AWARD NUMBER: W81XWH-19-1-0117

TITLE: Novel Methods of Augmenting Lung TB Immunity

PRINCIPAL INVESTIGATOR: Getahun Abate, MD PhD

CONTRACTING ORGANIZATION: Saint Louis University, St. Louis, MO

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Fort Detrick, Maryland 21702-5012

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5d. PROJECT NUMBER
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5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
Saint Louis University, 1100 South Grand Blvd.
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Washington University in Saint Louis, 660 South
Euclid Ave, 63100

8. PERFORMING ORGANIZATION REPORT NUMBER
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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 None listed.

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	27	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. (75% complete)

4. Determine the effects of a prime-pull vaccination approach on recall T cell immunity during Mtb infection. (40% complete)

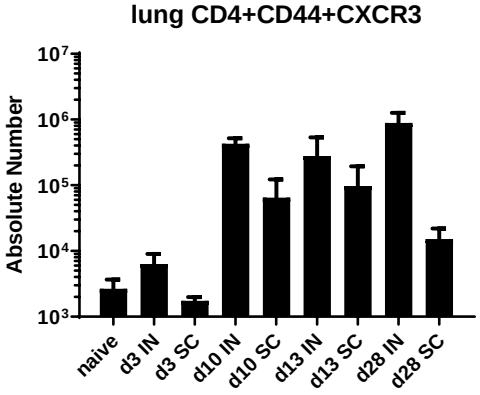
5. Determine the effects of a prime-pull vaccination approach on TB protective immunity. (20% complete)

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).

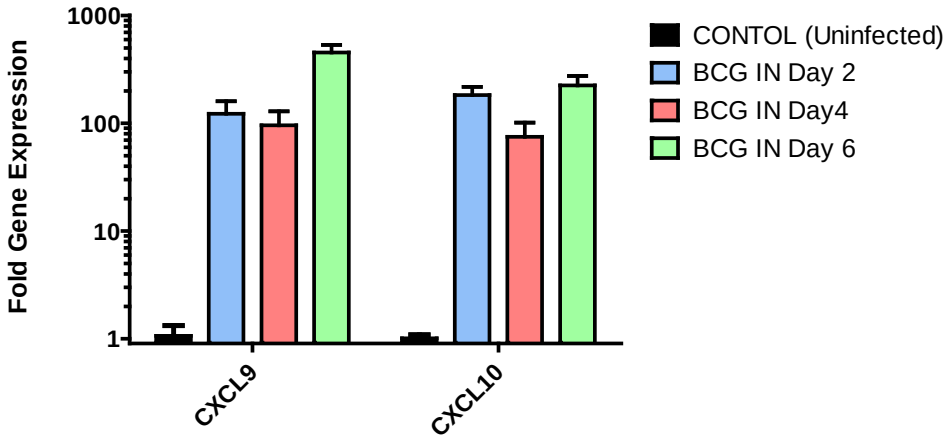
2. Determine CXCR3 expression and chemokine production during vaccination. We first performed experiments in which mice were vaccinated on different days with BCG by either systemic (subcutaneous; SC) or mucosal (intranasal; IN) routes. On days 3, 10, 13, and 28 post-infection, mice were i.v. injected 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.

