>K. Total Costs and Fee</b>		<b>Funds Requested (\$)*</b>
		<b>148,675.00</b>

<b>L. Budget Justification*</b>		File Name: Emory_Budget_Justification.pdf
(Only attach one file.)		

RESEARCH & RELATED Budget {F-K} (Funds Requested)

## RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 3

ORGANIZATIONAL DUNS\*: 6646993300000

**Budget Type\***:  Project  Subaward/Consortium

**Enter name of Organization:** Emory University

**Start Date\***: 04-01-2024

**End Date\***: 03-31-2025

**Budget Period:** 3

### A. Senior/Key Person

	Prefix First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1.	Rustom		Antia		Co-Investigator	199,300.00	0	0.5	0	8,305.00	2,467.00	10,772.00
2.	Veronika		Zarnitsyna		Co-Investigator	90,000.00	2	0	0	15,914.00	4,726.00	20,640.00
<b>Total Funds Requested for all Senior Key Persons in the attached file</b>												<b>0.00</b>
<b>Additional Senior Key Persons:</b> File Name:										<b>Total Senior/Key Person</b>		<b>31,412.00</b>

### B. Other Personnel

Number of Personnel*	Project Role*	Calendar	Months	Academic	Months	Summer	Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*	
1	Post Doctoral Associates		9.76		0		0		44,723.00		13,283.00
	Graduate Students										
	Undergraduate Students										
	Secretarial/Clerical										
<b>1</b>	<b>Total Number Other Personnel</b>								<b>Total Other Personnel</b>		<b>58,006.00</b>
									<b>Total Salary, Wages and Fringe Benefits (A+B)</b>		<b>89,418.00</b>

RESEARCH & RELATED Budget {A-B} (Funds Requested)

## RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 3

ORGANIZATIONAL DUNS\*: 6646993300000

Budget Type\*:  Project  Subaward/Consortium

Organization: Emory University

Start Date\*: 04-01-2024

End Date\*: 03-31-2025

Budget Period: 3

### C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
<b>Total funds requested for all equipment listed in the attached file</b>	<b>0.00</b>
<b>Total Equipment</b>	<b>0.00</b>
Additional Equipment: File Name:	

### D. Travel

	Funds Requested (\$)*
1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)	5,000.00
2. Foreign Travel Costs	0.00
<b>Total Travel Cost</b>	<b>5,000.00</b>

### E. Participant/Trainee Support Costs

1. Tuition/Fees/Health Insurance
2. Stipends
3. Travel
4. Subsistence
5. Other:

**Total Participant Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

## RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 3

**ORGANIZATIONAL DUNS\*:** 6646993300000

**Budget Type\*:**  Project  Subaward/Consortium

**Organization:** Emory University

**Start Date\*:** 04-01-2024

**End Date\*:** 03-31-2025

**Budget Period:** 3

<b>F. Other Direct Costs</b>		<b>Funds Requested (\$)*</b>
1. Materials and Supplies		582.00
2. Publication Costs		0.00
3. Consultant Services		0.00
4. ADP/Computer Services		0.00
5. Subawards/Consortium/Contractual Costs		0.00
6. Equipment or Facility Rental/User Fees		0.00
7. Alterations and Renovations		0.00
<b>Total Other Direct Costs</b>		<b>582.00</b>

<b>G. Direct Costs</b>		<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>		<b>95,000.00</b>

<b>H. Indirect Costs</b>		<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
<b>Indirect Cost Type</b>				
1 . MTDC				56.5 95,000.00 53,675.00
<b>Total Indirect Costs</b>				<b>53,675.00</b>
<b>Cognizant Federal Agency</b> (Agency Name, POC Name, and POC Phone Number)				

<b>I. Total Direct and Indirect Costs</b>		<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>		<b>148,675.00</b>

<b>J. Fee</b>		<b>Funds Requested (\$)*</b>
		<b>0.00</b>

<b>K. Total Costs and Fee</b>		<b>Funds Requested (\$)*</b>
		<b>148,675.00</b>

<b>L. Budget Justification*</b>		File Name: Emory_Budget_Justification.pdf (Only attach one file.)

RESEARCH & RELATED Budget {F-K} (Funds Requested)

## RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 4

ORGANIZATIONAL DUNS\*: 6646993300000

**Budget Type\***:  Project  Subaward/Consortium

**Enter name of Organization:** Emory University

**Start Date\***: 04-01-2025

**End Date\***: 03-31-2026

**Budget Period:** 4

### A. Senior/Key Person

	Prefix First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1.	Rustom		Antia		Co-Investigator	199,300.00	0	0.5	0	8,305.00	2,467.00	10,772.00
2.	Veronika		Zarnitsyna		Co-Investigator	90,000.00	2	0	0	16,391.00	4,868.00	21,259.00
<b>Total Funds Requested for all Senior Key Persons in the attached file</b>												<b>0.00</b>
<b>Additional Senior Key Persons:</b> File Name:										<b>Total Senior/Key Person</b>		<b>32,031.00</b>

### B. Other Personnel

Number of Personnel*	Project Role*	Calendar	Months	Academic	Months	Summer	Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*	
1	Post Doctoral Associates		9.76		0		0		44,723.00		13,283.00
	Graduate Students										
	Undergraduate Students										
	Secretarial/Clerical										
<b>1</b>	<b>Total Number Other Personnel</b>								<b>Total Other Personnel</b>		<b>58,006.00</b>
									<b>Total Salary, Wages and Fringe Benefits (A+B)</b>		<b>90,037.00</b>

RESEARCH & RELATED Budget {A-B} (Funds Requested)

## RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 4

ORGANIZATIONAL DUNS\*: 6646993300000

Budget Type\*:  Project  Subaward/Consortium

Organization: Emory University

Start Date\*: 04-01-2025

End Date\*: 03-31-2026

Budget Period: 4

### C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
<b>Total funds requested for all equipment listed in the attached file</b>	<b>0.00</b>
<b>Total Equipment</b>	<b>0.00</b>
Additional Equipment: File Name:	

### D. Travel

	Funds Requested (\$)*
1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)	4,963.00
2. Foreign Travel Costs	0.00
<b>Total Travel Cost</b>	<b>4,963.00</b>

### E. Participant/Trainee Support Costs

1. Tuition/Fees/Health Insurance
2. Stipends
3. Travel
4. Subsistence
5. Other:

**Total Participant Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

## RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 4

**ORGANIZATIONAL DUNS\*:** 6646993300000

**Budget Type\*:**  Project  Subaward/Consortium

**Organization:** Emory University

**Start Date\*:** 04-01-2025

**End Date\*:** 03-31-2026

**Budget Period:** 4

<b>F. Other Direct Costs</b>		<b>Funds Requested (\$)*</b>
1. Materials and Supplies		0.00
2. Publication Costs		0.00
3. Consultant Services		0.00
4. ADP/Computer Services		0.00
5. Subawards/Consortium/Contractual Costs		0.00
6. Equipment or Facility Rental/User Fees		0.00
7. Alterations and Renovations		0.00
<b>Total Other Direct Costs</b>		<b>0.00</b>

<b>G. Direct Costs</b>		<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>		<b>95,000.00</b>

<b>H. Indirect Costs</b>		<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
<b>Indirect Cost Type</b>				
1 . MTDC		56.5	95,000.00	53,675.00
<b>Total Indirect Costs</b>				<b>53,675.00</b>
<b>Cognizant Federal Agency</b>	DHHS, Steve Zuraf, 301-492-4855			
(Agency Name, POC Name, and POC Phone Number)				

<b>I. Total Direct and Indirect Costs</b>		<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>		<b>148,675.00</b>

<b>J. Fee</b>		<b>Funds Requested (\$)*</b>
		<b>0.00</b>

<b>K. Total Costs and Fee</b>		<b>Funds Requested (\$)*</b>
		<b>148,675.00</b>

<b>L. Budget Justification*</b>	File Name: Emory_Budget_Justification.pdf (Only attach one file.)
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RESEARCH & RELATED Budget {F-K} (Funds Requested)

## RESEARCH & RELATED BUDGET - SECTION A & B, Budget Period 5

ORGANIZATIONAL DUNS\*: 6646993300000

**Budget Type\***:  Project  Subaward/Consortium

**Enter name of Organization:** Emory University

**Start Date\***: 04-01-2026

**End Date\***: 03-31-2027

**Budget Period:** 5

### A. Senior/Key Person

	Prefix First Name*	Middle Name	Last Name*	Suffix	Project Role*	Base	Calendar	Academic	Summer	Requested	Fringe	Funds Requested (\$)*
						Salary (\$)	Months	Months	Months	Salary (\$)*	Benefits (\$)*	
1.	Rustom		Antia		Co-Investigator	199,300.00	0	0.5	0	8,305.00	2,467.00	10,772.00
2.	Veronika		Zarnitsyna		PD/PI	90,000.00	2	0	0	16,883.00	5,014.00	21,897.00
<b>Total Funds Requested for all Senior Key Persons in the attached file</b>												<b>0.00</b>
<b>Additional Senior Key Persons:</b> File Name:										<b>Total Senior/Key Person</b>		<b>32,669.00</b>

### B. Other Personnel

Number of Personnel*	Project Role*	Calendar	Months	Academic	Months	Summer	Months	Requested Salary (\$)*	Fringe Benefits*	Funds Requested (\$)*	
1	Post Doctoral Associates		9.76		0		0		44,723.00		13,283.00
	Graduate Students										
	Undergraduate Students										
	Secretarial/Clerical										
<b>1</b>	<b>Total Number Other Personnel</b>								<b>Total Other Personnel</b>		<b>58,006.00</b>
									<b>Total Salary, Wages and Fringe Benefits (A+B)</b>		<b>90,675.00</b>

RESEARCH & RELATED Budget {A-B} (Funds Requested)

## RESEARCH & RELATED BUDGET - SECTION C, D, & E, Budget Period 5

ORGANIZATIONAL DUNS\*: 6646993300000

Budget Type\*:  Project  Subaward/Consortium

Organization: Emory University

Start Date\*: 04-01-2026

End Date\*: 03-31-2027

Budget Period: 5

### C. Equipment Description

List items and dollar amount for each item exceeding \$5,000

Equipment Item	Funds Requested (\$)*
<b>Total funds requested for all equipment listed in the attached file</b>	<b>0.00</b>
<b>Total Equipment</b>	<b>0.00</b>
Additional Equipment: File Name:	

### D. Travel

	Funds Requested (\$)*
1. Domestic Travel Costs ( Incl. Canada, Mexico, and U.S. Possessions)	4,325.00
2. Foreign Travel Costs	0.00
<b>Total Travel Cost</b>	<b>4,325.00</b>

