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TITLE: Novel Methods of Augmenting Lung TB Immunity

PRINCIPAL INVESTIGATOR: Getahun Abate, MD PhD

CONTRACTING ORGANIZATION: Saint Louis University

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Fort Detrick, Maryland 21702-5012

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6. AUTHOR(S)

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5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

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Washington University in Saint Louis, 660 South
Euclid Ave, 63100

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)

U.S. Army Medical Research and Development Command
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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Effector T cells have been shown to be key mediators of immunologic responses to Mtb. This novel prime-pull approach provides a promising avenue to modulate this immunologic axis with vaccines designed to augment mucosal immunity. Our capacity to modulate cytokine profiles in the lung uniquely positions us to test the effectiveness of prime-pull strategies for Mtb mucosal immunization. **Our findings will be highly relevant for TB vaccinology**. In addition, validating our new approach for TB may provide a more generalizable method to exploit targeted gene delivery and prime-pull for a wide range of mucosal immunization contexts.

Aim 1. Evaluate the effects on T cell recruitment of lung chemokine delivery during systemic TB vaccination

First, we will determine the kinetics of circulating 'mucosally relevant' CXCR3+ T cells after BCG vaccination of wild type B6 mice. We next will optimize the 'prime-pull concept for TB vaccination and immunotherapy, comparing chemokine delivery methods, timing, and doses and their effects on lung T cell recruitment.

Aim 2. Evaluate the effects of lung chemokine delivery during BCG vaccination on Mtb infection & disease.

After optimization of the prime-pull strategy for BCG vaccination determined in aim 1 we will test whether this method translates to better control of TB infection. Mice will be vaccinated with BCG and sub-groups of mice will be treated with CXCL9/10 proteins or genes. After 1-3 months, mice will be challenged with aerosolized *M. tuberculosis*. At 7-28 days after challenge, we will evaluate lung T cell responses and determine efficacy by enumerating mycobacteria in the lungs and spleens.

15. SUBJECT TERMS

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
a. REPORT	b. ABSTRACT	c. THIS PAGE			USAMRMC
Unclassified	Unclassified	Unclassified	Unclassified		19b. TELEPHONE NUMBER *(include area code)*

TABLE OF CONTENTS

1. INTRODUCTION:

It is estimated that one-third of the world's population is infected with *Mycobacterium tuberculosis* (Mtb), with about 9 million new cases of tuberculosis (TB) and 1.5 million deaths annually. Enhancing lung mucosal immunity will likely result in increased Mtb clearance. A prime-pull approach using chemokines to recruit immune cells into the lungs will help control TB infection and disease. Targeted immunotherapies that enhance mucosal immunity will likely increase the ability to contain and even eradicate Mtb. Our "prime-pull" strategy involves delivery of a systemic TB vaccine to prime immunity, and then pulling Mtb-specific T cells to the pulmonary mucosa with relevant chemokines. The results from our studies will have direct application for developing immunotherapeutics for both latent and active TB infections. Furthermore, the "prime-pull' approach might enhance efficacies of new TB vaccines.

2. KEYWORDS:

Tuberculosis; immunotherapy; vaccine; chemokine; mucosal immunology.

3. ACCOMPLISHMENTS:

What were the major goals of the project?

1. Generation of Adenovectors expressing CXCL9 and CXCL10. (100% complete)

2. Determine CXCR3 expression and chemokine production during vaccination. (100% complete)

3. Optimization of the chemokine-induced pull of vaccine-specific T cells into the lung. (50% complete)

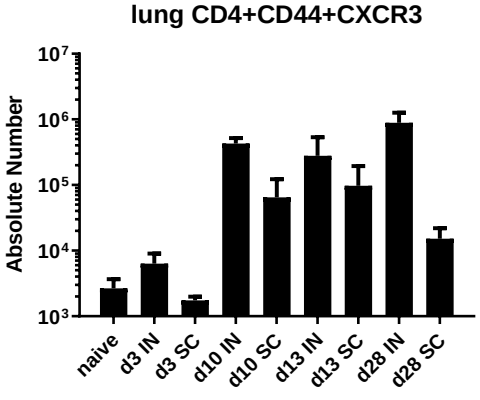
4. Determine the effects of a prime-pull vaccination approach on recall T cell immunity during Mtb infection. (not started)

5. Determine the effects of a prime-pull vaccination approach on TB protective immunity. (not started)

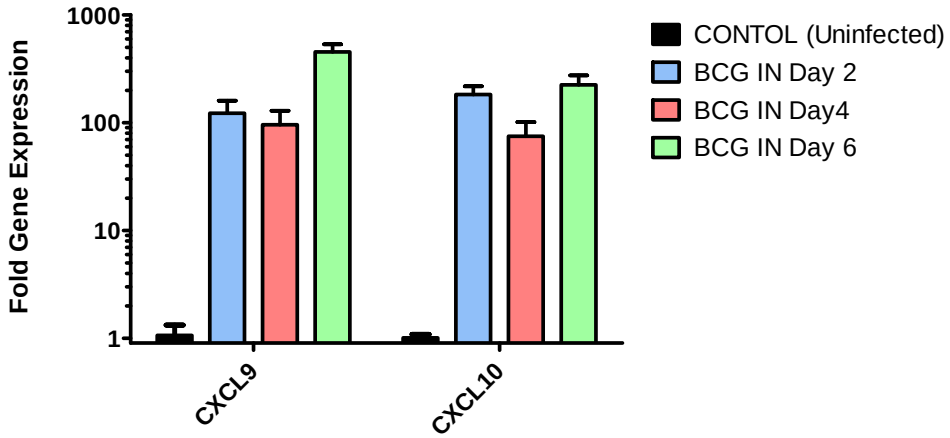
What was accomplished under these goals?

