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TITLE: Understanding Plasma Cell Differentiation in SLE

PRINCIPAL INVESTIGATOR: Betty Diamond

CONTRACTING ORGANIZATION: The Feinstein Institutes for Medical Research
Manhasset, NY

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5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

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The Feinstein Institutes for Medical Research
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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Our immune system functions to eradicate pathogens from our body. One arm of this defense is through antibodies which facilitate pathogen clearance. However, if antibodies target our own body, autoimmune diseases, such as Systemic Lupus Erythematosus (SLE), can arise. Most SLE patients have anti-nuclear antibodies (ANA). These antibodies recognize an array of molecules that normally reside in the nucleus of cells. However, when an injury or infection occurs, these molecules can be released from the nucleus of dying cells, thereby becoming accessible to binding by ANA, which usually results in an inflammatory response. Plasma cells are the immune cells that produce antibodies, and they can arise from B cells through different pathways. Our previous results have shown that the differentiation of most ANA+ B cells to plasma cells is prevented in healthy individuals, a process we call tolerance. In SLE, this tolerance process is unsuccessful, thereby leading to secretion of ANA and to subsequent inflammatory reactions throughout the body. Our previous research has shown that SLE patients can be separated in two groups based on their pattern of ANA+ plasma cells. In the proposed project, we aim to study the pathways that lead to the emergence of ANA+ plasma cells in SLE. Included among ANA+ PCs are cells making anti-DNA and anti-Sm antibodies, both of which are known to contribute to disease in SLE. We will compare the two groups of patients; we hypothesize that each group has a distinct pathway for the development of ANA+ plasma cells. Moreover, we will determine how to cause the differentiation of a naïve or memory ANA+ cells to PCs to provide insights into prevention.

15. SUBJECT TERMS

None listed.

16. SECURITY CLASSIFICATION OF:			**17. LIMITATION OF ABSTRACT**	**18. NUMBER OF PAGES**	**19a. NAME OF RESPONSIBLE PERSON**
					USAMRDC
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1. Introduction

We have previously shown that a major breach to B cell tolerance in patients with systemic lupus erythematosus (SLE) is the enhanced differentiation of IgG plasma cells. Based on this observation, the goal of this study is to understand the induction of plasma cells in SLE. We propose to determine if there is a difference in plasma cell differentiation when they arise through an extrafollicular vs a germinal center pathway, and whether there is a difference in the differentiation of plasma cells directed to nuclear antigens (ANA+) and those without this auto-specificity. We also propose to develop approaches to blocking IgG plasma cell differentiation.

2. Keywords

Systemic lupus erythematosus; B cells: plasmablasts/plasma cells; IgG; extrafollicular; germinal center; B cell repertoire

3. Accomplishments

- **What were the major goals of the project?**

List the major goals of the project as stated in the approved SOW. If the application listed milestones/target dates for important activities or phases of the project identify these dates and show actual completion dates or the percentage of completion.	Percentage of completion
Specific Aim 1 *Cellular origin of ANA+ PCs in SLE patients*	Percentage of completion
Major Task 1: Deep sequencing of the ANA+ plasmablast/ *B cell repertoire from SLE patients*	90%
Specific Aim 1 *Cellular origin of ANA+ PCs in SLE patients*	Percentage of completion
Major Task 2: Data analysis: repertoire	70%

Specific Aim 2 *Phenotype of ANA+ PCs related to PC differentiation pathway*	Percentage of completion
Major Task 3: Phenotype of ANA+ plasmablasts in SLE	75%
Specific Aim 2 *Phenotype of ANA+ PCs related to PC differentiation pathway*	Percentage of completion
Major Task 4: RNA sequencing of ANA+ plasmablasts	50%
Specific Aim 3 *BCR AND TLR7/9 stimulation pathways for PC differentiation*	Percentage of completion
Major Task 5: Induction of ANA+ plasmablasts	50%

- **What was accomplished under these goals?**

Specific Aim 1:

We have been studying whether we can determine through molecular analyses of the B cell receptor (BCR) the pathway for the generation of plasma cells in SLE patients. We have isolated ANA+ and ANA- naïve, memory and age/autoimmunity associated B cells (ABCs) and plasmablasts from SLE patients and subjected these to DNA sequencing of the B cell receptor.

We identify two groups of patients. In one group, plasma cells are most clonally related to naïve B cells; we believe these are patients in whom plasma cells are generated through an extrafollicular pathway. In the second group, plasma cells are clonally most related to memory B cells; we believe plasma cells in these individuals arise through a germinal enter pathway. We further observe an increased frequency of somatic mutation in BCRs of those plasmablasts we believe arise from the germinal center response.

We have been trying to determine the best way to analyze the data as the number of plasma cells isolated from each patient is different. We have now decided on an analysis plan and are preparing a manuscript on the data.

We have performed many experiments to see if ANA+ plasma cells derive from ABCs as has been reported in some previous studies. We have found no stimulation cocktail that can cause the differentiation of ANA+ ABCs to plasma cells; in contrast, we find ABCs to be the most effective B cell subset for activation of T cells. We also have observed that we cause approximately 80% of memory cells and approximately 50% of naive marginal zone cells to become antibody secreting cells, showing that ABCs are unique in their resistance to becoming plasma cells.

Thus, we believe that the plasma cells in SLE patients derive from either marginal zone or memory cells but not from ABCs.

Specific Aim 2:

We have begun the transcriptional analysis of ANA+ and ANA- plasmablasts. We obtained these cell populations from 5 healthy and 5 SLE individuals. We are currently applying quality control metrics to the data and analyzing the results.