### E. Participant/Trainee Support Costs

1. Tuition/Fees/Health Insurance
2. Stipends
3. Travel
4. Subsistence
5. Other:

**Total Participant Trainee Support Costs**

RESEARCH & RELATED Budget {C-E} (Funds Requested)

## RESEARCH & RELATED BUDGET - SECTIONS F-K, Budget Period 5

**ORGANIZATIONAL DUNS\*:** 6646993300000

**Budget Type\*:**  Project  Subaward/Consortium

**Organization:** Emory University

**Start Date\*:** 04-01-2026

**End Date\*:** 03-31-2027

**Budget Period:** 5

<b>F. Other Direct Costs</b>		<b>Funds Requested (\$)*</b>
1. Materials and Supplies		0.00
2. Publication Costs		0.00
3. Consultant Services		0.00
4. ADP/Computer Services		0.00
5. Subawards/Consortium/Contractual Costs		0.00
6. Equipment or Facility Rental/User Fees		0.00
7. Alterations and Renovations		0.00
<b>Total Other Direct Costs</b>		<b>0.00</b>

<b>G. Direct Costs</b>		<b>Funds Requested (\$)*</b>
<b>Total Direct Costs (A thru F)</b>		<b>95,000.00</b>

<b>H. Indirect Costs</b>		<b>Indirect Cost Rate (%)</b>	<b>Indirect Cost Base (\$)</b>	<b>Funds Requested (\$)*</b>
Indirect Cost Type				
1 . MTDC		56.5	95,000.00	53,675.00
<b>Total Indirect Costs</b>				<b>53,675.00</b>
<b>Cognizant Federal Agency</b>				DHHS, Steve Zuraf, 301-492-4855
(Agency Name, POC Name, and POC Phone Number)				

<b>I. Total Direct and Indirect Costs</b>		<b>Funds Requested (\$)*</b>
<b>Total Direct and Indirect Institutional Costs (G + H)</b>		<b>148,675.00</b>

<b>J. Fee</b>		<b>Funds Requested (\$)*</b>
		<b>0.00</b>

<b>K. Total Costs and Fee</b>		<b>Funds Requested (\$)*</b>
		<b>148,675.00</b>

<b>L. Budget Justification*</b>	File Name: Emory_Budget_Justification.pdf (Only attach one file.)
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RESEARCH & RELATED Budget {F-K} (Funds Requested)

# **Emory Budget Justification**

Dr. Rustom Antia (The Department of Biology), Co-Investigator (effort = 0.5 academic months), and Dr. Veronika Zarnitsyna (The Department of Microbiology & Immunology), Co-Investigator (effort = 2 calendar months) will contribute their expertise to model development and fitting. They will jointly supervise a postdoctoral fellow (TBN, effort = 9.76 months), who will undertake developing models, implementing them in Monolix, and performing statistical analyses. Dr. Zarnitsyna and Dr. Antia share a common space in which the post-doc will work.

Fringe benefits are calculated at the current Emory University rate of 29.7%.

## **Travel**

The travel budget includes \$5,000 year1-3, \$4963 YR 4, and \$4325 YR 5, for Dr. Antia, Dr. Zarnitsyna and a postdoc which will be one meeting in the US annually.

## **Computer supplies**

Small costs for computer supplies (\$3,532 total in 5 years) are requested by Dr. Zarnitsyna.

Indirect Costs are calculated at the rate of 56.5%.

## RESEARCH & RELATED BUDGET - Cumulative Budget

	Totals (\$)
Section A, Senior/Key Person	157,149.00
Section B, Other Personnel	290,031.00
Total Number Other Personnel	5
Total Salary, Wages and Fringe Benefits (A+B)	447,180.00
Section C, Equipment	0.00
Section D, Travel	24,288.00
1. Domestic	24,288.00
2. Foreign	0.00
Section E, Participant/Trainee Support Costs	0.00
1. Tuition/Fees/Health Insurance	0.00
2. Stipends	0.00
3. Travel	0.00
4. Subsistence	0.00
5. Other	0.00
6. Number of Participants/Trainees	0
Section F, Other Direct Costs	3,532.00
1. Materials and Supplies	3,532.00
2. Publication Costs	0.00
3. Consultant Services	0.00
4. ADP/Computer Services	0.00
5. Subawards/Consortium/Contractual Costs	0.00
6. Equipment or Facility Rental/User Fees	0.00
7. Alterations and Renovations	0.00
8. Other 1	0.00
9. Other 2	0.00
10. Other 3	0.00
Section G, Direct Costs (A thru F)	475,000.00
Section H, Indirect Costs	268,375.00
Section I, Total Direct and Indirect Costs (G + H)	743,375.00
Section J, Fee	0.00
Section K, Total Costs and Fee (I + J)	743,375.00

**Total Direct Costs less Consortium F&A**

NIH policy (NOT-OD-05-004) allows applicants to exclude consortium/contractual F&A costs when determining if an application falls at or beneath any applicable direct cost limit. When a direct cost limit is specified in an FOA, the following table can be used to determine if your application falls within that limit.

<b>Categories</b>	<b>Budget Period 1</b>	<b>Budget Period 2</b>	<b>Budget Period 3</b>	<b>Budget Period 4</b>	<b>Budget Period 5</b>	<b>TOTALS</b>
Total Direct Costs less Consortium F&A	498,862	483,297	492,430	498,881	493,733	<b>2,467,203</b>

# PHS 398 Cover Page Supplement

OMB Number: 0925-0001

Expiration Date: 02/28/2023

## 1. Vertebrate Animals Section

Are vertebrate animals euthanized?       Yes       No

If "Yes" to euthanasia

Is the method consistent with American Veterinary Medical Association (AVMA) guidelines?

Yes       No

If "No" to AVMA guidelines, describe method and provide scientific justification

.....

## 2. \*Program Income Section

\*Is program income anticipated during the periods for which the grant support is requested?

Yes       No

If you checked "yes" above (indicating that program income is anticipated), then use the format below to reflect the amount and source(s). Otherwise, leave this section blank.

\*Budget Period    \*Anticipated Amount (\$)    \*Source(s)

## PHS 398 Cover Page Supplement

### 3. Human Embryonic Stem Cells Section

\*Does the proposed project involve human embryonic stem cells?  Yes  No

If the proposed project involves human embryonic stem cells, list below the registration number of the specific cell line(s) from the following list: [http://grants.nih.gov/stem\\_cells/registry/current.htm](http://grants.nih.gov/stem_cells/registry/current.htm). Or, if a specific stem cell line cannot be referenced at this time, check the box indicating that one from the registry will be used:

Specific stem cell line cannot be referenced at this time. One from the registry will be used.

Cell Line(s) (Example: 0004):

### 4. Human Fetal Tissue Section

\*Does the proposed project involve human fetal tissue obtained from elective abortions?  Yes  No

If "yes" then provide the HFT Compliance Assurance

If "yes" then provide the HFT Sample IRB Consent Form

### 5. Inventions and Patents Section (Renewal applications)

\*Inventions and Patents:  Yes  No

If the answer is "Yes" then please answer the following:

\*Previously Reported:  Yes  No

### 6. Change of Investigator/Change of Institution Section

Change of Project Director/Principal Investigator

Name of former Project Director/Principal Investigator

Prefix:

\*First Name:

Middle Name:

\*Last Name:

Suffix:

Change of Grantee Institution

\*Name of former institution:

# PHS 398 Research Plan

OMB Number: 0925-0001

Expiration Date: 02/28/2023

## Introduction

1. Introduction to Application  
(for Resubmission and Revision applications)

## Research Plan Section

2. Specific Aims                                  Specific\_Aims.pdf
3. Research Strategy\*                              Research\_Plan.pdf
4. Progress Report Publication List

## Other Research Plan Section

5. Vertebrate Animals                              Vertebrate\_Animal.pdf
6. Select Agent Research
7. Multiple PD/PI Leadership Plan
8. Consortium/Contractual Arrangements                              Emory\_Institutional\_Agreement.pdf
9. Letters of Support                                Letters\_of\_Support.pdf
10. Resource Sharing Plan(s)                        Resource\_Sharing.pdf
11. Authentication of Key Biological and/or Chemical Resources

## Appendix

12. Appendix

## **Computationally Optimized Dose for Influenza Vaccines (CODIV)**

### **Specific Aims**

Vaccination is a highly effective method of protection against viral infections. The inoculum dose, i.e., the amount of antigen or live attenuated pathogen that is used in the vaccine, is an important component of any vaccine, as it affects the strength of generated immunity and possible side effects.

Currently, dose is chosen during pre-clinical and phase I and II stages of vaccine development. Based on expert assessment of the accumulated, limited data, most phase III trials are performed with a single dose level of the vaccine. If such trials are successful, licensure is sought for that dose level. Generally, this single dose is independent of host characteristics (e.g., sex or BMI), with occasional dose differences based on age. A more thorough approach to dose optimization could lead to improvements in vaccine efficacy, while minimizing side effects and maximizing vaccine availability.

**Our long-term goal is to build a robust framework that combines data and models to predict the impact of dose for current and future vaccines and in specific host populations, and thus, allows dose optimization to become an integral part of the vaccine development process.**

The development, calibration, and validation of computational models, and use of such models to predict vaccination outcomes such as efficacy, safety, and availability for any dose, can help optimize vaccines without increased costs. An optimal dose can then be chosen based on predictions, potentially tailored to host characteristics. Such a proposed framework that involves a combination of models and data is similar to the widely used pharmacokinetics/pharmacodynamics (PK/PD) approach. PK/PD, which combines modeling with data, is successfully used for drug dose finding and encouraged by the FDA for licensure but is currently not applied to vaccines. For this project, we will develop such a modeling framework.

We will focus on influenza virus vaccines. For existing and especially future universal influenza virus vaccines, it is important to optimize immune protection against both vaccine strains and other circulating strains, while at the same time maximizing safety and availability. **We aim to develop, calibrate, and test mechanistic computational models that can explain the underlying processes and mechanisms by which vaccine dose impacts both strength and breadth of the immune response following influenza vaccination. These models can then be used to predict optimal dosing given specific host characteristics.** We will accomplish our goal through these specific aims:

Aim 1: Generate longitudinal immune response data from vaccination of ferrets using split-inactivated FluZone influenza virus vaccine at several different dose levels and for different host characteristics (immunologically naïve, pre-immune, obese, or aged).

Aim 2: Build and fit models to data obtained in aim 1. Elucidate the processes and mechanisms by which dose impacts strength and breadth of the immune response. Make predictions.

Aim 3: Use data from a human cohort of FluZone influenza virus vaccine recipients to test model predictions. Further refine models. Determine model prediction successes and failures and thus identify gaps in understanding for future studies.