Figure 1



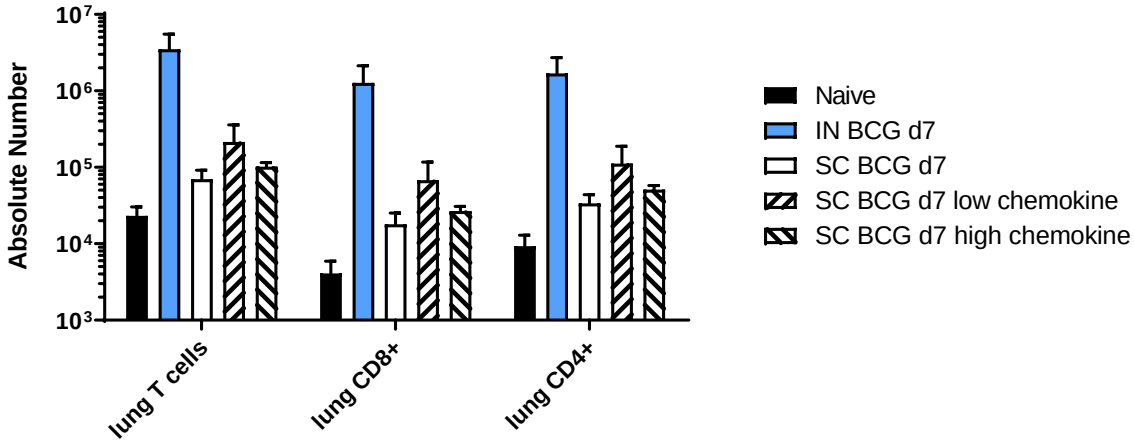
As shown above, T cells rapidly infiltrated the lungs beginning as soon as 3 days post-IN BCG vaccination, and seem to reach a plateau 10-30 days after administration. To evaluate the kinetics of chemokine expression after mucosal BCG delivery, we next performed studies in which mice were treated with 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.

Figure 2



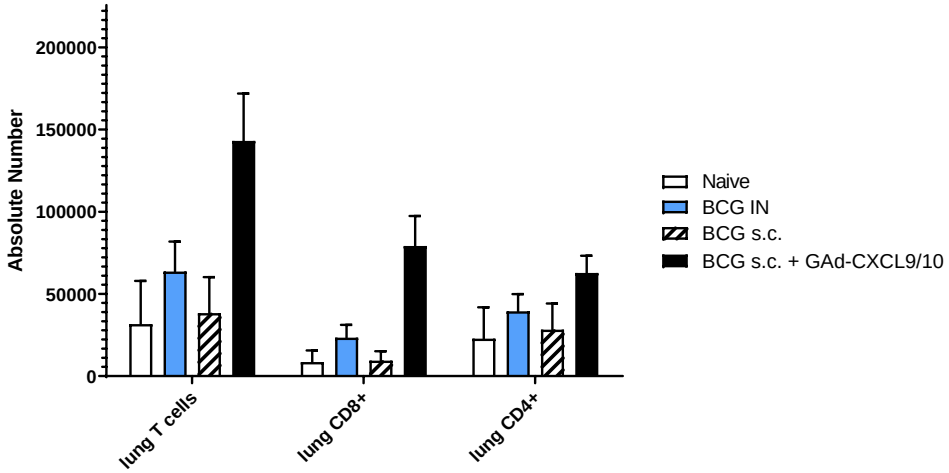
3. Optimization of the chemokine-induced pull of vaccine-specific T cells into the lung. Based on results above we sought to induce the chemokine pull directly after delivery of BCG systemically. Mice were vaccinated with either IN or SC BCG. Approximately 0.5µg (low dose) or 100µg (high dose) of recombinant 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).

Figure 3



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 were planned to evaluate this possibility (see next section).