1. Generation of Adenovectors expressing CXCL9 and CXCL10. To express murine CXCL9 and CXCL10 genes, Drs. Curiel and Dmitriev at Washington University employed both human adenovirus serotype 5 (Ad5) and gorilla adenovirus (GAd) vectors essentially as described previously (PMID: 31484074; 29242639). To this end the Ad5 and GAd genomic plasmids were constructed to contain the CXCL9 and CXCL10-coding sequences under transcriptional control of the human cytomegalovirus (CMV) major immediate early promoter in place of the early E1 region deleted in viral genome. The resultant plasmids were validated by PCR and sanger sequencing, propagated, and digested with either PacI (Ad5) or PmeI (GAd) restriction enzymes to liberate viral genomes to be transfected to 293 cells (PMID: 886304). The replication incompetent Ad5-CXCL9, Ad5-CXCL10, GAd-CXCL9, and GAd-CXCL10 vectors were rescued and upscaled in 293 cells and then purified by equilibrium centrifugation in CsCl gradients by a standard protocol. Vector preparations were dialyzed against PBS and stored at -80°C. Viral particle (vp) concentrations were determined by 260 nm absorbance by the method of Maizel et al. (PMID: 5669982) using a conversion factor of 1.1 × 10(12) vp/absorbance unit. The expression of CXCL9 or CXCL10 by each vector was validated in mouse fibroblast NIH/3T3 cells infected at multiplicity of infection of 500 vp/cell using mouse CXCL9/MIG immunoassay ELISA kit (R&D systems catalog number MCX900) and mouse IP-10(CXCL10) SimpleStep ELISA kit (abcam catalog number ab214563) following the manufacturer recommendations, accordingly. The transduced cells indeed produced the expected chemokines (not shown).

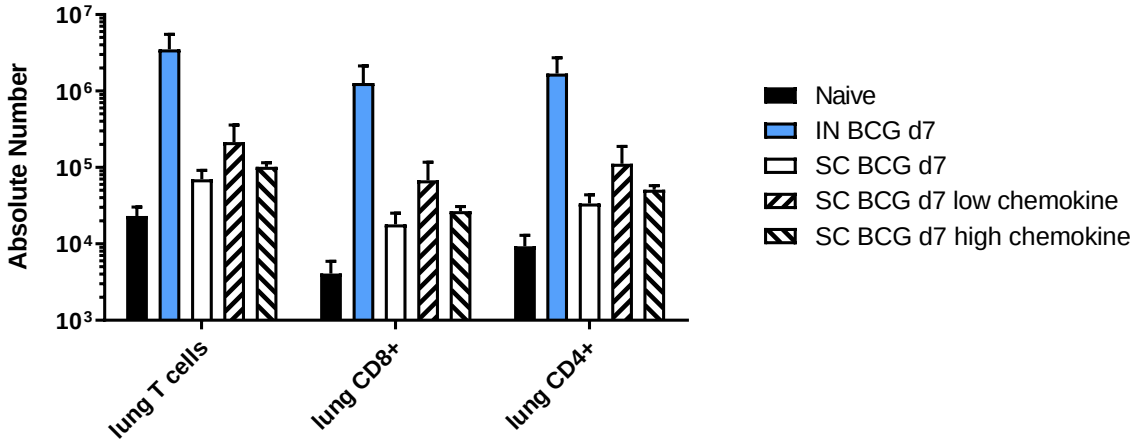
2. Determine CXCR3 expression and chemokine production during vaccination. We first performed experiments in which mice were vaccinated on different days with BCG by either systemic (subcutaneous; SC) or mucosal (intranasal; IN) routes. On days 3, 10, 13, and 28 post-infection, mice were i.v. injected with fluorescently labeled anti-CD45 and then euthanized 3-5 minutes later, allowing sufficient timing to stain cells in the vasculature but not those in the tissues. Lungs were extracted and digested with collagenase/DNase. Next, single cell suspensions were prepared flow cytometric studies performed. Shown below are the absolute numbers of memory $CD4^+$ cells expressing the mucosal homing marker CXCR3 present in the lungs. These data demonstrate that as soon day 3 post-mucosal vaccination, T cells begin to infiltrate the lungs. By day 10, massive T cell influxes are seen, regardless of whether BCG is delivered by system or mucosal route (though intranasal vaccination results in greater lung T cell recruitment than systemic vaccination). Thus, optimal influx of T cells occurs prior to day 10 post-vaccination.