## Research Strategy

### A. SIGNIFICANCE

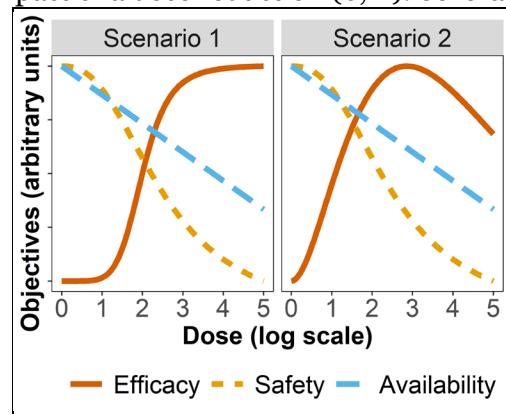
Vaccines are among the best interventions against infectious diseases (1). An important consideration in any vaccine formulation is the inoculum dose, i.e., the amount of antigen or live attenuated pathogen that is used (2). Determining the dose that optimizes the impact of any vaccine is a critical consideration in the development of new and improvement of existing vaccines (3). The goal is to find the dose that leads to the best possible protection by maximizing efficacy (through maximizing protective immunity), while at the same time also maximizing safety (minimizing vaccine side effects) and maximizing availability (minimizing costs and maximizing vaccine units).

The most common assumption that is made when choosing a dose is that efficacy increases with dose in a monotone manner, likely showing a nonlinear, saturating relation. Similarly, it is generally assumed that side effects increase (safety decreases) with dose, while availability is expected to decrease with increasing dose. In such a situation, there is a trade-off between the goal of maximizing efficacy and maximizing safety and availability (**Figure 1, Scenario 1**) (4).

A recent example of such a trade-off is the yellow-fever vaccine. Starting in 2015, several large yellow-fever outbreaks led to vaccine shortage (5,6). The question arose if one could increase availability by reducing dose, without substantially reducing efficacy. Based on fairly limited data (7,8), the WHO decided to approve vaccination with reduced dose if shortages exist as an emergency response (9). Vaccines that contained a fraction of the original dose were widely used (10). Since this decision was based on limited data, there was some concern regarding the impact of a dose reduction (6,11). Several studies have since suggested that the reduced dose properly induced strong and long-lasting immunity and did not affect safety (10,12–14). Some of these follow-up studies were large, time-consuming, and expensive clinical trials. We believe that increased attention toward the role of dose during the vaccine development phase, using a combination of data and models as proposed here, would have saved a large amount of time and money, as well as lives, by making more vaccine available from the beginning.

For the yellow-fever vaccine, current evidence suggests that increased dose leads to increased efficacy in a monotone, albeit nonlinear, manner (7). While such a pattern likely occurs for some vaccines, for most vaccines the relation between dose and efficacy is poorly understood. It is possible that for some vaccines, efficacy peaks at some intermediate dose, and declines as dose increases further. This is shown schematically in **Figure 1, Scenario 2**.

An example for such a potentially peaked relation is the Sanaria PfSPZ Vaccine that is currently tested against malaria (15). Recent studies suggest that optimal protection occurs at an intermediate dose level. Increases in dose beyond that level reduce the vaccine's efficacy (16–18). Similar results, where an intermediate dose was possibly superior to a higher dose, were recently reported for H56, a TB vaccine candidate (19–22), and some adenovirus vectors that are used for vaccines (23). In a recent modeling analysis, we suggest that this peaked relation might hold for some acute viral infections (24).



**Figure 1.** Possible impact of dose on vaccine efficacy, safety, and availability. The most common assumption is shown in scenario 1. However, scenario 2 has also been reported. Scenarios where safety is non-monotone might also exist. Availability is always expected to decrease with dose.

**Independent of which Figure 1 scenario applies, the ability to determine the dose that optimizes vaccine efficacy, tailored to specific host characteristics, while also achieving ideal safety and availability objectives, could lead to substantial improvements and cost-savings for existing and future vaccines.**

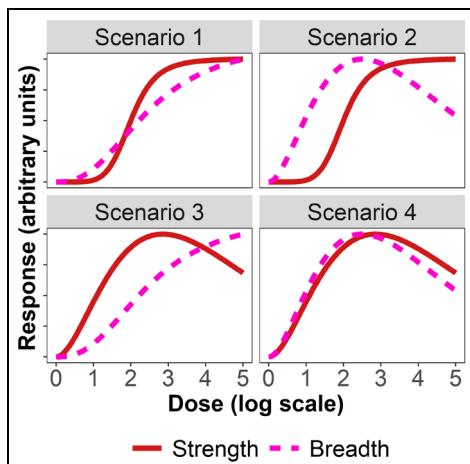
Given the likely nonlinear dependence of the different objectives on dose, relying solely on sparse data that is collected during vaccine development to determine vaccine dose is not optimal and is a major shortcoming of current vaccine design. While the importance of dose is generally acknowledged, evaluating more than a few dose levels during phase I and II clinical trials is cost-prohibitive. Often only a few doses are evaluated in pre-clinical studies as well. Based on the limited data, one dose is chosen, which is then taken forward into phase III trials and potentially production. Due to costs, trying to determine the potentially optimal dose in a more systematic and rigorous manner in human trials is not feasible. This is especially true with regards to tailored dosing based on host characteristics (e.g., sex, BMI, prior immunity).

**An approach that combines data with statistical and computational models will be critical towards optimal dosing for vaccines.** This idea of combining data with models to determine optimal dosing has a long history in the development and use of drugs, known there as pharmacokinetics/pharmacodynamics (PK/PD) modeling (25–29). PK/PD analyses are used to support FDA approval of drugs. In analogy to the PK/PD approach, the concept of combining data and models to optimize vaccine dose has recently been termed the immunostimulation/immunodynamic (IS/ID) framework (21). **We and others contend that the development and widespread use of such a framework for vaccine dose determination is critical for moving the vaccine field forward in a major way (4,24,30).**

While the framework of combining vaccine data with models to optimize dose determination is applicable to any vaccine, for our project we will focus on influenza vaccines. Influenza vaccines are an important tool in reducing disease burden (31). However, the vaccine's effectiveness varies and is at times low, especially in vulnerable groups (32,33). Further, because of the continuous evolution of the virus, vaccination needs to occur repeatedly. Major efforts are underway to develop vaccines that provide better and longer lasting protection (i.e., universal influenza vaccines) (3,34,35). As those vaccines are moving through development, an important question is the dose of antigen (killed virus, live attenuated virus, or protein content) that should be included in the vaccine (2).

**For our project, we will focus on the efficacy of influenza virus vaccines.** Efficacy will be quantified by *immunogenicity*, and more specifically antibody titers, which is known to be a strong – albeit not perfect – correlate of protection for influenza and is used by the FDA and other licensing agencies to determine influenza vaccine approval (36).

For future universal influenza vaccines, it will be important to induce two types of immunogenicity. One, a **strong**



**Figure 2.** Possible relations between dose and immune response **strength** and **breadth**. Scenario 1 shows the common assumption that both strength and breadth increase in a monotone way with dose. Scenarios 2 and 3 show situations where either the strength or breadth of the response increases, then peaks and decreases. For scenario 4, both strength and breadth peak at intermediate doses. Since going from no vaccine to some vaccine generally leads to an initial increased response, scenarios with a flat response or monotonic decrease with dose are not relevant.

**homologous response** against the vaccine strains is required. Two, a **broad heterologous response** that is cross-protective against strains not included in the vaccine is also needed. Both **strength** and **breadth** of the immune response can depend on dose in a monotone or peaked manner as illustrated in **Figure 2**.

Influenza vaccines have been used for decades. However, the impact of dose on immune response is still poorly understood. One currently approved influenza vaccine, Fluzone, exists in a standard-dose (SD) and high-dose (HD) formulation, with the latter for use in individuals 65+ years old. The HD formulation generally leads to a stronger response (37–40). Based on our preliminary work, increased dose may also lead to a broader response, though the evidence for this is still limited. Our goal is to determine the relation between dose and antibody immune response strength and breadth.

We will generate animal data, use it to build and calibrate models, then test the models on human data. Doing so, we will obtain novel insights regarding the processes and mechanisms by which dose impacts antibody immune response strength and breadth, and how this relationship is modulated by host characteristics such as sex and pre-vaccination immune status. This will allow us to start building predictive models that can be used to optimize vaccine dosing for existing and future influenza vaccines.

## B. INNOVATION

**B.1. We will advance our understanding regarding the impact of dose for the generation of protective immunity for influenza virus vaccines.** For any vaccine, including influenza virus, we currently do not understand how and why changes in inoculum dose impact vaccination outcomes. A systematic and mechanistic understanding of the impact of dose is sorely needed. Our project will provide such an understanding and thus start to fill a major gap in our knowledge on this topic.

**B.2. We will determine the impact of dose on both homologous and heterologous immunity, i.e., both strength and breadth of the immune response, and how this is modulated by host characteristics.** Current influenza vaccines are licensed based on their ability to induce immunity and protect against the influenza virus strains that are part of the vaccine. However, given that influenza virus is evolving rapidly, broad cross-protection is important and will need to be part of a future universal vaccine. Our project will provide insights that allow optimization of dose to induce not only strong homologous, but also broad heterologous immunity. Further, we will determine how dose-dependent strength and breadth are modulated by host characteristics (e.g., sex, BMI).

**B.3. We will develop a general framework to assess the impact of vaccine dose on immune protection that can be applied to other vaccines.** Our long-term goal is to develop a computational framework that combines models and data to optimize vaccine dose choice. While we focus on influenza, the approaches we will develop will apply beyond influenza. The insights and tools we will develop from this project can thus be applied to vaccines against other pathogens. Thus, a major innovation of our project will be to contribute to the overall nascent effort of providing a more rigorous framework that combines data and models to determine optimal vaccine dose, i.e., the IS/ID approach as a vaccine counterpart to the commonly used PK/PD approach in drug development (21,24,30).

## C. APPROACH

### **C.1. Investigator Team**

Our proposed project builds on multiple successful collaborations between team members. The project PI, Andreas Handel, has a long-standing collaboration with Rustom Antia and Veronika Zarnitsyna at Emory University (24,41–49). They have a long record of joint funding and publications and are currently collaborators on a funded project to better understand the immune responses following repeated influenza infection (U01AI150747). Handel also has ongoing collaborations with his UGA colleagues Ye Shen and Ted Ross (50–55). All are members of the *Center for Influenza Vaccine Research for High-Risk Populations (CIVR-HRP, contract 75N93019C00060)*, part of NIH's *Collaborative Influenza Vaccine Innovation Centers (CIVICs) Program* that is aimed toward development of universal influenza vaccines. The proposed project will complement our ongoing projects and will build on our strong track record working on influenza, vaccine studies and modeling.