We should soon have information on transcriptional profiles. We continue, however, to try to improve our strategy for obtaining high quality RNA from cells that have been permeabilized and fixed so as to identify the antigenic specificity of the plasmablasts. We now have an antigen capture protocol coupling ANA fragments to an anti-CD19 antibody and then probing with anti-IgG which should bind the nuclear fragment-anti-CD19 complex on ANA+ B cells.

Specific Aim 3:

We have optimized protocols for the generation of plasma cells from naïve B cells to mimic the extrafollicular pathway and from memory B cells to mimic the germinal center pathways. We have begun to explore potential mechanisms to block plasma cell differentiation. We have found that metformin can prevent plasma cell differentiation. This appears to reflect, in part, metformin induced decreased production of ROS which interferes with autophagy that is needed to allow B cells to be reprogrammed to a plasma cell.

We can also block plasma cell differentiation with a molecule we generated called RLCP which includes HMGB1 B box, a linker, and a peptide of C1q that binds LAIR-1. This molecule crosslinks RAGE and

LAIR-1 on the surface of the B cell and prevents internalization of nucleic acids which are needed for plasma cell differentiation.

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

Yemil Atisha-Fregoso is preparing a K08 based on his work on this project.

- **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?**

Aim 1: We are preparing a manuscript on BCRs of ANA+ and ANA- B cells of SLE patients.

We are also preparing a manuscript on the functionality of ABCs.

Aim 2: We will analyze the data we have obtained but will refine our methodology for obtaining high quality RNA from plasmablasts.

Aim 3: We are preparing a manuscript on the mechanism by which metformin blocks plasma cell differentiation.

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**

In Aim 3, we continue to revise our approach to obtaining high quality RNA.

- **Actual or anticipated problems or delays and actions or plans to resolve them**
    - *Describe problems or delays encountered during the reporting period and actions or plans to resolve them.*

We have obviously been delayed by the Covid-19 pandemic which has continued to limit the access of investigators to laboratories and to extend the length of time needed to perform studies. We continue to adhere to staggered schedules in order to maintain social distancing. We also had a moratorium on clinical research when we felt it was unsafe to bring patients in to obtain blood. This continued until vaccines were available to all and then was reinstituted when the omicron variant became prevalent. There has also been some post COVID hesitancy in patients with regards to participating in clinical research.

- **Changes that had a significant impact on expenditures**

See above

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

IRB approval date 04.04.2022

- **Significant changes in use or care of human subjects**

We have instituted precautions to protect patients and staff from Covid-19. This has no impact on the data obtained from the study but has slowed progress.

- **Significant changes in use or care of vertebrate animals.**

Not applicable

- **Significant changes in use of biohazards and/or select agents**

Not applicable

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:	Yemil Atisha-Fregoso

Project Role:	Graduate student, currently Instructor
Researcher Identifier (e.g. ORCID ID):	0000-0001-7702-8640
Nearest person month worked:	12 months
Contribution to Project:	Dr. Atisha-Fregoso has been involved in isolating B cell subsets and analyzing repertoire data. In addition he has performed in vitro studies of plasma cell differentiation
Funding Support:	Elmezzi Graduate Program and DOD

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

What other organizations were involved as partners?

Nothing to Report

i. **Organization Name:** Broad Institute and University of Texas at Austin

ii. **Location of Organization:** Domestic

iii. **Partner's contribution to the projec**t *(identify one or more)*

1. **Financial support;**
2. **In-kind support** *(e.g., partner makes software, computers, equipment, etc., available to project staff)*;

3. **Facilities** *(e.g., project staff use the partner's facilities for project activities)*;
4. **Collaboration**: The Broad Institute and the University of Texas supervise the RNA sequencing and B cell receptor repertoires studies.
5. **Personnel exchanges** *(e.g., project staff and/or partner's staff use each other's facilities, work at each other's site)*; and
6. **Other.**

8. Special Reporting Requirements

COLLABORATIVE AWARDS:

QUAD CHARTS:

Appendices

Award Log Number: LR190120
Award Title : Understanding Plasma Cell Differentiation in SLE Award

PI: Betty Diamond, Feinstein Institutes, NY **Budget:** 525,000

Topic Area: Lupus Research Program **Mechanism:** W81XWH-19-LRP-IA

Research Area(s): SCS Coding (0500,0500) **Award Status:** Period of Performance Dates 9/15/2021 – 09/14/2022

Study Goals:

We have previously shown that a major breach to B cell tolerance in patients with systemic lupus erythematosus (SLE) is the enhanced differentiation of IgG plasma cells. Based on this observation, the goal of this study was to understand the induction of plasma cells in SLE. We propose to determine if there is a difference in plasma cell differentiation when they arise through an extrafollicular vs a germinal center pathway, and whether there is a difference in the differentiation of plasma cells directed to nuclear antigens (ANA+) and those without this auto-specificity. We also propose to develop approaches to blocking IgG plasma cell differentiation.

Specific Aims:

Specific Aim 1:

We have been studying whether we can determine through molecular analyses of the B cell receptor (BCR) the pathway for the generation of plasma cells in SLE patients. We have isolated ANA+ and ANA- naïve, memory and age/autoimmunity associated B cells and plasmablasts from SLE patients and subjected these to DNA sequencing of the B cell receptor.