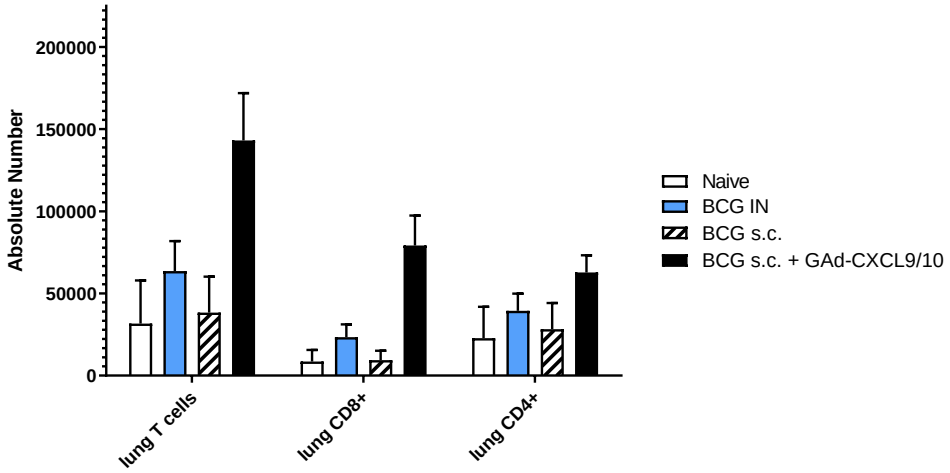
As shown above, T cells rapidly infiltrated the lungs beginning as soon as 3 days post-IN BCG vaccination, and seem to reach a plateau 10-30 days after administration. To evaluate the kinetics of chemokine expression after mucosal BCG delivery, we next performed studies in which mice were treated with IN BCG and then lung CXCL9/10 expression profiles determined 2-6 days later. ELISA assays to evaluate CXCL9 and 10 in lung homogenates were inconsistent, thus, we measured CXCL9 and CXCL10 mRNA expression profiles via RT-PCR (normalized to actin gene expression). Results shown below indicate that CXCL9 and 10 genes expression increases >100-fold as quick as 2 days post-BCG delivery and remain elevated for the first week post-BCG delivery.



3. Optimization of the chemokine-induced pull of vaccine-specific T cells into the lung. Based on results above we sought to induce the chemokine pull directly after delivery of BCG systemically. Mice were vaccinated with either IN or SC BCG. Approximately 0.5µg (low dose) or 100µg (high dose) of recombinant CXCL9 and CXCL10 were delivered via aerosol route on days 2, 4, and 6 post SC BCG administration. On day 7, the numbers of lung T cells (total and CD4/CD8 subsets) were evaluated using the methods described above. IN BCG resulted in >2 log increased numbers of lung T cells, while SC BCG resulted in less than 1 log increases. No significant effects of the aerosol chemokine delivery were observed (below). We performed IFN-γ ELISPOT assays to determine if aerosolized chemokine treatment resulted in increased antigen-specific cells in the lungs and failed to find differences between chemokine treated and untreated mice (not shown). These results were consistent with results obtained 1 month post-treatment (not shown).



We also evaluated whether gorilla adenovirus (GAd) vectors expressing CXCL9/10 would produce the desired T cell "pull" into the lungs. In these experiments, mice were vaccinated with either SC or IN BCG and 5x10(10) viral particles of GAd-CXCL9 and GAd-CXCL10 were delivered i.v. the following day. On days 8 and 30, mice were treated with anti-CD45 i.v., euthanized 3-5 minutes later, and flow cytometry studies conducted on lung cells as described above. Large influxes of total, CD4+, and CD8+ T cells into the lungs were observed with GAd-CXCL9/10 delivery on day 8 (below) and similar elevations of lung T cells were observed 1 month later (not shown). Interestingly, no differences in antigen-specific T cells were observed in BCG vaccinated mice treated with GAd-CXCL9/10 as determined by intracellular cytokine staining assays (not shown). Therefore, GAd-CXCL9/10 delivery may be nonspecifically recruiting T cells into the lungs. Additional studies are planned to evaluate this possibility (see next section).



What opportunities for training and professional development has the project provided?

Nothing to report.

How were the results disseminated to communities of interest?

Nothing to report.

What do you plan to do during the next reporting period to accomplish the goals?
If this is the final report, state "Nothing to Report."

Describe briefly what you plan to do during the next reporting period to accomplish the goals and objectives.

We plan to complete our optimization studies of the chemokine-induced pull of vaccine-specific T cells into the lung. We will evaluate 1) whether the GAd-CXCL9/10 alone (without SC BCG vaccination) results in elevated lung T cell numbers, 2) whether control GAd (not expressing chemokines) results in T cell influx into the lungs, and 3) whether lung T cells (isolated by FACS) induced by systemic BCG vaccination but recruited into the lungs are indeed antigen-specific. We will also determine whether this strategy results in enhanced protection against TB challenge.

We also plan to modify our IACUC and ACURO protocols to include intranasal delivery of soluble recombinant chemokines, since we have not observed lung T cell recruitment post aerosol delivery of the same chemokines. This will allow for a direct seeding of a known dose of chemokines into mucosal surfaces rather than estimated doses delivered post-aerosol exposure. Here, mice will be vaccinated with BCG SC, and a subset of animals treated with IN rCXCL9&10 on days 2, 4, and 6. We will evaluate total lung T cell influx by flow cytometry as described earlier, and monitor antigen-specific responses in the lungs via ELISPOT assay. Based on results from this experiment, we will proceed to evaluate the efficacy of the strategy against an aerosol TB challenge.

4. **IMPACT:** D*escribe distinctive contributions, major accomplishments, innovations, successes, or any change in practice or behavior that has come about as a result of the project relative to:*

What was the impact on the development of the principal discipline(s) of the project?
If there is nothing significant to report during this reporting period, state "Nothing to Report."

Describe how findings, results, techniques that were developed or extended, or other products from the project made an impact or are likely to make an impact on the base of knowledge, theory, and research in the principal disciplinary field(s) of the project. Summarize using language that an intelligent lay audience can understand (Scientific American style).