### **C.2.1 Aim 1**

**Background and previous work:** While the ultimate goal is to optimize dose for human vaccines, there are logistic, ethical, and resource limitations to what kind of data can be obtained from humans. Thus, animal studies are commonly used to obtain additional information, and such studies are also regularly performed for any new vaccine candidate before any humans are exposed to it. For influenza, several different animals are frequently used, with unique strengths and weaknesses. Ferrets are generally considered the most relevant for influenza due to the similarity of the respiratory tract with humans, the natural susceptibility of ferrets to human influenza viruses, and the wealth of previously generated data from this animal model (56–60). Because of this, and since most future influenza vaccine candidates are expected to be tested in ferrets before humans, we will use the ferret model for our project. By collecting data in this aim specifically for our purpose of dose exploration, we can obtain the type of data we need for our analyses in aim 2. Such data currently do not exist.

The Ross laboratory has extensive experience with studies involving influenza infection and vaccination in naïve, pre-immune and aged ferrets (52,57,61–65). For obese ferrets, we will follow protocols established by one of our close collaborators and co-PI of the *Center for Influenza Vaccine Research for High-Risk Populations*, Dr. Stacey Schultz-Cherry (see letter of support). Dr. Ross' group has established protocols for infection and vaccination of the animals, and collection and analysis of samples. Assays and reagents are available that allow measurement of immune responses, and standard methods (e.g., hemagglutination inhibition (HAI) assays and flow cytometry) are well established in the group. For the novel Fluidigm assay (see below), we will work another of our close collaborators, Dr. Paul Thomas (see letter of support).

**Proposed work:** For this project, we propose to investigate the impact of dose for the quadrivalent human Fluzone influenza virus vaccine. We chose this vaccine since it was used in the human study that we propose to analyze in aim 3, and thus will allow model building and testing for the same vaccine. Ferrets produce a robust immune response if vaccinated with Fluzone (63,66). We will perform preliminary dose-finding studies with a small number of animals. The goal is to find a range at which the lowest dose produces a small, but still measurable antibody response, while the highest dose induces the maximum response (if the underlying relation is saturating) or is beyond the peak (for an underlying peaked response). Once we establish the dose range, we will vaccinate each group of animals at 5 different dose levels (**Table 1**). To account for potential differential responses due to sex (67,68), half of the ferrets will be females and the other half males.

We will perform the main dose-response experiments for 4 consecutive groups of animals with different host characteristics (**Table 1**). The first few weeks following vaccination are the most important in determining the subsequent course of the B-cell/antibody immune response, based on innate response kinetics (69). Therefore, we will initially sample daily (alternating between groups of animals). To capture the potential decline of antibodies following the peak (expected around day 20-30), we will continue to take less frequent samples up to around 2 months of observation.

While we do not expect vaccination to lead to noticeable signs and symptoms, high doses of the vaccine might trigger transient signs such as a rise in temperature. We will thus track temperature and weight, and the vaccination site will be monitored for rash development and discoloration, following our previous approaches (65). While these data might give some indication regarding potential dose-safety relations, we will not make use of them in our main analysis and consider them ancillary. This also holds for the nasal wash samples. The vaccine is injected intramuscularly; thus, we expect most of the immune response to occur in the blood. Since the response is systemic, we might see elevated immune responses in nasal washes, and it is easy to collect such samples. We will perform select ELISA analyses on the nasal wash samples to measure cytokines on days when we expect to see the strongest signal (the first few days post vaccination). If measurable increases in immune response are noticeable in nasal wash, we will process and analyze the samples using the Fluidigm platform (see below). If we do not find any noticeable response, we will focus on the blood samples, which are our main target. Currently, we make the conservative assumption that only data from blood samples will provide strong enough signals to be suitable for modeling. The blood samples will be used to quantify the longitudinal kinetics of different immune response components. Since antibody levels measured by HAI are the main correlate of protection used for the approval of influenza vaccines, we will focus on those as the main quantity and a proxy for vaccine immunogenicity and efficacy. We will quantify HAI titers both against the vaccine strains and a panel of non-vaccine H1N1, H3N2 and B strains, using those strains for which we also have human data (see aim 3 and (70,71)). The HAI measurements will be used to determine strength and breadth of the vaccine response.

<b>Host characteristics</b>	1) Immunologically naïve, 2) Pre-immune, 3) Obese, 4) Aged.
<b>Vaccine</b>	Fluzone, quadrivalent formulation (H1N1, H3N2, two influenza B strains, one each of the Yamagata and Victoria lineages), 2022 vaccine formulation.
<b>Dose Levels</b>	5 (anticipated to be 3.75, 15*, 60*, 240, 960 µg). *Current human standard- and high-dose vaccines. Dose levels will be finalized after preliminary dose-ranging studies. Since pre-vaccination values will serve as baseline for each animal, a control/no-vaccine group will not be used.
<b>Animals per dose</b>	12 (6 female, 6 male)
<b>Sample Collection</b>	blood (split into serum and PBMC), nasal wash.
<b>Timepoints</b>	Nasal wash will be collected daily from all animals. For blood collections, animals will be divided into sample groups (3 groups of 4) and each group sampled daily starting at pre-vaccination and continuing until 21 days post-vaccination (p.v.), such that each animal is sampled every 3 days (7 times). After that, all animals are sampled weekly for 5 weeks.
<b>Assays</b>	HAI, Fluidigm, flow cytometry

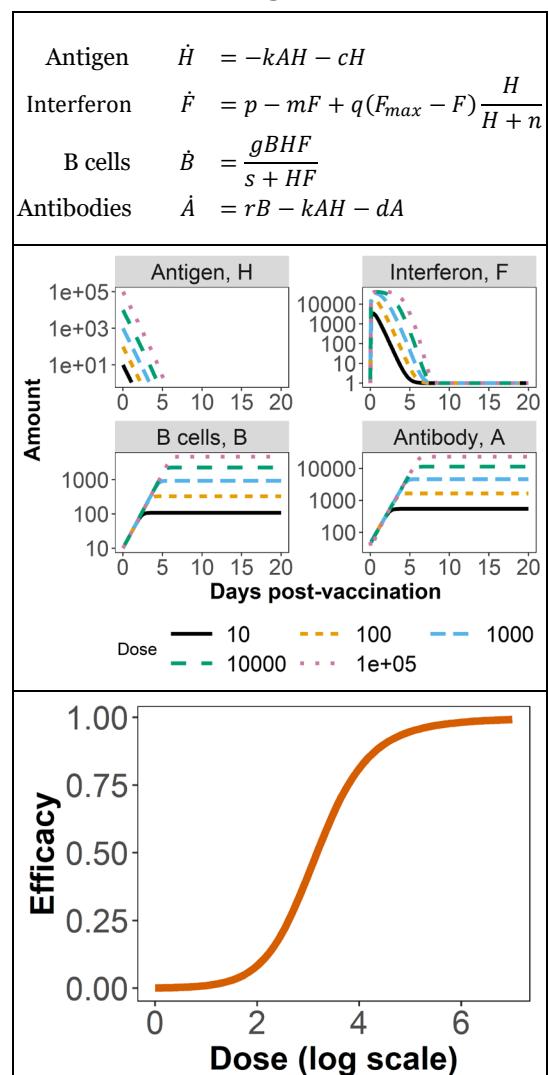
**Table 1.** Proposed animal studies. After initial dose-finding studies, the first experiment will be performed in a group of 60 (5 doses, 12 animals per dose) ferrets that are immunologically naïve for influenza, are middle-aged adults and not overweight. This will be followed by a second group of animals that have been made pre-immune by administration of a mixture of H1N1 (A/California/07/2009), H3N2 (A/Hong Kong/4801/2014) and B (B/Brisbane/60/2008 and B/Phuket/3073/2013) strains 60 days prior to vaccination. A third experiment will be performed with a group of obese animals, followed by a fourth group of aged/old ferrets.

To track other components of the immune response known to be important for induction of B-cell and antibody responses (72), we will use the Fluidigm platform (73,74). Fluidigm is a nanofluidic, automated platform for high throughput RT-PCR to allow for detection of up to 96 genes in 96 samples simultaneously in one run. This platform requires minimal cDNA input and reduced reagents for a more cost-effective approach for high quality data. Further, the Fluidigm platform allows for custom design of primers with their primer design team for specific genes and for non-standard species. Specifically for ferret transcriptional responses, we have validated primers to look at important immune response components for T cell markers and response genes (*CD3E*, *CD8A*, *CD4*, *IL7R*, *SELL*, *TBX21*, *TGFB1*, *TGFB2*, *TNF*), Interferon (IFN) genes (*IFNA*, *IFNG*, *IFNAR2*), and IFN stimulated genes (*MX1*, *IRF3*, *IRF9*, *STAT3*) (75). We will combine genes that are relevant for specific immunological quantities (e.g., interferon related genes) and map those onto the equivalent variables in our models. Lastly, we will follow standard flow cytometry protocols to measure total CD4 and CD8 T-cells and B-cells (76–78).

Data collected from this aim will be combined with the models as described in the next aim to study the processes and mechanisms by which dose impacts immune responses.