We identify two groups of patients. In one group, plasma cells are most clonally related to naïve B cells; we believe these are patients in whom plasma cells are generated through an extrafollicular pathway. In the second group, plasma cells are clonally most related to memory B cells; we believe plasma cells in these individuals arise through a germinal center pathway. Consistent with he this hypothesis, we observe an increased frequency of somatic mutation in BCRs of those plasmablasts we believe arise from the germinal center response. We continue to analyze the BCR sequences in these patients and find an increased CDR3 sequence length in ANA+ B cells. Most interestingly, we observe an altered pattern of somatic hypermutation in the ANA+ B cells. There are fewer mutations in AID hot spots and more mutations that seem to be generated by error prone polymerase. As ANA+ B cells in general will have BCRs that chaperone nucleic acids to endosomal toll-like receptors. This may suggest that engagement of endosomal TLRs modulates the program of CG B cells with respect to somatic mutation.

Specific Aim 2:

We have begun the transcriptional analysis of ANA+ and ANA- plasmablasts. We obtained these cell populations from 5 healthy and 5 SLE individuals. We are currently applying quality control metrics to the data and analyzing the results.

We have also begun the transcriptional analysis of ANA+ANA- ABCs as it has been reported that these cells are poised to become plasma cells. We observe an increase in transcripts related to antigen presentation in B cells with the most pronounced ABC phenotype. This has led us to hypothesize that ABCs may be important antigen presenting cells.

Specific Aim 3:

We have optimized protocols for the generation of plasma cells from naïve B cells to mimic the extrafollicular pathway and from memory B cells to mimic the germinal center pathways. We have begun to explore potential mechanisms to block plasma cell differentiation. We have found that metformin can prevent plasma cell differentiation. This appears to be through metabolic alterations which prevent the production of reactive oxygen specifies needed for the autophagy that enables the transition from B cell to plasma cell.

DOD -- Diamond, Betty, M.D.

Completed

GMS Margaret G Dowd Tel
Lupus Research Institute (Diamond) 02/01/14 – 01/31/17
LRI
Autoantibodies and prolactin participate in a positive feedback loop
This is a study of the role of anti-NMDAR antibodies in triggering autoantibody production.

A subset of antibodies to double stranded (ds) DNA binds also to the NR2A and NR2B subunits of the N-methyl-D-aspartate receptor (NMDAR). These antibodies, termed DNRAbs, are present in approximately 30 to 40% of patients with systemic lupus erythematosus (SLE); their presence in cerebrospinal fluid (CSF) associates with symptoms of neuropsychiatric lupus (NPSLE). NMDARs, the target antigen, are receptors for the neurotransmitter glutamate and are best characterized for their critical role in learning and memory. DNRAbs bind the NR2A and NR2B subunits of the NMDAR by recognizing a consensus pentapeptide D/E W D/E Y S/G (DWEYS) present in a solute-exposed region of the extracellular domain of NR2A and NR2B, but not in NR2C or NR2D. We have shown that the antibodies are not true receptor agonists; they preferentially bind already activated receptors, augmenting the effects of glutamate. Thus, they function as receptor modulators to enhance, but not initiate, NMDAR signaling. Thus DNRAb augment NMDAR signaling, enhancing excitatory post-synaptic potentials. When they engage receptors containing the NR2A subunit, they induce neuronal apoptosis. These antibodies can lead to manifestations of neuropsychiatric lupus in a mouse model. They cause cognitive impairment when they access hippocampal neurons and behavioral impairment when they access neurons in the amygdala, but only if they are able to penetrate the blood-brain barrier (BBB). DNRAbs are present in 30-40% of lupus patients.

In this project we will:
1) Determine if DNRAbs regulate prolactin synthesis by pituitary neurons.
2) Determine whether decoy antigens that block antibody from binding NMDAR can decrease prolactin levels *in vivo*.
3) Determine if decreasing prolactin leads to a decrease in B cell autoreactivity.

These studies will extend our understanding of neural endocrine and immune interactions. Importantly, if we determine that DNRAbs upregulate prolactin levels, we will have a mechanistic biomarker for a rapid, focused, proof-of-principle, clinical trial of a DNRAb blocker that we have recently developed which protects kidney and brain and can be tested for its ability to reduce serum prolactin and restore a compromised B cell tolerance checkpoint. If we can show DNRAbs consistently augment serum prolactin, we will have a marker for effective antibody neutralization in a clinical trial.

GMS Shoenfeld Yehuda Tel
Binational Science Foundation (BSF)(subcontract Dr. Ilan Ben Zv) 10/01/14 – 09/30/17
The role of HMGB1 and TLRs 2 and 4 in the pathogenesis of inflammation in familial Mediterranean fever
(Diamond co-investigator)
This is a study of HMGB1 in familial Mediterranean fever.

Autoinflammatory diseases are a group of genetic disorders characterized by spontaneous activation of the innate immune system, resulting in periodic bursts of short-lasting inflammation involving the serous membranes, skin, joints and other systems, and accompanied by high fever. Familial Mediterranean fever (FMF) is the most common and prototypical of the autoinflammatory diseases, resulting from mutation in the MEFV gene, leading to mutated pyrin protein and activation of an inflammasome, culminating in the release of IL1β and an inflammatory attack. To date, the mechanism by which mutated pyrin induces inflammation in FMF is still not clear and the triggers for the spontaneous acute inflammatory attacks in FMF have yet to be elucidated. In this project we will study the role of toll-like receptors 2+4 and HMGB1 in triggering attacks of

inflammation in FMF. We will study their activation-status in FMF-PBMCs and in THP1 cells that are deficient in the MEFV gene. We will also develop novel HMGB1 blockers, and assess whether HMGB1 blockade can inhibit the inflammatory reaction in cells from FMF patients, substantiating a rational for a clinical trial with HMGB1 blockers in FMF patients.

This project will contribute to elucidating the molecular mechanism of FMF, and other diseases involving the innate immune system, mainly the autoinflammatory syndromes.