Nothing to report in year 1.

What was the impact on other disciplines?
.

Nothing to report in year 1.

What was the impact on technology transfer?

Nothing to report in year 1.

What was the impact on society beyond science and technology?

Nothing to report in year 1.

5. CHANGES/PROBLEMS:

Nothing to report in year 1.

Actual or anticipated problems or delays and actions or plans to resolve them

Planned experiments after March 1, 2020 have been postponed as our laboratories were closed because of COVID-19 pandemic. Research labs are slowly opening now with very limited number of staff but the priority is for projects related to COVID-19. We will resume this project as soon as we are permitted to carry out activities with full capacity.

Changes that had a significant impact on expenditures

Describe changes during the reporting period that may have had a significant impact on expenditures, for example, delays in hiring staff or favorable developments that enable meeting objectives at less cost than anticipated.

Because of the delays noted above, some funds originally scheduled for use in year 1 will be utilized in the next period.

Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents

Nothing to report.

Significant changes in use or care of human subjects

No human subject use.

Significant changes in use or care of vertebrate animals

Nothing to report.

Significant changes in use of biohazards and/or select agents

Nothing to report.

6. PRODUCTS:

- **Publications, conference papers, and presentations**

Journal publications.

Nothing to report.

Books or other non-periodical, one-time publications.

Nothing to report.

Other publications, conference papers and presentations.

Nothing to report.

- **Website(s) or other Internet site(s)**

Nothing to report.

- **Technologies or techniques**

Nothing to report.

- **Inventions, patent applications, and/or licenses**

Nothing to report.

- **Other Products**

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

What individuals have worked on the project?

Name:	Getahun Abate, M.D., Ph.D.
Project Role:	Principal Investigator
Research Identifier:	NA
Nearest person month worked:	1 CM
Contribution to project:	Served as a PI for this project (He provided oversight)
Funding support:	NA (effort funded by this award)
Name:	Christopher Eickhoff,, M.S.
Project Role:	Co-Investigator
Research Identifier:	NA
Nearest person month worked:	2 CM
Contribution to project:	Chris planned, performed, and analyzed experiments to evaluate the kinetics of lung T cell recruitment after BCG vaccination and the effects of the recombinant adenovirus vectors.
Funding support:	NA (effort funded by this award)
Name:	Krystal Meza.
Project Role:	Laboratory
Research Identifier:	NA
Nearest person month worked:	2 CM
Contribution to project:	Krystal performed experiments to evaluate the kinetics of chemokine production in the lungs after BCG vaccination and the effects of recombinant adenovirus vectors
Funding support:	NA (effort funded by this award)
Name:	Igor Dmitriev, PhD
Project Role:	Co-Investigator
Research Identifier:	NA
Nearest person month worked:	1
Contribution to project:	He worked closely with Dr. Curiel to design the genomes of recombinant adenovirus vectors
Funding support:	NA (effort funded by this award)

Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?

Saint Louis University

Getahun Abate, M.D., Ph.D.
Effort began on W81XWH1910117 start date 04/01/19.
Effort began on HHSN272201300017I/A032499 start date 07/01/19.
Effort began on UM1AI148685 start date 12/11/19.
Revised other support page is attached.

Christopher Eickhoff, M.S.
Effort has ended on OPP1118659, R21AI128270, and R01AI048391, and U24AI118665.
Effort began on W81XWH1910117 start date 04/01/19.
Revised other support page is attached.

Washington University

David Curiel, M.D., Ph.D.
Effort has ended on R33 HL120760, OTM11023, R21 AI131254, DARPA-16-33-Office-Wide-BAA-FP-042.
Effort was started on OC170200, R41 TR001869, PR182272, R01 EB026468, UG3 TR002851, R01 CA240983,
Revised other support page is attached.

Igor Dmitriev Ph.D.
Effort has ended on R21 AI131254 and DARPA-16-33-Office-Wide-BAA-FP-042
Effort was started on UH3 HL141800, 18-06, 20-FY19-01, PR182272, R01 EB026468, and UG3 TR002851.
Revised other support page is attached.

What other organizations were involved as partners?

Organization: Washington University
Location: St. Louis, MO, USA
Contribution: Dr. Curiel's group at Washington University serves as a subcontract site on this project. They are responsible for creation of the replication deficient Adenovirus vaccine encoding CXCL9 and CXCL10.

8. SPECIAL REPORTING REQUIREMENTS

W81XWH1910117: Novel Methods of Augmenting Lung TB Immunity

PI: Getahun Abate, MD,PhD. Saint Louis University, Missouri **Budget:** $275,548

Topic Area: PRMRP-Tuberculosis **Mechanism:** W81XWH-18-PRMRP-DA

Research Area(s): 0500, 0608 **Award Status:** Apr 1, 2019 – Sep 30, 2020

Study Goals:

1. To identify the natural kinetics of chemokine expression and T cell recruitment after mucosal vaccination.
2. To develop recombinant protein and adenoviral-based vectors to deliver chemokines in the lungs

Specific Aims:

Aim 1. Evaluate the effects on T cell recruitment of lung chemokine delivery during systemic TB vaccination.

Aim 2. Evaluate the effects of lung chemokine delivery during BCG vaccination on Mtb infection & disease.