### C.2.2. Aim 2

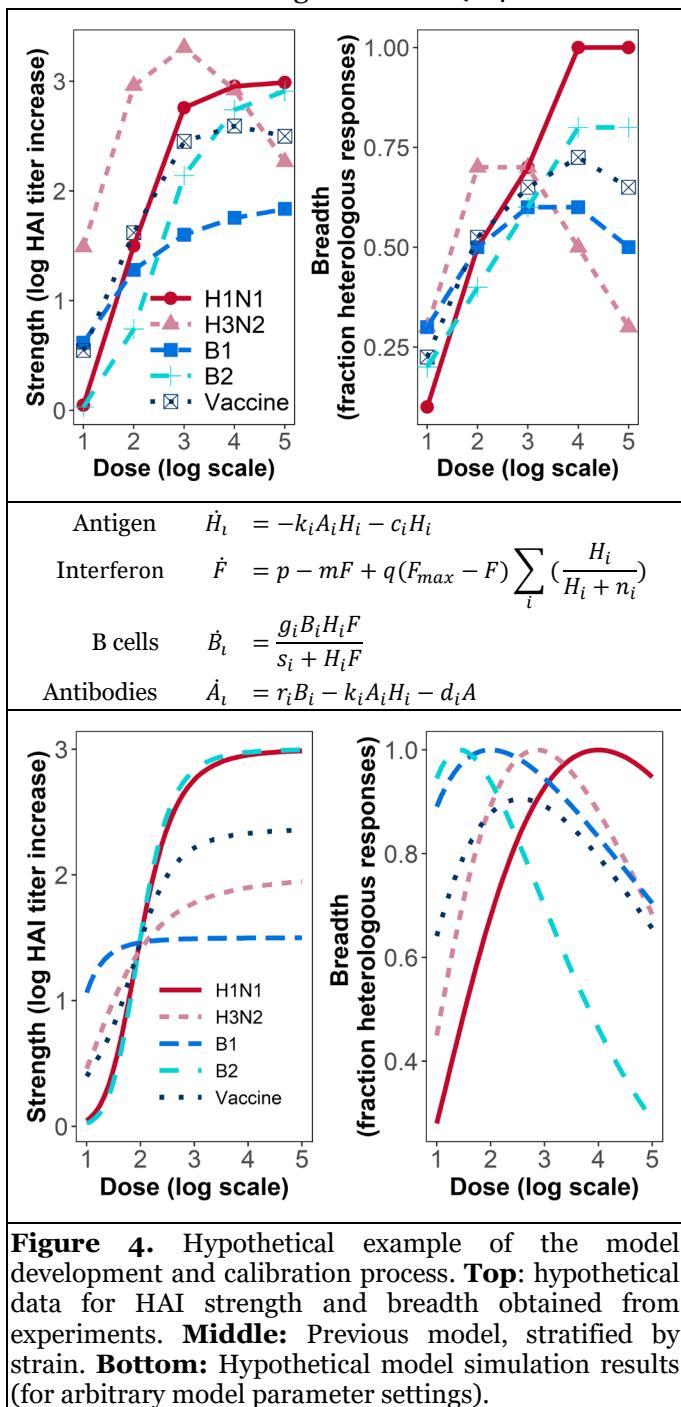
**Background and previous work:** Our team has a long record of modeling the immune response following infection and vaccination. We have performed several studies that investigated the role of dose. In an early study, we investigated acute infections from different viral pathogens and modeled dose-dependent patterns seen in the data to discern the mechanisms that might explain those observed patterns (79). We explored this further in a follow-up study, focusing on influenza (48). We are also working on analyses of the role of dose following norovirus infection and vaccination (part of a separately funded effort, R01GM124280). Most relevant for the project proposed here are our studies published in (24) as well as (41,42). In (24), we proposed mechanistic models of the dynamics of virus/antigen, type I interferon (a crucial aspect of the innate influenza response (75,80)), B-cells and antibodies following infection or vaccination, and explored the models to study the impact of dose on antibody generation. An adaptation of one of the models and results from it are shown in **Figure 3**.



**Figure 3.** One of our previous models of antigen and immune response dynamics following vaccination. **Top:** Model equations tracking the dynamics of vaccine antigen, interferon, B-cells and antibodies. **Middle:** Time-series for each model variable for 5 different antigen doses (starting values of variable H). **Bottom:** Model predicted vaccine efficacy (assumed proportional to antibody levels) as a function of dose. For this model, the shape of these outcomes follows Scenario 1 in **Figure 1**, i.e., a monotone increase. Model and results are adapted from our previous work (24), see there for more details. Note that we did not have data suitable for fitting to the model, and thus our previous results were exploratory. For this project, we will produce the data needed for model fitting and calibration.

**Proposed work:** From our animal experiments, we will obtain the data needed to build and calibrate our computational models. We provide a hypothetical example to illustrate the approach. The main outcome of interest will be antibodies as quantified by HAI titer following vaccination. We can quantify *strength* of the response against the influenza virus vaccine strains by computing the (log transformed) increase in titer against each strain. This will be done for each vaccine strain separately, as well as the average across all 4 strains. For *breadth*, we will, for each vaccine strain, determine the fraction for which one finds at least a 4-fold increase in HAI titer across all heterologous strains (a 4-fold increase is a common definition for a response). An overall vaccine response can be defined as the average strength or breadth for the 4 strains. Doing so, we might obtain hypothetical results as shown in **Figure 4**, top. While we will obtain time-series data and will eventually fit the full data (see below), for this example we consider a single time-point post vaccination (e.g., the final one).

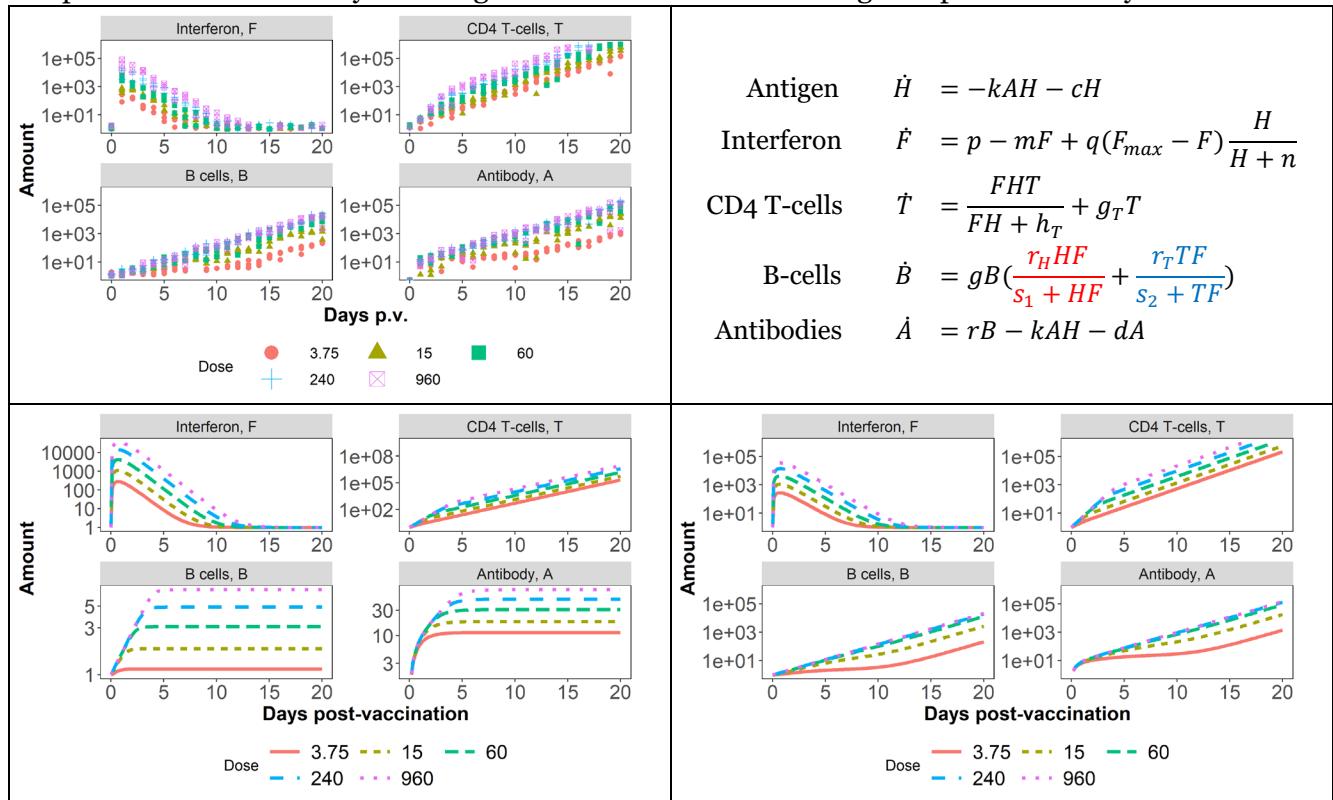
To compare these data to results from our model, we need to include strain-specific compartments for antigen, antibodies and B-cells (41). An example of such a model extension for the model in **Figure 3** is shown in **Figure 4**. Simulating this model will produce model predictions relating dose (starting values for antigen in the model) to antibody levels at the end. We can compare the model predictions to the data and thus perform a first round of model selection, determining which models are consistent with the data and which are not. In this example, the model predictions (for arbitrary choices of model parameter values) do not fully agree with the hypothetical data (compare **Figure 4** top and bottom), suggesting that the model needs to be refined. E.g., we might need to include interactions between strain components that are very likely present. Building and testing models based on the data for input of interest (dose) and outcome of interest (antibody levels) is a useful first level of analysis. In the next step, we will make use of the full longitudinal time-series data we will collect for antibodies and other immunological components. This will allow us to perform in-depth assessments of putative mechanisms and processes by which dose is linked to antibody responses.



**Figure 4.** Hypothetical example of the model development and calibration process. **Top:** hypothetical data for HAI strength and breadth obtained from experiments. **Middle:** Previous model, stratified by strain. **Bottom:** Hypothetical model simulation results (for arbitrary model parameter settings).

To illustrate this, we show hypothetical time-series data for several immune response components in **Figure 5**. This is similar to what we will obtain from our experiments. Assume that we want to explore alternative hypotheses regarding the mechanism by which B-cells (which are proportional to antibody levels) are induced and proliferate. In one possible model, induction and proliferation of B-cells is assumed to be *proportional to antigen and interferon* (red colored part of model in **Figure 5**). An alternative process could be one where induction is *proportional to CD-4 T-cells and interferon* (blue colored part of model in **Figure 5**). By comparing results from simulations of those alternative models with the data, we can discriminate between those mechanisms. For this example, visual comparison of the model predictions with the hypothetical data suggests that the process in which CD-4 T-cells provide B-cell stimulation is more consistent with the data (**Figure 5** bottom panels versus top left panel).

For our project, we will fit the models to the data in a statistically rigorous manner (24,41,43,81). We will use frequentist approaches, which have the main advantage of faster run-times, and Bayesian approaches, which have the main advantage of allowing constraints on parameters through informative priors, based on pre-existing biological knowledge (82–84). Fitting will be done using a combination of the *pomp* R package (85), which performs robust likelihood-based estimation using iterated particle filtering; the Monolix software (Lixoft) (86), which uses a Stochastic Approximation Expectation-Maximization (SAEM) algorithm; and the *brms* R package (87), which uses *Stan* (88) and its no-U-turn sampler as the backend Bayesian engine and allows efficient fitting of sophisticated Bayesian models.



**Figure 5.** Detailed model analysis example. **Top left:** Hypothetical time-series data of several immune response component as will be obtained from animal experiments. For simplicity, 3 data points/animals per day are shown. Antigen will not be measured and is not shown in the plots. **Top right:** An extended model that incorporates two processes by which B-cells are induced and grow. The red process assumes growth proportional to interferon and antigen. The blue process assumes growth proportional to interferon and CD-4 T-cells. (Note that CD-4 T-cells themselves are induced by antigen). **Bottom:** Predictions from the model where antigen and interferon induce B-cells (red process, left figure) and where antigen and CD-4 T-cells induce B-cells (blue process, right figure). Note that for simplicity, we only show a single strain example. The same multi-strain modeling approach as outlined in the previous paragraph will be used when building models and fitting the actual data.