GMS Mark E Langer Tel301.451.8216
R21 AR063929 (Diamond) 07/01/13-06/30/17
Nelfinavir in SLE: A pilot phase IIa clinical trial
This is a pilot clinical trial of nelfinavir in SLE.

Systemic lupus erythematosus (SLE) is an autoimmune disease that preferentially afflicts young women. SLE harms a variety of organ systems, including the skin, joints, kidney and brain. Management of active SLE frequently requires the use of multiple non-specific immunosuppressive and cytotoxic drugs that have significant associated toxicities and often have limited efficacy. Recently, we have made the surprising discovery that certain FDA-approved Human Immunodeficiency Virus (HIV) protease inhibitors show promise in a variety of preclinical lupus models. Among these, nelfinavir (brand name Viracept), possesses a relatively benign safety profile in HIV patients and is not likely to be immunosuppressive or cause adverse events in lupus patients. On the strength of our preclinical data demonstrating that nelfinavir acts, in part, as a decoy antigen to quench pathogenic lupus anti-dsDNA autoantibodies in critical tissues (e.g., kidney and brain), we propose to assess the safety and preliminary efficacy of nelfinavir as a lupus therapeutic in a pilot feasibility phase IIa clinical trial. We will pre-screen subjects for elevated anti-dsDNA autoantibody titers and incorporate early surrogate efficacy measures into this trial design. These and other innovations will bring a personalized medicine approach to lupus and contribute to the likelihood of the trial's success. Moreover, it has not escaped our notice that the repurposing of an FDA-approved drug into a new indication will facilitate an extremely rapid path into an urgent unmet medical need.

GMS Susan M Dellinger
AR130137 Department of Defense (Diamond) 9/30/14 – 09/29/17
DOD
Maternal brain-reactive antibodies and autism spectrum disorder
To understand the impact of brain-reactive antibodies cloned from mothers of a child with ASD on fetal brain development.

Specific Aims: We have generated approximately 50 monoclonal brain-reactive antibodies from blood B cells of mothers of a child with ASD. These antibodies bind to mouse brain and to human fetal brain lysates; we have identified antigens bound by several of these monoclonal antibodies. We propose to:

1) Identify those antibodies that alter fetal brain development and lead to behavioral deficits.
2) Screen sera of mothers of an ASD child for specific antigenic reactivity as defined by our monoclonal antibodies to try to correlate antibody specificity with phenotypic characteristics in the child.

GMS Yen Thach Tel
NIH R21 AR067012-01A1 (Diamond) 06/01/15 – 05/31/17
Function of the IRF5 risk allele for SLE in B cells
This is a study of the functionality of the IRF5 risk allele in B cells of healthy individuals.

Specific Aims:

To address these goals, we will:

1. Investigate the expression and function of IRF5 in different B cell subsets as a function of IRF5 genotype.
2. Investigate the effects of estradiol alone and in conjunction with type 1 interferon on B cell function as a function of IRF5 genotype. We will determine if B cells with the IRF5 risk allele exhibit an

enhanced response to TLR-7 and 9 ligands and if this is further enhanced by exposure to estrogen and type 1 interferon.

The innovation in this proposal is to examine IRF5 in B cells, as opposed to myeloid cells, as the function of this gene in B cells in SLE may be equally important. Studies such as this are highly significant in that they may permit us to identify patient stelubsets that have unique therapeutic targets for maintenance of remission.

GMS Yen Thach Tel
NIH R01 AR065209 (Kim) 04/01/14-03/31/18
(Diamond co-investigator)
The Blimp-1 SLE risk variant regulates inflammatory function in dendritic cells
This grant is to study the function of the PRDM1 SNP rs548234 in dendritic cells for predisposition to SLE.

Specific Aims:
Systemic Lupus Erythematosus (SLE) is an autoimmune disease which primarily affects young women and is characterized by the generation of self-reactive antibodies. Many of the autoantibodies have specificity for nuclear antigens and contribute to irreversible damage in multiple organs. As is characteristic of most complex diseases, genetic and environmental factors contribute to the development of SLE. Many genome-wide association studies (GWAS) have now helped identify genetic variants associated with the development of SLE. A major challenge remains in translating how these variants alter cell physiology to predispose to risk and progression of autoimmune disease.

Specifically, in healthy subjects, I will address the following aims:
(1) Identification of the molecular mechanism for decreased expression of Blimp-1 in DCs of risk allele carriers. We hypothesize that the risk allele alters the regulation of Blimp-1 expression in DCs through decreased transcription.
(2) Identification of new molecular targets of Blimp-1 in DCs which regulate DC differentiation and activation. We hypothesize that the alterations induced by low Blimp-1 enhance antigen presentation ability and skew T cell subsets.
(3) Identification of the role of estrogen in the regulation of Blimp-1 expression and DC phenotype. Our hypothesis is that estrogen influences Blimp-1 expression and the inflammatory phenotype in DCs, in a PRDM1 risk allele specific fashion.

GMS Gregory P Smith Tel240.669.2993
NIH 1UG3OD023391-0 (Gregersen & Diamond) 09/21/16 -08/31/19
Prenatal autoimmune and inflammatory risk factors for Autism Spectrum Disorders
This is a study of neurodevelopmental abnormalities in offspring of women with autoimmune disease.

SPECIFIC AIMS

In specific aim 1, we will test the hypothesis that clinical or subclinical autoimmunity in the mother at the time of pregnancy predisposes to a child with ASD. We will expand our existing cohort to enroll and serially sample a cohort of 4,500 pregnant mothers, including mothers with evidence of clinical or subclinical autoimmunity, along with control mothers. We will monitor their children for the presence of ASD-related phenotypes and other neurodevelopmental problems at two time points – age 2-2.5 years and 3.5–4 years.