Key Accomplishments and Outcomes:

1. Mucosal BCG induced rapid induction of CXCL9&10 expression (2 days)
2. T cells migrate to the lungs by day 3 post-mucosal BCG delivery and peak by day 10.
3. Aerosolized CXCL9&10 delivered post-systemic BCG failed to recruit T cells to the lungs.
4. Gorilla Ad-vectored CXCL9&10 resulted in elevated lung T cell numbers 1-4 weeks post delivery.

Publications: none to date
Patents: none to date
Funding Obtained: none to date

9. APPENDICES:

OTHER SUPPORT

Getahun Abate

ACTIVE

HHSN272201300021 (Hoft) 09/16/13 – 09/15/23 2.28 CM

NIH/NIAID $2,203,329

Vaccine and Treatment Evaluation Units (VTEU)

The primary objectives of this project are to develop innovative clinical trial designs to evaluate new vaccines, to reassess older vaccines using contemporary clinical trial designs, to extend knowledge of existing vaccines to new uses, to bring new vaccines and treatments to high risk populations not targeted by industry and to conduct focused epidemiology studies.

W81XWH1910117 (Abate) 04/01/19 – 09/30/20 0.60 CM

Department of Defense $198,611

Novel methods of augmenting lung TB immunity

The primary goals of this project are to determine whether a prime-pull approach using chemokines to recruit immune cells into lungs will help control TB infection and disease and to determine if targeted immunotherapies that enhance mucosal immunity will increase the ability to contain and even eradicate Mtb.

HHSN272201300017I/A032499 (Abate) 07/01/19 – 12/31/20 0.60 CM

NIH/NIAID/Duke University $336,441

DMID Protocol 13-0053 subcontract from Duke University

The goal of this subcontract is to assist Duke University with A Phase I, single dose, open-label, parallel group study comparing the pharmacokinetics and safety of PA-824 in subjects with mild, moderate, and severe hepatic impairment to matched, normal, healthy subjects

UM1AI148685 (Hoft) 12/11/19 – 11/30/26 0.72 CM

NIH/NIAID $606,000

Vaccine and Treatment Evaluation Unit at Saint Louis University

The primary goals of this project are to develop innovative clinical trial designs to evaluate new vaccines, to reassess older vaccines using contemporary clinical trial designs, to extend knowledge of existing vaccines to new uses, to bring new vaccines and treatments to high risk populations not targeted by industry and to conduct focused epidemiology studies.

PENDING

None.

OTHER SUPPORT

Chris Eickhoff

ACTIVE

HHSN272201300021 (Hoft)	09/16/13 – 09/15/23	3.60 CM
NIH/NIAID	$2,203,329	

Vaccine and Treatment Evaluation Units (VTEU)

The primary objectives of this project are to develop innovative clinical trial designs to evaluate new vaccines, to reassess older vaccines using contemporary clinical trial designs, to extend knowledge of existing vaccines to new uses, to bring new vaccines and treatments to high risk populations not targeted by industry and to conduct focused epidemiology studies.

W81XWH1910117 (Abate)	04/01/19 – 09/30/20	1.20 CM
Department of Defense	$198,611	

Novel methods of augmenting lung TB immunity

The primary goals of this project are to determine whether a prime-pull approach using chemokines to recruit immune cells into lungs will help control TB infection and disease and to determine if targeted immunotherapies that enhance mucosal immunity will increase the ability to contain and even eradicate Mtb.

W81XWH1810140 (Hoft)	05/01/18 – 10/31/20	1.68 CM
Department of Defense	$200,000	

Universal Influenza T cell Targeted Mucosal Vaccines

The primary goal of this project is to determine whether dendritic cell-targeted, mucosal T cell vaccines can provide broadly protective influenza immunity.

PENDING

None.

Dmitriev, Igor

Active

R01 CA211096 (Curiel) 6/19/2017-5/31/2022 0.6
National Institutes of Health $228,750 calendar
Novel targeted adenovirus
The goal of this project is to develop targeted adenoviral vectors and thereby address key proof-of-principle issues of field wide relevance.
Role: Co-Investigator

UH3 HL141800 (George) 9/1/2017-7/31/2022 2.0
National Institutes of Health $966,067 calendar
A 3D in vitro disease model of atrial conduction
The central objective of this proposal is to create and validate a robust 3D in vitro microphysiological model Of human atrial conduction utilizing patient-derived induced pluripotent stem cells. The model can be used to test the safety and efficacy of drugs to treat atrial arrhythmias such as atrial fibrillation (AF) in a precision Medicine format. In addition, we will create and test an adenoviral-based strategy to delivery CRISPRi technology to selectively and inducibly knockdown gene regulatory transcription factors as a novel strategy to intervene in atrial arrhythmias such as AF.
Role: Co-Investigator

18-06 (Curiel) 1/1/2019-12/31/2020 1.2
University of Missouri $125,000 calendar
TARGETED GENE THERAPY FOR SPINAL TUMORS
The goal of this project is to advance targeting to tumor endothelial cells to realize vector technology that will make effective gene therapy for intramedullary glioma feasible. We hypothesize that our optimized targeting to tumor neoangiogenesis will feasibilize an effective gene therapy for glioma IMSCT, providing the basis of a novel translational approach for this intractable cancer.
Role: Co-Investigator