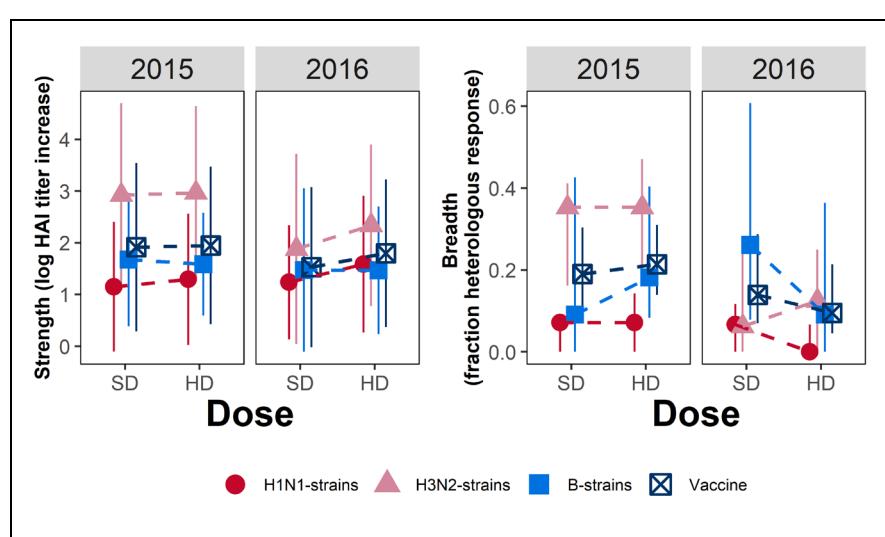
Each of these tools and approaches has certain advantages. The *pomp* package allows easy fitting of both deterministic ordinary differential equation models and their stochastic counterparts, thus allowing exploration of the potential role of process uncertainty. *Monolix* allows for convenient fitting of differential-equation based hierarchical mixed-effects models in a frequentist framework. Since our longitudinal data consists of repeat measures of individual ferrets (i.e., panel data), the use of a hierarchical modeling approach could be more powerful by accounting for within-subject correlations from multiple measurements. *Stan* and *brms* are powerful tools to fit Bayesian models, also in a hierarchical framework. Using a Bayesian approach with informative priors based on prior biological knowledge can help minimize the problem of overfitting that frequentist models are sometimes prone to. The PI, Handel, and his team are currently using both *pomp* and *brms* for several ongoing projects. Antia and Zarnitsyna at Emory are using *Monolix* for some of their ongoing projects. Thus, among the investigators, we have the technical expertise to implement these different analysis approaches.

By statistical comparison of models to data and the use of model selection approaches (e.g. cross-validation, information criteria), we can discriminate between competing hypotheses and thus between mechanisms and processes (89,90). Thus, through this stepwise approach of model development and evaluation through fitting, we can home in on the likely processes and mechanisms that link dose to immune response strength and breadth. By building and testing mechanistic, process-based models through data comparison, we can obtain models that go deeper than the powerful, but less detailed statistical (systems) approaches that are often used for the analysis of responses to infection and vaccination (68,91). By applying our proposed analysis approach to the 4 different types of host groups, we will obtain a detailed understanding how dose impacts antibody strength and breadth, and how this is modulated by host characteristics such as sex, pre-immune status, weight, and age.

### **C.2.3. Aim 3**

**Background and previous work:** Since 2014, and **independently funded to continue until at least 2024**, Dr. Ross and his group have been collecting data from human volunteers annually vaccinated with one of the licensed seasonal influenza vaccines. The studies and data collection methodology have been described in detail previously (71,77,78,92,93). The majority receive trivalent or quadrivalent FluZone (Sanofi Pasteur). Individuals below 65 years of age receive the standard-dose (SD) vaccine. Those 65 years or older are offered a choice between the high-dose (HD) or SD vaccine. Blood (70–90 ml) is collected from each subject at the time of vaccination, and post-vaccination around 7–9 days, 21–28 days, 60–90 days and 180 days. Blood samples are processed for serum, plasma, and peripheral blood mononuclear cells (PBMC) at all three time points. Sera from samples collected pre-vaccination and on day 21–28 post vaccination are analyzed using the HAI assay. Additional assays measure total and neutralizing antibodies. Cytokine levels within the plasma are quantified. PBMC are used for T-cell and B-cell quantification and characterization. Information on host characteristics (BMI, age, sex, etc.) are also recorded. So far (influenza seasons 2014–2020), 2286 individuals have received the FluZone vaccine, 348 of them (age 65+ years) received the HD vaccine. The remaining individuals received the SD vaccine, among them 191 individuals 65+ years. Around 65% of the study participants are female, the age range among all recipients is 11–85 years (we will be focusing on those 65+ that did or did not get the HD vaccine), and there is a large range for BMI, from 15–60. Study participants also had various levels of pre-immunity to the vaccine strains from prior infections or vaccinations. Thus, we have a good distribution of host characteristics that match our animal groups (age, sex, pre-immune status, BMI).

**Proposed work:** We will evaluate the predictions of our models that were built and calibrated using the animal data on this human dataset. Our main outcome is again HAI levels since it is a known strong correlate of protection for influenza and used for FDA approval. We have pre- and post-vaccine HAI measurements for all vaccine strains. Since all influenza vaccines, including FluZone, are regularly updated to match the evolution of the virus, different years of the vaccine contain different vaccine strains. So far, for the 2014-2020 flu seasons, 4 different H1N1 strains, 6 H3N2, 3 B-Victoria, and 2 B-Yamagata have been part of the vaccine. For each season, the response of the vaccine to panels of historic



**Figure 6.** Preliminary analysis of the strength and breadth of antibody responses for the standard-dose (SD) and high-dose (HD) 2015 and 2016 FluZone vaccine. Shown are responses as measured by HAI changes between pre- and post-vaccination for HD and SD vaccines (same quantities as shown in Figure 4). 2015 HD vaccine strains are H1N1/California/2009, H3N2/Switzerland/2013 and B/Phuket/2013, for 2016 the strains are and H1N1/California/2009, H3N2/Hong Kong/2014 and B/Brisbane/2008. Note that only 3 strains are shown since the HD vaccine was trivalent until 2020, when it became quadrivalent. It now contains the same 4 strains as the SD vaccine.

strains (15 strains for H1N1, 16 for H3N2, and 13 for the B strains) is also measured. FluZone is only approved at two doses, and we thus have only two dose levels from the human data. However, we do have results for multiple years and thus multiple vaccine formulations. An example of the kind of data we have is shown in **Figure 6**. The time resolution for the human cohort vaccine data is not as fine-grained as what we will obtain from our animal experiments. However, we do have several time points. We always have a pre- and post-vaccination time points. For the more recent cohorts starting in 2018, we also have samples from days 3, 7, and 90. For our animal experiments, we will use one of the seasonal FluZone vaccines (the 2022 formulation) and the same panels of historic strains. This will allow us to compare results for the same homologous and heterologous HAI responses between animal experiments, model predictions and human data. We will also have multiple additional seasons/vaccines for the human data, thus can evaluate how well the model predictions generalize to other FluZone formulations.

We also have details on host characteristics that match our different animal groups: namely sex, pre-existing immunity, age, and BMI. This will allow us to investigate the impact of those characteristics on the dose-response patterns and evaluate how these compare to the animal data and model predictions. As an example, in previous work we used mechanistic models similar to the ones shown above to predict that there is an inverse relation between host pre-vaccination immunity levels and HAI titer increase following vaccination, and that curve is shifted based on the vaccine dose (**Figure 7, top** and (41,42)). A preliminary analysis of our human cohort data suggests that there is qualitative agreement with the model predictions for some vaccine strains, but not others (**Figure 7, bottom left**). Our previous model does not make predictions for breadth. Once we have implemented and calibrated a multi-strain model following the approach described in aim 2, we can use it to test predictions for breadth such as those shown in **Figure 7, bottom right**.

In addition to the main outcome of interest, antibody levels, we also have other immunological data for the human cohort, such as B- and T-cell counts and a panel of cytokines and chemokines, measured using the same assays that we will use for our animal studies (78,92). We will use these data in the same way as described in aim 2 for the animal data to further test and refine the models.

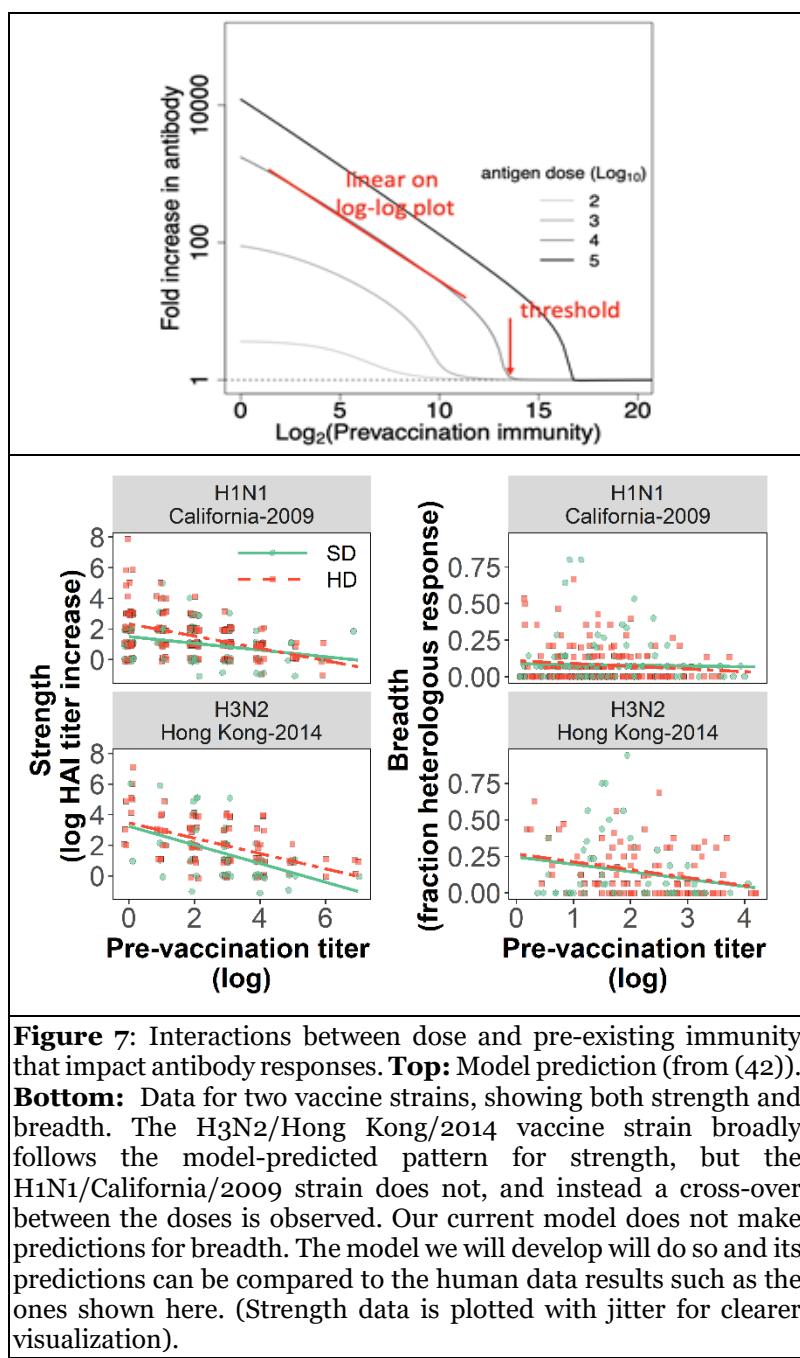
Overall, by comparing predictions from the models built in aim 2 to the human data, and refining and re-fitting the models, we will be able to further validate, calibrate and improve them. This will also identify crucial knowledge gaps to be addressed in further work.