In specific aim 2, we will test the hypothesis that the presence of maternal anti-brain antibodies during pregnancy predisposes to a greater risk of a child with ASD or neurodevelopmental problems.

In specific aim 3, we will explore the hypothesis that maternal immune activation or increased cytokine levels at during pregnancy predisposes to ASD in the child. We will assess maternal serum cytokine levels and modular patterns of whole blood gene expression in the second and third trimesters of women with an ASD child or a typically developing child in order to assess the correlation of maternal immune and inflammatory factors with ASD-related phenotypes in offspring.

GMS Kelvin D Lyons Tel

NIH P01 AI102852 (Diamond & Tracey) 04/01/14 – 03/31/20 1.8 cal mons
NIH/NIAID - **Cognitive and immune impairments in sepsis survivors**
Project 2 (Diamond) NCE
Immune function in sepsis survivors
Study of immune impairment in monocytes following sepsis
Specific Aims:
We will explore the molecular basis of altered immune function in sepsis surviving mice through the following three aims:

Aim 1: To determine the contribution of splenic monocytes/macrophages to immune impairment in sepsis surviving mice. *Hypothesis:* Monocytes/macrophages in sepsis surviving mice exhibit a sustained alteration in phenotype and function that contributes to immune impairment.

We will identify the monocyte/macrophage populations residing in the spleens of sepsis survivors and analyze gene and protein expression and intracellular signaling cascades in those monocyte/macrophage subsets at baseline and in response to LPS challenge, and whether monocyte/macrophage subsets from sepsis-surviving mice can alter immune function in naïve mice. We will ask which alterations observed in sepsis survivors are present in mice given systemic HMGB1, IL-1, TNF or other cytokines that are present at high level during the acute phase of sepsis or during the recovery phase. Finally, we will determine if monocytes/macrophages from sepsis surviving mice can provide the systemic signals to cause memory impairment.

Aim 2: To evaluate the functional competence of acetylcholine producing T cells in sepsis surviving mice. *Hypothesis*: Acetylcholine-producing T cell ($ChAT^+$ T cell) number and function are altered in sepsis survivors and no longer suppress splenic monocytes/macrophages.

We will determine the number and phenotype of $ChAT^+$ T cells in spleens of sepsis surviving mice and evaluate whether $ChAT^+$ T cells in sepsis surviving mice secrete acetylcholine in response to appropriate in vivo or in vitro stimulation. Finally, we will ask whether ChAT-GFP^+ T cells from sepsis surviving mice function appropriately in nude mice.

Aim 3: To establish where the immunological memory of sepsis resides. *Hypothesis*: Alterations in a long-lived cell lineage serves to maintain abnormal immune function in sepsis surviving mice.

GMS Jenny L Greer 240.669.2949
NIH/NIAID 1UM1AI1095650 (Nepom. G) 05/01/14 – 06/30/20 0.6 cal mons
Co-Chair Diamond
CALIBRATE – Rituximab Plus Cyclophosphamide followed by Belimumab
This is a clinical trial to determine if rituximab followed by belimumab reduces autoreactive B cell repertoire.

Study treatment will be rituximab, cyclophosphamide (CTX), and Solumedrol. This treatment will be followed by prednisone and belimumab in one group, and by prednisone without belimumab in the other group.

This trial will be conducted as a prospective randomized phase 2 open label multicenter study in individuals with active lupus nephritis age 18 and older. There will be two treatment arms with 1:1 randomization of a total of 40 participants.

During the treatment phase, all participants will receive infusions of Solumedrol 100mg, rituximab 1000mg, and CTX 750mg intravenously (IV) at week 0 and week 2. Prednisone 40 mg per day will be administered with a guided steroid taper to 10mg per day by week 12.

Participants will be randomized at week 4 to either the Rituximab/Cyclophosphamide (RC) Group or the Rituximab/Cyclophosphamide/Belimumab (RCB) Group.

The RC Group will be maintained on prednisone. The RCB Group will receive IV belimumab 10mg/kg at weeks 4, 6, 8, and then every 4 weeks through week 48 in addition to prednisone.

During the tolerance assessment phase, intravenous study medication will be discontinued after week 48, and all participants will be maintained on prednisone through week 96 of the study.

The primary objective of the study is to assess the safety of belimumab administration following treatment with rituximab and CTX, in terms of infectious adverse events.

GMS Ella Silayeva Tel
The NLM Family Foundation (Diamond) 04/01/18 – 03/31/20 0.6 cal mons
Maternal antibody as a contributor to Autism Spectrum Disorder
This is a proposal to develop a decoy antigen to protect the fetal brain from autism related antibodies

Specific Aims
We propose the following aims:
Aim 1: We will explore the activation state of microglia in mice exposed in utero to anti-Caspr2 antibody. Our preliminary data suggest on-going microglial activation in these brains. Microglia are a druggable target in other neurologic diseases; therefore, understanding the activation state of microglia in a model of ASD might lead to therapeutic strategies. We will explore microglia using immuno-histochemistry, transcriptional profiling and microPET studies with a ligand that binds activated microglia.

Aim 2: We will explore the gender bias in the anti-Caspr2-induced model of ASD. We are intrigued that we observe that only male offspring exhibit a vulnerability to in utero exposure to anti-Caspr2 antibody as the incidence of ASD in children is strongly biased to males. We have, however, also determined that women with anti-Caspr2 reactivity sometimes have an affected female child, and that the ratio of male to female affected offspring of women with anti-Caspr2 reactivity is reflective of the overall ratio of males to females affected with ASD. We hypothesize that the female fetus will develop anti-Caspr2-mediated neurodevelopmental impairments only if there is a “second hit” and that maternal microbiome or material response to infection will render female offspring susceptible to maternal anti-Caspr2-mediated ASD.