20-FY19-01 (Gillanders/Curiel) 1/1/2019-12/31/2020 1.80
Siteman Cancer Center $300,000 calendar
Evaluation of a Novel Personalized Vaccine Strategy for Breast Cancer
The goal is to activate immune cells capable of recognizing and killing breast cancer using the "prime/boost" neoantigen vaccines, and then take the "brakes" off these immune cells using checkpoint blockade therapy. This combination has the potential to be a synergistic and highly effective strategy in TNBC, and in other cancers, particularly cancers resistant to checkpoint blockade therapy alone.
Role: Co-Investigator

PR182272 (Abate) 4/1/2019-9/30/2020 0.6
Department of Defense $200,000 calendar
A novel approach to enhance TB lung immunity
A prime-pull approach using chemokines to recruit immune cells into the lungs will help control TB infection and disease.
Role: Co-Investigator

R01 EB026468 (Curiel) 7/1/2019-3/31/2023 1.0
National Institutes of Health $270,563 calendar
Novel Vector Platform for Gene Therapy
The goal of this proposal is to develop a novel gene therapy approach for alpha 1-antitrypsin deficiency (AAT) lung disease by expressing AAT in the lower respiratory tract and to demonstrate the efficacy of this strategy in a new murine model of the disease.
Role: Co-Investigator

Dmitriev, Igor

Active

UG3 TR002851 (Curiel) 8/15/2019-7/31/2022 2.64
National Institutes of Health $500,000 calendar
Endothelial-targeted adenovirus for organ-selective gene editing in vivo
The goal of this proposal is to develop adenoviral vectors targeted to endothelial subsets and to exploit this delivery technology to achieve gene editing at these cellular targets.
Role: Co-Investigator

(Ornitz) 2/1/2020-1/31/2023 0.60
Children's Discovery Institute $125,000 calendar
Targeting the FGF signaling pathway as a novel therapy for hypoxia-induced pulmonary hypertension
This proposal will investigate how FGF signaling regulates the pathogenesis of pulmonary hypertension, and how it can be used to prevent or treat pulmonary hypertension in premature infants and children with lung disease.
Role: Co-Investigator

Pending

UH3 not assigned (Curiel/George/Rentschler) 5/15/2020-5/14/2021 2.40
National Institutes of Health $150,000 calendar
A 3D IN VITRO DISEASE MODEL OF ATRIAL CONDUCTION (COVID SUPPLEMENT)
Mechanistic Studies and Model Development to Understand Cardiac Injury in SARS-CoV-2 Infection.
Specific Aim 1: Determine viral tropism in healthy and predisposed adult human cardiac tissue using human cardiac organotypic slices. Specific Aim 2: Delineate the mechanistic relationship between Notch signaling and the IL-6 release on cardiac electrophysiology. Specific Aim 3: Establishment of an *in vivo* murine model for testing SARS-CoV-2 cardiac effects.
Role: Co-Investigator

R01 AI148636 (Moreno) 7/1/2020-6/30/2025 2.40
National Institutes of Health $576,616 calendar
Malaria vaccination regimens for priming and liver compartmentalization of T cells via DC targeting
The major goal of this project is to develop a novel malaria vaccine strategy to prime, recruit, reposition and retain tissue-resident memory CD8+ T cell within the liver
Role: Co-Investigator

R01 AI152231 (Boon/Diamond/Fremont) 7/1/2020-6/30/2025 2.40
National Institutes of Health $250,000 calendar
Vaccines against emerging tick-borne virus
The focus of this proposal is to develop vaccines against emerging tick-borne viruses
Role: Co-Investigator

not assigned (Eberlein) 7/1/2020-6/30/2021 1.20
National Institutes of Health $75,000 calendar
Cancer Center Support Grant-Viral vectored vaccines against SARS-CoV-2
The long-term goal of this project is to compare vesicular stomatitis virus and chimp adenovirus vectored vaccines for the immunogenicity and protection against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
Role: Co-Investigator

not assigned (Hoft) 7/1/2020-6/30/2025 1.20
National Institutes of Health $250,000 calendar
Universal T cell targeted influenza vaccine
The goals of this project are to develop T-cell-based influenza vaccines which provide long term heterotypic immunity.
Role: Co-Investigator

Dmitriev, Igor

Pending

UG3 not assigned (Curiel)	8/1/2020-7/31/2021	1.00
National Institutes of Health	$500,000	calendar

Thermostable ovine adenoviral vector for maximized COVID-19 vaccine implementation
Adenoviral vectors have many useful attributes recommending their employ for COVID-19. Among defined adenoviruses, vectors derived from ovine adenovirus embody the unique property of exceptional thermostability allowing employment in cold chain-free vaccination schemas with key developing world implications. Here we will derive ovine adenovirus vector vaccines and evaluate their utility in a stringent nonhuman primate model.
Role: Co-Investigator

Overlap
none

Curiel, David T.

Active

R01 CA211096 (Curiel) 6/19/2017-5/31/2022 1.80
National Institutes of Health $228,750 calendar
Novel targeted adenovirus
The goal of this project is to develop targeted adenoviral vectors and thereby address key proof-of-principle issues of field wide relevance.
Role: Principal Investigator

not assigned (Aboody, Karen) 7/1/2017-6/30/2020 0.12
The Ivy Foundation $459,773 calendar
Neural Stem Cell -Oncolyric virotherapy for brain tumors
The overall objective of this application is to significantly advance NSC-mediated virotherapy as a novel treatment for newly diagnosed and recurrent glioma patients.
Role: Principal Investigator