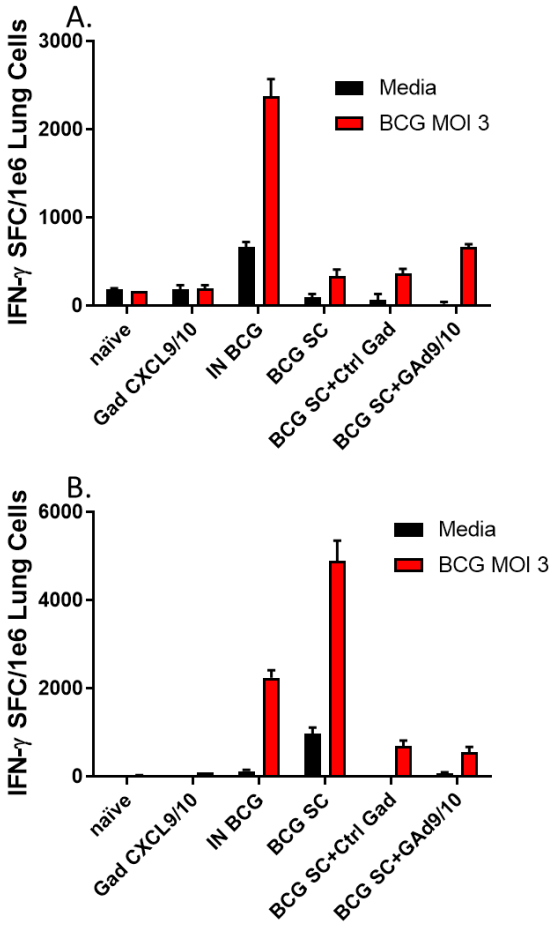
Figure 4



New experiments and findings in the current report period (June 2020-March 2021)

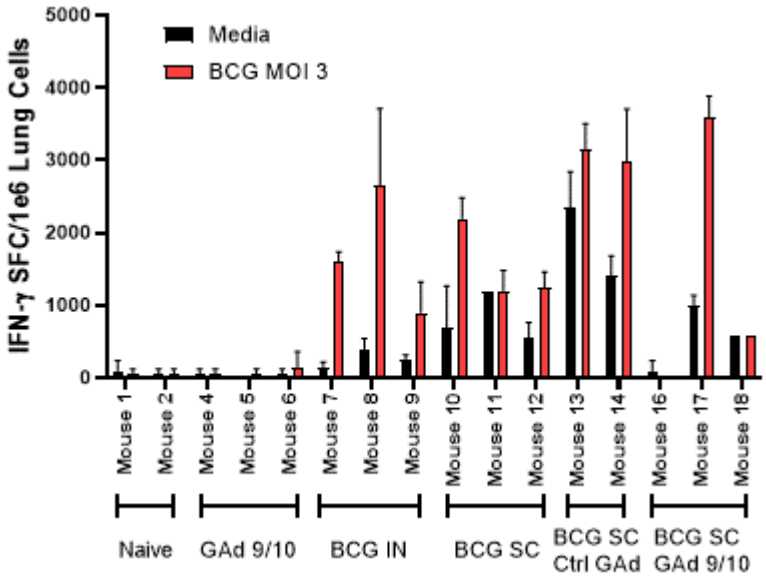
Specificity of rGAd to "pull" activated T cells to the lung following BCG vaccination. Subsequent experiments were done to determine the functionality of the recruited T cells. In these experiments, mice were vaccinated with BCG (IN or SC). Some of the mice that were vaccinated with SC BCG also received two doses of either control or CXCL9/10-expressing rGAd i.v., one and five days after BCG vaccination. Lungs were harvested on days 14 and 30 after vaccination. IFN-γ ELISPOT was performed by simulating lung cells with BCG overnight. Figure 5 shows that rGAd-CXCL9/10 increases the number of IFN-γ spot forming cells on day 14 in mice vaccinated with SC BCG with or without control GAd (Figure 5A) but not on day 33 (Figure 5B). In fact, on day 33, the number of IFN-γ spot forming cells in mice vaccinated with SC BCG was much higher than the number in mice vaccinated with IN BCG. This is unexpected and could be due to the growth of BCG in the lungs enough to continue to stimulate specific T cells. The number of BCG in the lungs starts to decline after week 3 following intranasal administration of BCG and the associated immunity on week 4 could be suboptimal (PMID 24120457).