GMS Ronald M Burch Tel
NIH 1R3MH106195-SBIR (Burch, R) 04/01/18 – 03/31/20 1.2 cal mons
Developing a prenatal biologic therapy to mitigate ASD risk from maternal autoantibodies to Casp
Co-Investigator
This proposal is to create a therapeutic biologic designed to neutralize maternal anti-Caspr2 autoantibodies and prevent or reduce the severity of ASD in an anti-Caspr2 autoantibody-relevant mouse model of ASD.

Specific Aims

Aim 1: Evaluate candidate biologics for ability to neutralize Ab that disrupt brain development.
Objectives: Screen a panel of eight candidate biologics for their ability to neutralize Caspr2-reactive antibodies (polyclonal human sera and monoclonal antibodies) *in vitro* and *in vivo*; determine the circulating half-life of candidates. *Milestones:* The top two candidates will block anti-Caspr2 antibodies in a mouse model of pathologic *in utero* exposure and exhibit circulating $t_{1/2} > 3$ days.

Aim 2: Examine toxicology of lead candidates in adult female mice.
Objectives: Administer repeat doses of candidate to virgin and pregnant female mice; conduct preliminary toxicology and immune complex deposition assessments in blood and tissue. *Milestones:* Candidates will not show toxicity in adult mice, or trigger spontaneous abortion.

Aim 3: Assess placental transport of lead candidates and toxicology in fetal mice.
Objectives: Measure amount of candidates in fetal circulation and tissues; conduct preliminary toxicology studies.
Milestones: Candidate in fetal:maternal circulation < 1:10, no toxicity or fetal abnormalities.
Aim 4: Assess immunotoxicity of lead constructs in mice with a humanized immune system.
Objectives: Conduct immunotoxicity study in mice with humanized immune system.
Milestones: Repeat dosing of candidates does not cause immunotoxicity in humanized mice.

Aim 5: Evaluate efficacy of candidate therapeutics for mitigating ASD phenotypes in a mouse model of ASD.
Objectives: Test efficacy of candidates to block pre-existing, polyclonal Caspr2 immunity during gestation.
Milestones: Treating with candidates rescues brain morphology and behavioral phenotypes in male progeny.

NIH 1P01 AI073693 (Adm Supplement) (Diamond) 07/01/2020 – 06/30/2022 0.6 cal mons
Effect of Covid-19 engagement of ACE2 on brain health and pathology
no cost extension
The goal of this study is to understand how the spike protein and its receptor binding domain affect the function of neurons, microglia and brain microvascular epithelial cells, all of which express ACE2, the receptor for Covid-19.
No overlap

We have been interested in the insidious consequences to the central nervous system of peripheral immune activation. These studies have led us to recognize the role of chronic neuroinflammation to altered cognition and behavior. In the course of these studies we have increasingly come to appreciate the role of the renin-angiotensin system (RAS) in modulating neuro-quiescence and neuroinflammation. There is a proinflammatoryarm consisting of angiotensin converting enzyme (ACE) which cleaves angiotensin-I to become angiotensin-II.

Angiotensin-II binds to the type-1 receptor (AT1) to activate the release of proinflammatory cytokines, and type-1 interferon. An anti-inflammatory arm consists of angiotensin-II binding to the type-2 receptor (AT2) to suppress the proinflammatory program, and a membrane-bound angiotensin converting enzyme (ACE2), that cleaves both angiotensin-I and angiotensin-II to an inactive form. When angiotensin-II is cleaved, a small peptide ang 1-7, is released that binds Mas, a G-protein coupled receptor that also suppresses an inflammatory response. That this pathway can be modulated for therapeutic effect has been shown in studies of ACE inhibitors which retard progression of human Alzheimer's disease, and prevent or reverse pathology ina mouse model of neuropsychiatric lupus (NPSLE) which we have extensively studied. Angiotensin receptor blockers (ARBs) also modulate this pathway by preferentially binding to AT1. The system is best studied in microglial cells, but neurons and brain microvascular endothelial cells also express AT1, AT2 and ACE2.

This pathway is now of particular interest as ACE2 is the receptor for several corona viruses, including Covid-19. It is not known, however, whether activated or quiescent microglia are more likely to internalize virus basedon the level of expression of ACE2. There is also a key unanswered question for the numerous individuals on ACE inhibitors or ARBs: does the use of these drugs increase or decrease the viral penetration of cells?

To address these questions, we propose to explore healthy mice and two mouse models that mimic human disease: a model of antibody-mediated NPSLE, and sepsis-surviving mice. In each case we have observed microglial activation and pathological pruning of neuronal dendrites.

Specifically, we propose to address the following hypotheses:

Aim 1. There will be diminished ACE2 expression and therefore diminished binding of the Covid-19 trimeric spike protein (S) or the receptor binding domain (RBD) of spike protein to microglia, neurons and brain endothelial cells in mice with chronic neuroinflammation. The rationale for this hypothesis is that elsewhere in the body chronic inflammation leads to decreased ACE2. We will quantitate the binding and uptake of S or RBD by microglia, neurons, and brain microvascular endothelial cells in healthy mice, mice withantibody-induced NPSLE, and sepsis-surviving mice.