UH3 HL141800 (George) 9/1/2017-7/31/2022 0.96
National Institutes of Health $966,067 calendar
A 3D in vitro disease model of atrial conduction
The central objective of this proposal is to create and validate a robust 3D in vitro microphysiological model Of human atrial conduction utilizing patient-derived induced pluripotent stem cells. The model can be used to test the safety and efficacy of drugs to treat atrial arrhythmias such as atrial fibrillation (AF) in a precision medicine format. In addition, we will create and test an adenoviral-based strategy to delivery CRISPRi technology to selectively and inducibly knockdown gene regulatory transcription factors as a novel strategy to intervene in atrial arrhythmias such as AF.
Role: Principal Investigator

OC170200 (Curiel) 6/1/2018-6/30/2020 0
Department of Defense $155,000 calendar
Novel ovarian cancer therapy
These studies will test a hypothesis regarding the biologic basis of virotherapy action that is of field-wide relevance. In addition, we will realize the database rationalizing translational development of a novel virotherapy agent for carcinoma of the ovary.
Role: Principal Investigator

R41 TR001869 (Curiel) 9/18/2018-8/31/2020 0.60
National Institutes of Health $77,414 calendar
NOVEL PLATFORM TECHNOLOGY FOR HEMOPHILIA GENE THERAPY
We propose to develop a novel vector approach that addresses the key limitations to current methods and utilizes the unique capacity to target pulmonary endothelium for reconstituting deficient serum factors. We will accomplish this by combining technologies from Washington University and Precision Virologics, Inc. In Phase I we will demonstrate the feasibility of the new platform technology to efficiently deliver to pulmonary endothelium and achieve stable long-term correction of factor VIII deficient mice.
Role: Principal Investigator

18-06 (Curiel) 1/1/2019-12/31/2020 0.60
University of Missouri $125,000 calendar
TARGETED GENE THERAPY FOR SPINAL TUMORS
The goal of this project is to advance targeting to tumor endothelial cells to realize vector technology that will make effective gene therapy for intramedullary glioma feasible. We hypothesize that our optimized targeting to tumor neoangiogenesis will feasibilize an effective gene therapy for glioma IMSCT, providing the basis of a novel translational approach for this intractable cancer.
Role: Principal Investigator

Curiel, David T.

Active

20-FY19-01 (Gillanders/Curiel) 1/1/2019-12/31/2020 1.20
Siteman Cancer Center $300,000 calendar
Evaluation of a Novel Personalized Vaccine Strategy for Breast Cancer
The goal is to activate immune cells capable of recognizing and killing breast cancer using the "prime/boost" neoantigen vaccines, and then take the "brakes" off these immune cells using checkpoint blockade therapy. This combination has the potential to be a synergistic and highly effective strategy in TNBC, and in other cancers, particularly cancers resistant to checkpoint blockade therapy alone.
Role: Principal Investigator

not assigned (Curiel) 4/1/2019-3/31/2022 0.30
Washington University SOM $57,500 calendar
Breast Cancer Project 1 - Centene ARCH Personalized Medicine Initiative Sponsored Research Agreement
The goal of this project is to use systemically administered adenovirus to demonstrate in vivo gene transfer to T-cells and study the anti-tumor efficacy of these T-cells in a murine model.
Role: Principal Investigator

PR182272 (Abate) 4/1/2019-9/30/2020 0.24
Department of Defense $200,000 calendar
A novel approach to enhance TB lung immunity
A prime-pull approach using chemokines to recruit immune cells into the lungs will help control TB infection and disease.
Role: Co-Investigator

R01 EB026468 (Curiel) 7/1/2019-3/31/2023 1.20
National Institutes of Health $270,563 calendar
Novel Vector Platform for Gene Therapy
The goal of this proposal is to develop a novel gene therapy approach for alpha 1-antitrypsin deficiency (AAT) lung disease by expressing AAT in the lower respiratory tract and to demonstrate the efficacy of this strategy in a new murine model of the disease.
Role: Principal Investigator

UG3 TR002851 (Curiel) 8/15/2019-7/31/2022 3.54
National Institutes of Health $500,000 calendar
Endothelial-targeted adenovirus for organ-selective gene editing in vivo
The goal of this proposal is to develop adenoviral vectors targeted to endothelial subsets and to exploit this delivery technology to achieve gene editing at these cellular targets.
Role: Principal Investigator

R01 CA240983 (Gillanders/Schreiber) 9/1/2019-7/31/2023 0.30
National Institutes of Health $404,968 calendar
Targeting Neoantigens in Triple Negative Breast Cancer
We propose both clinical and preclinical studies on neoantigen DNA vaccines +/- anti-PD-L1. We will conduct a randomized phase 1 clinical trial of neoantigen DNA vaccines +/- anti-PD-L1 (durvalumab) in patients with persistent triple negative breast cancer following neoadjuvant chemotherapy. Preclinical studies in breast cancer mouse models will focus on recombinant adenovirus-plasmid DNA neoantigen vaccine prime-boost strategies or targeting of macrophages in the tumor microenvironment. Combined, these studies will allow functional validation of our epitope prediction algorithms and inform the design of second generation neoantigen vaccine strategies.
Role: Co-Investigator

Curiel, David T.