Figure 5



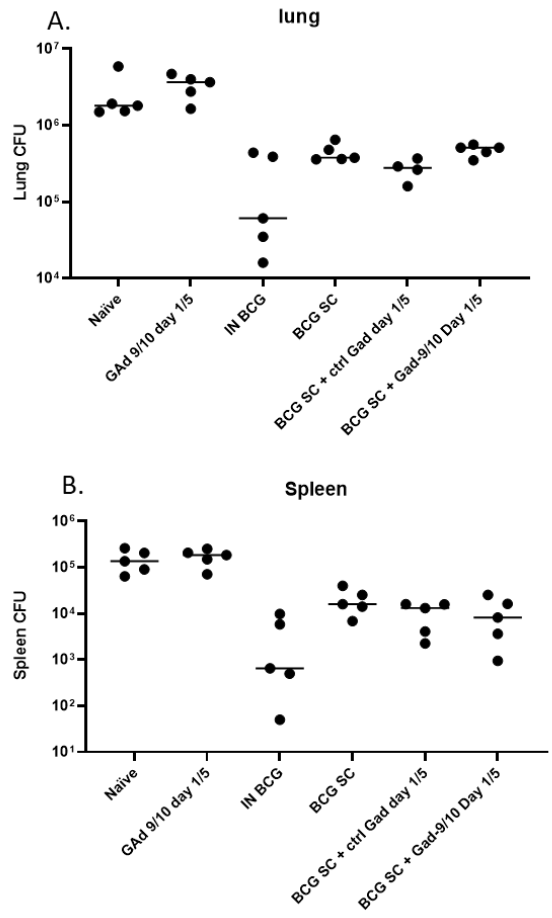
To determine if the prime-pull approach resulted in better T cell responses in the lungs after a mucobacterial challenge, we infected mice 1 month post the BCG prime and GAd-pull with BCG via intranasal delivery. Seven days after mycobacterial challenge, lungs were harvested and IFN-γ ELISPOT assays were performed by stimulating cells with BCG. Figure 6 shows that rGAd by itself does not increase effector T cells. The number of IFN-γ spot forming cells in the lung was higher in mice that received GAd or rGAd following vaccination compared to SC BCG alone. The comparative effects of GAd vs. rGAd should be studied in larger number of BCG-vaccinated mice to allow statistical analysis.

Figure 6



Effect of rGAd on protective function of SC BCG vaccination. In these experiments, mice were vaccinated with BCG (IN or SC). Some of the mice that were vaccinated with SC BCG also received two doses of rGAd i.v., one and five days after BCG vaccination. Mice were challenged with aerosolized Mtb 30 days after vaccination and mice were sacrificed 1 month later. The number of Mtb colony forming units in the lungs and spleen were quantified by plating on 7H10 media. Figure 7 shows that the number of CFU/ml in mice that received rGAd after BCG vaccination was similar to mice that received SC BCG alone. Mice that received IN BCG as controls had the lowest CFU/ml both in lungs (Figure 7A) and spleen (Figure 7B). It is important to further optimize “priming” vaccination strategy for use in experiments aimed at determining the “pulling” effects of rGAd.

Figure 7



In the above experiments, 1 x 10^7 SC BCG was used for priming. This dose of SC BCG in the above experiments may be already high enough to induce optimal immunity that limits the growth of Mtb. Therefore, lower doses of BCG should be tried alone and in combination with rGAd. A second approach is to use a different vaccination strategy that allows measurement of vaccine-specific T cells in the lungs as well as protection. ESAT-6 peptide 1-20, and dendritic cell vaccines, and ESAT-6 TCR transgenic mice are reliable tools that we have available that can be used to more carefully evaluate the prime-pull approach in mice (PMID 19620314, 18667699, 31331771). The use of dendritic cells pulsed with early secreted antigen ESAT-6 peptide pool as a vaccine to "prime' immunity and measurement of "pulling" of ESAT-6 specific T cells using tetramers will have the following advantages: i) allows measurement of vaccine-specific T cells in the lung, ii) gives a more reliable comparison vaccine-specific recruitment of T cells to the lung by rGAd vs control Gad, and iii) allows determine the association of vaccine-specific T cells and protection from Mtb.

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?

We plan to use a more robust method to determine the specificity of T cells pulled to the lung by GAd vs rGAD following TB vaccination.