Aim 2. There will be no effect of ACE inhibitors on levels of ACE2 in the brain, but there will be an increase of ACE2 induced by ARBs. The presence of S or RBD, however, will diminish the effectiveness of ACE inhibitors and ARBs. These hypotheses are predicated on data showing that these drugs do not alter ACE2 expression in renal tissue, although ARBs increase ACE2 in cardiac tissue, and the data showing that S can activate TACE to diminish levels of membrane-bound ACE2. We will quantitate the impact of ACE inhibitors and ARBs on binding of S or RBD to brain cells. Because we anticipate decreased ACE2 expression in the

presence of S and RBD, we hypothesize that ACE inhibitors andARBs will be less effective at modulating the effects of neuroinflammation in the presence of S or RBD. We will, therefore, assess the alterations in brain pathology induced by ACE inhibitors or ARBs in the presence of S or RBD.

Aim 3. The binding of S or RBD to brain cells will increase the pathology seen in NPSLE and in sepsis surviving mice. This hypothesis is based on the data that S binding to ACE2 increases shedding of theACE2 ectodomain by activating TNFγ converting enzyme (TACE). We will assess whether the binding of Sor RBD to brain cells alters their activation state, or alters *in vivo* pathology using immunohistology, transcriptional analysis, and PET scanning.

These studies should advance our understanding of the RAS system in neuropathological conditions, but moreimportantly they will inform us whether Covid-19 is more likely to infect the healthy brain or a brain exhibiting neuroinflammation and the consequences of frequently used anti-hypertensive medications on Covid-19- induced brain pathology. These studies cannot be performed in human subjects.

GMS Stephanie Kreider Tel
NIH NAMS UH2 AR067688 (Diamond) 09/24/14-05/31/2022 0.6 cal mons
PEARL: Pathway exploration and analysis in renal lupus *no cost extension*
This a proposal to apply state of the art genomic and immunophenotyping technologies to lupus nephritis.
No overlap
Specific Aims:
Lupus nephritis (LN) remains an unsolved medical problem. Current therapies are often ineffective, with a significant percent of patients progressing to end stage renal disease. In addition, current therapies invariably have adverse effects, including broad immunosuppression and, in some cases, death due to opportunistic infection, cancer, or other complications of treatment. Regrettably, recent trials of novel biologic approaches to treatment have failed. Thus, there is a need to refocus our efforts to understand the mechanisms of disease to guide us toward more effective, and safer, treatments.

We will pursue these goals through the following specific aims.

Aim 1: We will establish the infrastructure and SOPs for multi-site studies of LN.

Aim 2: Phase 0: We will determine the high resolution gene expression profile of resident kidney cells in order to understand changes that occur in LN. We will use RNA-seq of glomerular and interstitial tissue to localize particular immune subsets within the kidney. We will optimize techniques for obtaining RNA from cells in the urine, exploring single cell RNA-seq versus RNA-seq of hematopoietic and non-hematopoietic cells. We will additionally study LN biopsies to determine disease-specific changes in cell populations and gene expression profiles.

Aim 3 (Phase 1): We have two Phase 1 projects. We will study kidney biopsy, blood and urine of 20 patients with active nephritis in order to help focus the analyses of the Phase 2 study We will use blood samples collected in the ITN-funded trial of abatacept in LN to determine those cellular subsets in blood that may predict response to therapy or best reveal therapeutic response in lupus nephritis.

Aim 4 (Phase 2): We will enroll 200 patients in a longitudinal study to obtain kidney tissue, blood and urine at the time of initiation of therapy for LN and blood and urine at frequent intervals thereafter for 24 months. We will execute a focused analysis of cellular and molecular networks that define renal pathology and predict therapeutic response, and of blood and urine surrogates for renal tissue. We will identify early changes in blood and urine that correlate with subsequent therapeutic response.

Pilot Project: We will extend a novel histologic approach (cell distance mapping) to analyze cellular interactions within biopsy tissue using cell markers that are identified in the Phase 0/Phase 1 studies.

Supplement funded to PEARL 09/18/2020 – 05/31/2022

Pearl Pilot Program Supplement

The AMP has been focused on an analyzing of the transcriptome of both tissue resident and infiltrating cells in kidneys of patients with lupus nephritis (LN). The patient population is from North America, and includes a high percentage of African-American and Hispanic patients. That raises a question concerning how generalizable the results are.

In collaboration with Sang-Cheol Bae of Korea, we have collected 26 LN biopsies of Korean patients obtained using the AMP protocol. Currently, in the AMP phase 2 cohort we have 39 Asian patients, though it is probable that this includes a high percent of Chinese.

We believe it will be instructive to analyze the transcriptome of cells in the biopsies of Korean LN patients. If the data are the same as we see for Asian patients in the US, it suggests that the pathways of disease pathogenesis are independent of environmental factors. If the analysis identifies differences between the AMP and the Korean cohorts, it would propel us to a study of environmental modulators of disease perhaps beginning with the microbiome.

GMS Roberta D Wolcott Tel:
NIH U19AI144306-03S1 (Diamond) 05/19/2020-04/30/2022 1.2 cal. mons
Etiology and outcome of MIS-C
This is a study of Multisystem Inflammatory Syndrome in children and young adults with Covid-19 infection. The goal is to understand why some children get an acute disease and others MISC which is a delayed onset disease.
No overlap

Specific Aims
Multisystem Inflammatory Syndrome in Children (MIS-C) has recently been recognized as a late sequela of Covid-19 in the pediatric population. The syndrome arises late in disease when antibodiesare present, can be catastrophic and has some similarities to Kawasaki Disease (KD). Northwell Health has cared for approximately 40 patients with this diagnosis. Forty percent required ICU care; none have died. There is detailed annotation of the clinical course of all these children and stored plasma from some. More hospitalizations for acute disease and MIS-C are expected as the pandemic continues into the new school year.