### C.3. Potential problems and solutions

The Ross lab has ample expertise with the ferret experiments and immune response quantification methods we plan to perform. We thus do not foresee any problems with acquisition of the animal data. One issue that might arise is that the ferret data, might be fairly noisy, due to their outbred nature. In anticipation of this, we will be using 12 animals per dose, which is much larger than the standard 3-5 animals per group used in most experiments of this type. With such a

large number of animals, we expect to be able to discern the impact of dose, even in the presence of animal-to-animal variability.

The PI and the co-Is Antia and Zarnitsyna have a long history of using mechanistic computational models to study aspects of the immune response, especially for influenza. We usually apply our models to data that is not collected for the purpose of modeling. Despite the limitations that come with such data, we have a long track record of success in applying models to data (24,41–43,47,54,94,95). Since for this project, the animal data is explicitly collected with a goal of fitting it to models and elucidating mechanisms, we are confident that we will be able to make significant progress toward our goal of understanding the mechanisms and processes by which dose impacts immune response strength and breadth for influenza vaccines. To further strengthen the statistical expertise of our team, this project will include co-I Shen, who is a Biostatistician and long-term collaborator of the PI.



**Figure 7:** Interactions between dose and pre-existing immunity that impact antibody responses. **Top:** Model prediction (from (42)). **Bottom:** Data for two vaccine strains, showing both strength and breadth. The H3N2/Hong Kong/2014 vaccine strain broadly follows the model-predicted pattern for strength, but the H1N1/California/2009 strain does not, and instead a cross-over between the doses is observed. Our current model does not make predictions for breadth. The model we will develop will do so and its predictions can be compared to the human data results such as the ones shown here. (Strength data is plotted with jitter for clearer visualization).

The human data we will use is already collected or is scheduled to be collected by Dr. Ross and his team as part of ongoing, **independently funded** projects. Thus, barring another major emergency like the SARS-CoV-2 pandemic, we do not foresee problems with the human data acquisition. An inherent limitation of the human vaccine data is the fact that there are only two dose levels. With two doses, we can only detect if an increase in dose leads to an increased, decreased, or unchanged immune response. However, we have responses against multiple different vaccine strains and historic strains. Thus, the data is rather rich and will allow us to test our model predictions as outlined above.

#### **C.4. Summary**

For this project, we will be building and validating mechanistic models that explicitly describe the processes by which vaccine dose influences immune strength and breadth for influenza vaccines, and how this relationship is affected by important host characteristics (e.g., sex, BMI). Our models can be calibrated with future data that is collected during pre-clinical and phase I and II clinical vaccine studies. Calibrated models can then be used to predict the impact of the vaccine for any dose level and for specific types of hosts. This allows optimization of dose without having to perform costly experiments spanning a wide range and large number of doses across many different host populations.

From this study, we expect to make major improvements in our understanding regarding the role of dose for influenza vaccines. Since our models are being built and tested on the FluZone vaccine, we do not expect to have models that can be robustly applied to make reliable predictions for *any* future influenza vaccine candidate. However, we believe that this study will provide us with the crucial knowledge that will move us a major step in that direction, and we plan to apply what we learn from this study to future universal influenza vaccines, such as the COBRA vaccine candidates which are currently being developed and tested by members of our team (64,96–99).

The general modeling framework we will develop will also be applicable to other vaccines and thus help move the field of dose-response modeling and analysis for vaccines (termed IS/ID) forward in a major way, and to catch up with the already well-established PK/PD approach used in drug development.

#### **C.5. Timeline**

	<b>Year 1</b>	<b>Year 2</b>	<b>Year 3</b>	<b>Year 4</b>	<b>Year 5</b>
<b>Aim 1</b>	Dose-finding and naïve animal experiments	Pre-immune animals	Obese animals	Aged animals	Add-on experiments
<b>Aim 2</b>	Preliminary model building and exploration	Naïve animal analysis/modeling	Pre-immune animal analysis/modeling	Obese animal analysis/modeling	Aged and add-on animal analysis/modeling
<b>Aim 3</b>	Data cleaning and pipeline setup based on currently available data	Comparison of initial models to human data, based on matched and different vaccines	Naïve model prediction tests, comparison to FluZone (non-naïve) human data	Naïve and pre-immune model tests by comparison to human data	Comparison of all models to human data, investigating predictions for different host characteristics

Table 2. Proposed project timeline. Note that the human data will be collected, and samples processed on an ongoing basis outside our project. We expect to perform the bulk of the animal experiments in years 1–4, with possibly smaller add-on studies in the last year if we determine that some additional data would be useful (e.g., another dose level outside the original range).

# PHS Human Subjects and Clinical Trials Information

OMB Number: 0925-0001

Expiration Date: 02/28/2023

## Use of Human Specimens and/or Data

Does any of the proposed research in the application involve human specimens and/or data \*

Yes       No

Provide an explanation for any use of human specimens and/or data not considered to be human subjects research.

Are Human Subjects Involved

Yes       No

Is the Project Exempt from Federal regulations?

Yes       No

Exemption Number

1     2     3     4     5     6     7     8

Other Requested Information

**Human Subject Studies**

<b>Study#</b>	<b>Study Title</b>	<b>Clinical Trial?</b>
<u>1</u>	Computationally Optimized Dose for Influenza Vaccines (CODIV)	No

## Section 1 - Basic Information (Study 1)

OMB Number: 0925-0001

Expiration Date: 02/28/2023

### 1.1. Study Title \*

Computationally Optimized Dose for Influenza Vaccines (CODIV)

### 1.2. Is this study exempt from Federal Regulations \*

Yes  No

### 1.3. Exemption Number

1  2  3  4  5  6  7  8

### 1.4. Clinical Trial Questionnaire \*

1.4.a. Does the study involve human participants?

Yes  No

1.4.b. Are the participants prospectively assigned to an intervention?

Yes  No

1.4.c. Is the study designed to evaluate the effect of the intervention on the participants?

Yes  No

1.4.d. Is the effect that will be evaluated a health-related biomedical or behavioral outcome?

Yes  No

### 1.5. Provide the ClinicalTrials.gov Identifier (e.g.

NCT87654321) for this trial, if applicable

## **Section 2 - Study Population Characteristics (Study 1)**

2.1. Conditions or Focus of Study

2.2. Eligibility Criteria

2.3. Age Limits

Min Age:

Max Age:

2.3.a. Inclusion of Individuals Across the Lifespan

2.4. Inclusion of Women and Minorities

2.5. Recruitment and Retention Plan

2.6. Recruitment Status

2.7. Study Timeline

2.8. Enrollment of First Participant

## 2.9. Inclusion Enrollment Reports

IER ID#	Enrollment Location Type	Enrollment Location
The study does not have any IERs		

### **Section 3 - Protection and Monitoring Plans (Study 1)**

3.1. Protection of Human Subjects

Protection\_of\_Human\_Subjects.pdf

3.2. Is this a multi-site study that will use the same protocol to conduct non-exempt human subjects research at more than one domestic site?

Yes       No       N/A

If yes, describe the single IRB plan

3.3. Data and Safety Monitoring Plan

3.4. Will a Data and Safety Monitoring Board be appointed for this study?

Yes       No

3.5. Overall structure of the study team

## **Protection of Human Subjects**

This project is exempt from human subjects review as it is a secondary analysis of data that is collected under different, independent funding mechanisms.

The information we will have available for our analysis, namely biological samples and basic demographic information about the participants, means the individuals in the study cannot be identified.

While we fully support sharing of data as part of the publication process, we will ensure that any data that is made publicly available is further stripped of information not needed to reproduce our findings.

Overall, the proposed study does not pose any additional risk to the human subjects.

## **Section 4 - Protocol Synopsis (Study 1)**

### **4.1. Study Design**

#### **4.1.a. Detailed Description**

#### **4.1.b. Primary Purpose**

#### **4.1.c. Interventions**

Type	Name	Description
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#### **4.1.d. Study Phase**

Is this an NIH-defined Phase III Clinical Trial?  Yes  No

#### **4.1.e. Intervention Model**

4.1.f. Masking  Yes  No

Participant  Care Provider  Investigator  Outcomes Assessor

#### **4.1.g. Allocation**

### **4.2. Outcome Measures**

Type	Name	Time Frame	Brief Description
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### **4.3. Statistical Design and Power**

### **4.4. Subject Participation Duration**

4.5. Will the study use an FDA-regulated intervention?  Yes  No

4.5.a. If yes, describe the availability of Investigational Product (IP) and Investigational New Drug (IND)/Investigational Device Exemption (IDE) status

4.6. Is this an applicable clinical trial under FDAAA?  Yes  No

### **4.7. Dissemination Plan**

**Delayed Onset Studies**

Delayed Onset Study#	Study Title	Anticipated Clinical Trial?	Justification
The form does not have any delayed onset studies			

## Vertebrate Animals

The proposed study will utilize ferrets.

### **1. Description of Procedures**

Animal Housing. All housing meets the Laboratory and Animal Biosafety Level 1, 2+ and 3 requirements recommended for animal studies in the CDC/NIH publication "Biosafety in Microbiological and Biomedical Laboratories". Protective clothing and equipment are strategically located in the facility. The items available include hooded coveralls, head covers, shoe covers, gloves, powered air purifying respirators, N95-surgical masks, plastic face shields, and safety goggles.

Ferrets. Male and female Fitch ferrets will be vaccinated or infected with influenza virus. Ferrets will be observed for morbidity (weight loss and temperature) and mortality. Ferrets will be housed in compliance with USDA regulations and monitored daily for weight loss, behavior, and adverse reaction. Ferrets will be anesthetized with vaporized isoflurane following UGA IACUC guidelines prior to procedures.

Randomization of Animals. Ferrets for each vaccination study will be randomized according to age and weight.

Infections or Vaccinations. Some ferrets will be administered influenza virus intranasally to induce pre-immunity. As per the research plan, 60 animals (5, doses, 12 each) will be pre-immunized with virus. Ferrets will be administered virus in sterile 0.9% saline directly into the nares (1 ml total volume). All ferrets (4 groups, 12 animals at 5 doses per group) will be vaccinated via intramuscular (IM) injection with Fluzone quadrivalent vaccine at several doses (500 µl total volume). Animals will be anesthetized with vaporized isoflurane prior to IM vaccination in the hindleg.