1) We will use dendritic cells pulsed with ESAT-6 peptides 1-20 to vaccinate (prime) mice followed by pulling with GAd vs rGAd. The mice will be previously seeded with naïve, ESAT-6 TCR Tg mice. In these experiments, we will be able to measure the numbers of ESAT-6 specific T cells pulled to the lungs using ESAT-6 tetramers.
2) We will assess the effects of ESAT-6 primed T cells in the protection against TB
3) We will study the effects of rGAD to enhance the protective effects of SC BCG at doses 1 and 2 logs lower than what was used in previous experiments (1×10^7 was used for SC vaccination)

We also plan to modify our IACUC and ACURO protocols to include ESAT-6 pulsed dendritic cells as a vaccine to prime the immune system.

4. IMPACT:

What was the impact on the development of the principal discipline(s) of the project?

Nothing to report.

What was the impact on other disciplines?

.

Nothing to report.

What was the impact on technology transfer?

Nothing to report.

What was the impact on society beyond science and technology?

Nothing to report

5. CHANGES/PROBLEMS:

Changes in approach and reasons for change

GAd and rGAd enhance recruitment of T cells to the lung. A larger number of mice should be used to assess the staitsical difference between GAd and rGAd to "pull" T cells to the lung. The vaccine-specificity of the T cells "pulled" to the lungs using GAd or rGAd following BCG vaccination is not known and will be difficulty to study *in vitro* using BCG as an antigen as some proinflammatory T cells reactive against GAd may cross react against BCG. Therefore, it is important to test the vaccine specificity of T cells recruited to the lung using a robust system. We plan to use dendritic cells pulsed with ESAT-6 peptides (1-20) for priming and measurement of T cells 'pulled" by GAd vs rGAd using ESAT-6 tetramer in flow cytometry assays.

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

The grant period has been extended because of delays related to COVID-19 pandemic. There is no anticipated problems or delays.

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.

Nothing to report.

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.

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.

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:	1 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:	David Curiel, M.D. PhD
Project Role:	Co-Investigator
Research Identifier:	NA
Nearest person month worked:	0.24
Contribution to project:	Serves as PI of the subcontract at Washington University
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 ended on HHSN272201300017I/A032499.
Effort began on WU-20-458 start date 03/01/20.
Revised other support page is attached.

Christopher Eickhoff, M.S.
Effort ended on W81XWH1810140.
Effort began on R01AI130190 start date 09/01/20.
Effort began on RGF 319011 start date 02/01/19.
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, 2021

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.
5. Pulling T cells to the lungs with Gorilla Ad vectored CXCL9 & 10 did not enhance the effector immunity of SC BCG vaccination ($1x10^7$), indicating the need to use lower doses of BCG or a different vaccine (or priming) platform.

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 0.60 CM

NIH/NIAID

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.

UM1AI148685 (Hoft) 12/11/19 – 11/30/26 2.40 CM

NIH/NIAID

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.

W81XWH1910117 (Abate) 04/01/19 – 09/30/21 0.60 CM

Department of Defense

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.

WU-20-458 (Hoft) 03/01/20 – 02/28/22 1.47 CM

Washington University

WU INSTITUTE OF CLINICAL AND TRANSLATIONAL SCIENCES

The primary goal of this project it to provide both mentoring and consultation to CTSA trainees and investigators.

PENDING

None.

OTHER SUPPORT

Chris Eickhoff

ACTIVE

R01AI130190 (Hoft) 09/01/20 - 08/31/24 7.56 CM

NIH Universal T cell

targeted influenza vaccine

The primary goals of this project are to identify CD4+ and CD8+ T cell epitopes protective in diverse populations against all influenza A virus strains and to generate and test novel universal T cell-targeting influenza vaccines.

W81XWH1910117 (Abate) 04/01/19 – 09/30/21 0.36 CM

Department of Defense

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.