Active

(Ornitz) 2/1/2020-1/31/2023 0.36
Children's Discovery Institute $125,000 calendar
Targeting the FGF signaling pathway as a novel therapy for hypoxia-induced pulmonary hypertension
This proposal will investigate how FGF signaling regulates the pathogenesis of pulmonary hypertension, and how it can be used to prevent or treat pulmonary hypertension in premature infants and children with lung disease.
Role: Co-Investigator

not assigned (Curiel) 3/2/2020-3/1/2022 0.60
Emerson Collective Cancer Research Fund $100,000 calendar
In vivo generation of CAR T-cells for cancer immunotherapy
We have developed adenovirus-based vectors capable of gene transfer to specific target cells in an intact human. This highly original approach will thus allow more facile local and worldwide implementation of CAR T-cell immunotherapy, thereby allowing application of this promising approach for the widest range of patients and cancers.
Role: Principal Investigator

Pending

not assigned (Curiel) 12/1/2019-11/30/2019 0.60
CMMN-Cancer Center $70,000 calendar
Bone marrow niche mobilization for metastatic disease
The major challenge to exploit metastatic niche endothelium for therapeutic intent is the issue of selective access to this site. We potentially have a solution to this barrier. We have developed adenoviral (Ad) vectors that are capable of selective gene delivery to EC. Now we are positioned to address the heretofore elusive hypothesis that malignant cellular eviction from metastatic niches will control tumor growth and also function in combination with antineoplastic therapies.
Role: Principal Investigator

UH3 not assigned (Curiel/George/Rentschler) 5/15/2020-5/14/2021 0.60
National Institutes of Health $150,000 calendar
A 3D IN VITRO DISEASE MODEL OF ATRIAL CONDUCTION
Mechanistic Studies and Model Development to Understand Cardiac Injury in SARS-CoV-2 Infection.
Specific Aim 1: Determine viral tropism in healthy and predisposed adult human cardiac tissue using human cardiac organotypic slices. Specific Aim 2: Delineate the mechanistic relationship between Notch signaling and the IL-6 release on cardiac electrophysiology. Specific Aim 3: Establishment of an *in vivo* murine model for testing SARS-CoV-2 cardiac effects.
Role: Principal Investigator

714542 (Curiel/DeSelm) 7/1/2020-6/30/2021 0.60
ST. BALDRICK'S FOUNDATION $100,000 calendar
In vivo generation of CAR T-cells for Burkitt lymphoma immunotherapy
The goal of this project is to achieve anti-tumor immunotherapy using a novel gene delivery vehicle to convert T-cells into anti-tumor T-cells within the patient’s body.
Role: Principal Investigator

88636 (Curiel) 7/1/2020-6/30/2021 0.60
Mary Kay Ash Charitable Foundation $86,950 calendar
In vivo generation of CAR-T cells for ovarian cancer immunotherpy
In this proposal our goal is to establish proof-of-concept with respect to the in situ CAR-T approach for ovarian cancer.
Role: Principal Investigator

Curiel, David T.

Pending

R01 AI148636 (Moreno)	7/1/2020-6/30/2025	0.60
National Institutes of Health	$576,616	calendar

Malaria vaccination regimens for priming and liver compartmentalization of T cells via DC targeting
The major goal of this project is to develop a novel malaria vaccine strategy to prime, recruit, reposition and retain tissue-resident memory CD8+ T cell within the liver
Role: Co-Investigator

Curiel, David T.

Pending

R01 AI152231 (Boon/Diamond/Fremont) 7/1/2020-6/30/2025 0.60
National Institutes of Health $250,000 calendar
Vaccines against emerging tick-borne virus
The focus of this proposal is to develop vaccines against emerging tick-borne viruses
Role: Co-Investigator

not assigned (Achilefu) 7/1/2020-12/31/2021 0.60
Siteman Cancer Center $130,000 calendar
Targeting the perivascular niche via adenovirus-nano vectors to achieve chemosensitization as a novel approach for metastatic cancer of the breast
The pan-therapeutic resistance of breast metastases is linked to host multicellular niches which appear to regulate quiescence of a population of tumor cells that evidence stemlike features. An important facet of the metastatic niche is the vascular endothelial cell (EC). The major challenge to exploit this biology for therapeutic intent is the issue of selective access to this site. We have developed adenoviral (Ad) vectors that are capable of selective gene delivery to EC, and we are thus positioned to address the heretofore elusive hypothesis that malignant cellular eviction from metastatic niches will control tumor growth and also function in combination with antineoplastic therapies.
Role: Principal Investigator

not assigned (Eberlein) 7/1/2020-6/30/2021 0.60
National Institutes of Health $75,000 calendar
Cancer Center Support Grant-Viral vectored vaccines against SARS-CoV-2
The long-term goal of this project is to compare vesicular stomatitis virus and chimp adenovirus vectored vaccines for the immunogenicity and protection against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).
Role: Principal Investigator

not assigned (Hoft) 7/1/2020-6/30/2025 0.30
National Institutes of Health $250,000 calendar
Universal T cell targeted influenza vaccine
The goals of this project are to develop T-cell-based influenza vaccines which provide long term heterotypic immunity.
Role: Principal Investigator

UG3 not assigned (Curiel) 8/1/2020-7/31/2021 0.30
National Institutes of Health $500,000 calendar
Thermostable ovine adenoviral vector for maximized COVID-19 vaccine implementation
Adenoviral vectors have many useful attributes recommending their employ for COVID-19. Among defined adenoviruses, vectors derived from ovine adenovirus embody the unique property of exceptional thermostability allowing employment in cold chain-free vaccination schemas with key developing world implications. Here we will derive ovine adenovirus vector vaccines and evaluate their utility in a stringent nonhuman primate model.
Role: Principal Investigator

Overlap

none