Sample Collection. Nasal wash and peripheral blood samples will be collected before and after immunizations from animals as described in the research plan.

Post-Procedure Monitoring. All animals will be allowed to recover from anesthesia on a heated pad with continued observation until the animals are bright, alert, and active. Once sternal, the animals will be observed every 12 hours for appetite, activity and stool consistency. Procedure sites will be monitored for inflammation and all changes will be immediately reported to the veterinarian. Analgesic and other interventions will be administered as necessary to minimize discomfort and distress, as deemed necessary by the attending veterinarian.

### **2. Justifications**

Influenza causes disease in humans, vaccines are our best tools of protection. Understanding the processes by which the vaccine, and specifically the vaccine dose induces protective immunity require the study in animal models that closely mimic the human immune system. Influenza vaccination studies require an animal model, the ferret is the most suitable small animal model to study influenza.

The number of animals per dose (12) and the number of doses (5) are chosen to provide enough data to allow answering the scientific questions of interest, while at the same time minimizing the use of the needed number of animals. The 4 different groups of animals are chosen because of their relevance to human vaccination scenarios. As few as possible additional animals will be used to determine the right dosing for the main experiments, and to produce any additional data that might be needed to address any data gaps that might be identified.

### **3. Minimization of Pain and Distress**

Regulatory Compliance. All research involving animals at the facility is approved by the UGA Institutional Animal Care and Use Committee (IACUC). The Committee is responsible for insuring proper care, use and humane treatment of animals used in research, testing and education. Animals are not assigned to any specific project until IACUC approval is granted. The University of Georgia IACUC Committee is composed of 12 individuals. Each animal protocol that is received by the IACUC Committee is assigned a primary and secondary reviewer. All protocols are discussed by the full Committee, and approval is by vote at a formal meeting. All research protocols receive a thorough review, and protocols may be approved, approved with stipulation, disapproved or deferred for clarification and further discussion in accordance with IACUC policies. In addition to the approval of research applications, the IACUC also inspects all research and animal facilities, and provides semi-annual evaluations of the animal care program.

The UGA Animal Facility is a USDA inspected and American Association for Accreditation of Laboratory Animal Care (AAALAC) approved research facility. It is in compliance with the standards for animal care outlined in the Guide for the Care and Use of Laboratory Animals as published in the DHHS Publication Number (NIH) 85-23 (or succeeding editions), and Public Health Service Policy on Humane Care and Use of Laboratory Animals, as Revised September, 1986. The IACUC committee meets regularly to inspect the facility and protocols are reviewed monthly. Animal care is provided by the division of Veterinary Medicine. All species are maintained on a regimen of ferret chow, fed daily. All animals are housed in cages that are in compliance with USDA and AAALAC standards.

All experimental animals will be maintained at the facility in accordance with guidelines established by the Animal Welfare Act and the "NIH Guide". The center has a well-trained, experienced clinical veterinary and animal caretaker staff for the care and maintenance of ferrets.

Routine Veterinary Care and Husbandry. All animals in these studies will be monitored on a daily basis to document their clinical appearance and general health status. At periodic intervals, ferret will be anesthetized with isoflurane for a general physical examination and collection of blood for routine blood chemistries, virological and immunological evaluations. Body weights will be recorded each day after a procedure.

Animal Records. UGA has an onsite information technology (IT) group that provides support for all IT operations at the Institute. The group has modified the Blacksmith database to incorporate an animal records system that tracks clinical, husbandry, pathology and research information on all animals in the colony from acquisition until release. Information from the database is accessible to approved users, which include research scientists, veterinarians, administrators and managers. Individual animal records are maintained in the Center's SUN

Minicomputer and are updated daily. Data includes basic demographic data, history of housing locations, assignment history, TB test dates, weights, breeding history, clinical laboratory data, surgical procedure reports, clinical records, genetic test results, viral testing results, and gross and microscopic pathology reports.

Control of Pain, Discomfort and Distress. All invasive procedures are carried out with the animals under sedation with vaporized isoflurane and will be monitored and allowed to recover on a warm pad to maintain body temperature. No protocol in this research project will require withholding of analgesics or anesthesia deemed necessary by the attending veterinarian to alleviate pain or distress. For all routine procedures such as blood collection and physical examination, animals will be fully anesthetized.

Euthanasia. If life threatening clinical conditions indicates the life expectancy of the animal is less than 7 days, or at the end of the study, animals will be euthanized by overdose of barbiturates under the direction of the attending veterinarian. This is in keeping with recommendations of the American Veterinary Medical Association on euthanasia.

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## Subrecipient Letter of Intent

Subrecipient:	Emory University	Pass-Through Entity:	University of Georgia
Subrecipient DUNS:	066469933	Pass-Through Entity DUNS:	619003127
Principal Investigator:	Antia, Rustom N	Principal Investigator:	Handel, Andreas
Internal Project Identifier (optional):	%63824	Internal Project Identifier (optional):	
<b>Institutional Administrator</b>		<b>Institutional Administrator</b>	
Name/Title:	Holly Sommers, Director	Name/Title:	Catherine Cuppett, Director
Phone:	(404) 727-2503	Phone:	
Email:	osp@emory.edu	Email:	cathya15@uga.edu
Project Title:	Computationally Optimized Dose for Influenza Vaccines (CODIV)		
Awarding Agency:	NIH	Project Period:	4/1/2022 – 3/31/2027
Total Proposed Amount:	\$743,380	Subrecipient Cost Sharing Amount (if applicable):	N/A
Human Subjects [Y/N]:	N	Vertebrate Animals [Y/N]:	N

This proposal has been reviewed and approved by the appropriate official of the Subrecipient identified above and certified to its accuracy and completeness. The appropriate programmatic and administrative personnel of each institution involved in this grant application are aware of the awarding agency's policies, agree to accept the obligation to comply with award terms, conditions and certifications, and are prepared to establish the necessary inter-institutional agreement consistent with that policy.

The following documents are attached to this Statement of Intent:

- Statement of Work
- Detailed Budget
- Budget Justification
- Other:

**Teresa Sussman**

Digitally signed by Teresa Sussman  
DN: cn=Teresa Sussman, o=Emory University, ou=Office of Sponsored Programs, email=osp@emory.edu, c=US  
Date: 2021.06.02 12:30:19 -04'00'

Signature of Subrecipient's Authorized Official

Date

Teresa P. Sussman, Associate Director; Emory University Office of Sponsored Programs (OSP)  
Name and Title of Authorized Official



Stacey Schultz-Cherry, PhD  
Full Member (Professor)  
Department of Infectious Diseases  
St. Jude Children's Research Hospital  
(901) 595-6629  
[stacey.schultz-cherry@stjude.org](mailto:stacey.schultz-cherry@stjude.org)

June 1, 2021

Dear Andreas,

This letter is to enthusiastically support your proposal “Computationally Optimized Dose for Influenza Vaccines (CODIV)”.

For any next-generation influenza vaccine, be this a universal or a more limited type of vaccine, a thorough understanding of the role of dose will be critical, and thus your proposed project is of great importance.

Since the ferret model is arguably the most relevant animal model for influenza, I am excited that you propose to include ferret experiments in your project. As you know, over the last several years, we have made significant advances in developing an obese ferret model. We have been able to successfully show that this ferret model mimics important findings regarding influenza vaccination and infection observed in obese humans.

For your project, we will be happy to share with you and Ted Ross all our expertise and help ensure that you are able to successfully perform influenza vaccination experiments using the obese ferret model.

As co-PIs on the Center for Influenza Vaccine Research for High-Risk Populations (CIVR-HRP, contract 75N93019C00060), Ted and I already collaborate very closely. This project will further strengthen our collaborations and I'm looking forward to working with you on this exciting project!

Best,

*Stacey Schultz-Cherry*  
Stacey Schultz-Cherry, PhD



*Paul G. Thomas, Ph.D.*

Member

Department of Immunology  
office 901.595.6507 fax 901.595.3107  
[paul.thomas@stjude.org](mailto:paul.thomas@stjude.org)

May 27, 2021

Dear Andreas,

I am enthusiastically supporting your proposal “**Computationally Optimized Dose for Influenza Vaccines (CODIV)**”.

I believe that a better understanding of the role of dose for influenza vaccines is crucial, especially as we work towards the next generation of (universal) influenza vaccines. Since the ferret model is arguably the most relevant animal model for influenza, I am excited that you propose to include ferret experiments in your project.

As you know, over the last several years, we have made significant advances in developing assays and reagents to quantify the immune response to influenza infection and vaccination in the ferret model. Specifically, we have generated several panels of well-validated primers on the Fluidigm platform that we have used to characterize innate and adaptive immune responses in multiple studies. We also have successfully run and analyzed single cell RNA-Seq for ferret BAL and nasal wash and could apply these techniques. For your project, we will be happy to share with you and Ted Ross all our expertise and materials related to these methods.

I have long-standing and successful collaborations with you and several of the other project investigators through our joint the Center for Influenza Vaccine Research for High-Risk Populations (CIVR-HRP, contract 75N93019C00060), our influenza immune response modeling project (U01AI150747), as well as many prior joint projects and collaborations.

This project will further strengthen our collaborations and I’m looking forward to working with you on this exciting project!

Sincerely,

Paul G. Thomas

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262 Danny Thomas Place, Suite E7054, Memphis, TN 38105-3678 USA [www.stjude.org](http://www.stjude.org)

## **RESOURCE SHARING PLAN**

Any findings generated from the research described in this proposal will be presented at scientific meetings and published in scientific journals, with preference given to open access journals. All publications and presentations will comply with NIH Public Access Policies. All investigators are expected to participate in regular national and international conferences and present the results from this project.

In addition to the scientific results, we will produce data and models that will be shared with the wider community. Those will be disseminated as follows:

- Data will be deposited in the appropriate NIH repositories (e.g., ImmPort) and will also be supplied as supplementary material with any paper we publish on the data, to allow full reproducibility of our work.
- Any models we develop will be deposited to appropriate model repositories such as BioModels.Net and others. They will also be available through public GitHub repositories and posted to a webpage dedicated to this project. The models will be made available in common and open formats, such as R scripts and SML, to allow the widest possible dissemination and re-use. All models will be published under an open license (CC, MIT, or similar).
- Any materials and documentation (e.g., materials developed to explain our model and its results), will be made publicly and freely available online and licensed under a Creative Commons licenses (mainly CC-BY-SA).

Non-compliance of any team member with these rules will result in an initial warning, and continued non-compliance will lead to their removal and redirection of any research funds to other investigators.