RGF 319011 (Abate) 02/01/19-12/31/21 0.36 CM

Saint Louis University

Abate – Research Growth Fund

The objectives of this project are to develop new drugs and to test interactions of selected compounds with first-line antimycobacterial drugs, perform limited murine experiments to study the pharmacokinetics (PK) of selected drugs, use the invitro structure activity relationship (SAR) and in vivo PK data to design improved structural analogs, and evaluate the efficacy of antimycobacterial activities of selected drugs in a murine model.

HHSN272201300021 (Hoft) 09/16/13 – 09/15/23 1.20 CM

NIH/NIAID

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.

PENDING

None.

Curiel, David T.

Active

R01 CA211096 (Curiel) 6/19/2017-5/31/2022 1.52
National Institutes of Health 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) 7/1/2017-5/11/2021 0.12
The Ivy Foundation 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) 0.60
9/1/2017-7/31/2022 National Institutes of Health 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

R41 TR001869 (Curiel) 9/18/2018-8/31/2021 0.60
National Institutes of Health 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) 1/1/2019-12/31/2021 0.36
University of Missouri 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) 1/1/2019-12/31/2021 1.12
Siteman Cancer Center 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 0.24
Washington University SOM 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 anit-tumor efficacy of these T-cells in a murine model.
Role: Principal Investigator

R01 EB026468 (Curiel) 7/1/2019-3/31/2023 1.20
National Institutes of Health 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 3.72
National Institutes of Health 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 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) 0.36
2/1/2020-1/31/2023 Children's Discovery Institute 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 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

R01 EB026468 (Curiel) 1/711/2021-1/8/2022 0.60
National Institutes of Health calendar
COVID-19 therapy via selective expression of soluble ACE2 in the lower respiratory tract
We will develop adenoviral vectors to achieve selective gene delivery to the pulmonary endothelium in a mouse model of COVID-19. This will enable us to test the hypothesis that high/local concentrations of the SARS- CoV2 inhibitor, soluble ACE, can mitigate COVID-19 associated with pulmonary disease. Our novel approach embodies direct translational possibilities.
Role: Principal Investigator

R01 AI130190 (Curiel) 9/1/2020-8/31/2024 0.30
SLU/National Institutes of Health calendar
Universal T Cell targeted influenza vaccine
We will identify and evaluate vaccine targets relevant for human infection with highly diverse strains of influenza A virus which cause seasonal epidemics or more serious pandemics. We will prepare several novel vaccines focused on inducing relevant immune cell types, and test these vaccines in humanized mice with the ultimate goal of developing a universally relevant influenza vaccine.
Role: Principal Investigator

Curiel, David T.

Overlap
none

Dmitriev, Igor

Active

R01 CA211096 (Curiel) 6/19/2017-5/31/2022 .60
National Institutes of Health 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 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) 1/1/2019-12/31/2021 0.00
University of Missouri 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) 1/1/2019-12/31/2021 0.60
Siteman Cancer Center 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

R01 EB026468 (Curiel) 7/1/2019-3/31/2023 2.20
National Institutes of Health 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 2.04
National Institutes of Health 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 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

R01 EB026468 (Curiel) Supplement 1/7/2021-1/08/2022 2.40
National Institutes of Health calendar
COVID-19 therapy via selective expression of soluble ACE2 in the lower respiratory tract
We will develop adenoviral vectors to achieve selective gene delivery to the pulmonary endothelium in a Mouse model of COVID-19. This will enable us to test the hypothesis that high/local concentrations of the SARS- CoV2 inhibitor, soluble ACE, can mitigate COVID-19 associated with pulmonary disease. Our novel approach embodies direct translational possibilities.
Role: Co-Investigator

R01 AI130190 (Curiel) 9/1/2020-8/31/2024 1.20
SLU/National Institutes of Health calendar
Universal T Cell targeted influenza vaccine
We will identify and evaluate vaccine targets relevant for human infection with highly diverse strains of influenza A virus which cause seasonal epidemics or more serious pandemics. We will prepare several novel vaccines focused on inducing relevant immune cell types, and test these vaccines in humanized mice with the ultimate goal of developing a universally relevant influenza vaccine.
Role: Co-Investigator

Overlap
none