It is our hypothesis that children with MIS-C will have a TLR-mediated immune complex disease while those with acute Covid-19 disease with have pathology mediated through the Renin- Angiotensin System (RAS). Which of these mechanisms dominates is expected to determine the anti-viral antibody response in these children. We posit that those patients with severe acute diseasewill have a germinal center-derived response with long lived immunity and neutralizing antibody and those with MIS-C will have an extrafollicular response with short term immunity and poor neutralizing titers. This model is supported by the observations that those with acute disease exhibit low interferonlevels, that pediatric cases of acute Covid-19 are relatively rare which is consistent with higher ACE2 levels in children being protective, and that patients with KD, a syndrome presumed to be similar to MIS-C have upregulation of genes in the interferon pathway.
We propose the following hypotheses and aims:

Aim 1: We hypothesize that those children with MIS-C will harbor alleles of genes in the interferonpathway that lead to high interferon levels. We will assess this through assigning an interferon risk score to each patient in each group that is based on the number of high interferon risk alleles.

Aim 2: We hypothesize that children with MIS-C will have an array of soluble inflammatory mediators consistent with TLR- mediated immune activation while those with acute COVID-19 infection will have an array of cytokines consistent with activation of the RAS. We will test serum of children with acute disease and children with MIS-C for levels of 54 analytes using an MSD platform.

Aim 3: We hypothesize that children with MIS-C will have higher IgM levels, and a clonally more diverse, low affinity IgG antibody to COVID-19 spike protein, likely associated with lower neutralization titer. Children who have recovered from acute infection will have higher affinity serum antibodies and a less diverse antibody repertoire dominated by clones to the receptor binding domain(RBD) and more likely to be neutralizing. We

expect that the serum antibodies from the two groups will have differential ability to engage the activating Fc receptors on neutrophils and macrophages.

Aim 4: We hypothesize that the plasma metabolomic profile will differ between acute infection andMIS-C and will predict longterm outcome of MIS-C. We will assess this by HPLC mass spectrometry.

We will enroll all new pediatric patients with acute Covid-19 infection or with MIS-C and will obtain blood for DNA and blood samples longitudinally throughout a patient's hospital stay and for 1 year beyond. We will also analyze DNA and serology on all previously hospitalized pediatric patients with either acute Covid-19 infection or MIS-C. We will have a control group of healthy children who are sero-negative. As testing becomes more prevalent, we will add an asymptomatic sero-positive cohort.These comparisons will allow us to determine the features that are specific to children with MIS-C, the reasons that such different conditions can be triggered by the same virus and the implications for long term immunity and cardiac function.

Current

GMS Adam Graham Tel
NIH 1P01 AI073693-06 (Diamond) 09/01/2008 – 06/30/2025
NIH/NIAID –**Anti-NMDA receptor antibodies in adult brain dysfunction, & fetal brain development**
Project 3 (Diamond) 1.2 cal mons **Mechanisms of DNRAb-mediated damage to the fetal brain**
This is a study of the effect of lupus antibodies on the developing fetal brain.
No overlap

Specific Aims:
Systemic Lupus Erythematosus (SLE) is an autoimmune disease characterized by the production of anti-nuclear antibodies, with anti-DNA antibodies being the most common and both diagnostic and pathogenic. The disease affects multiple organ systems with inflammatory damage initiated by autoantibodies in most, if not all, involved organs. While there has been intensive investigation of kidney disease in SLE, and numerous studies of skin manifestations and abnormalities in the coagulation pathway, there have been fewer studies of neuropsychiatric SLE (NPSLE) and no approved therapies for NPSLE exist. Yet NPSLE is among the classification criteria for the diagnosis of SLE, and a recent FDA-sponsored Patient-Focused Drug Development meeting identified many of the clinical manifestations of NPSLE, especially cognitive impairment, as among the most concerning to patients [1].

We have identified an antibody, DNRAb, which cross-reacts with DNA and the N-methyl D-aspartate receptor (NMDAR). The effect of DNRAb on the adult and fetal brain is the focus of the current proposal in 1) a mouse model of neuropsychiatric lupus (NPSLE); 2) in SLE patients; and 3) in mice exposed in utero to maternal DNRAb.

Project 1: To understand the mechanism of microglial activation following DNRAb-mediated neuronal death, and the mechanism by which ACE inhibitors reverse microglial activation.
Project 2: To understand the correlation of DNRAb with microglial activation and blood-brain barrier breach in the hippocampus and to study longitudinally the progression of metabolic and structural abnormalities in DNRAb+ and DNRAb- patients.
Project 3: To understand how DNRAbs affect fetal health and develop a strategy to protect the fetus from maternal DNRAbs.

These projects are supported by 3 cores. The Administrative Core will facilitate the work of all projects and the scientific cores. The Monoclonal Antibody Core will generate reagents and perform ELISAs to ensure consistencies within and among projects. The Behavioral and Electrophysiology Core will perform behavioral and cognitive assessments and the electrophysiology to ensure comparability among all studies.

These studies will position us to perform among the first clinical trials in NPSLE and the first prevention trials to protect the offspring of DNRAb+ mothers.

GMS Cynthia M Rojas Tel
NIH U19AI144306 PIs Diamond/Davidson 04/1/2019 – 03/31/2024 1.2 cal mons
Heterogeneous pathways to autoantibody production: Implications for prognosis and therapeutic targeting
This is a study of autoreactive plasma cells in SLE.
No overlap

OVERVIEW Specific Aims:
Our ACE proposal entitled "Heterogeneous pathways to autoantibody production: implications for prognosis and therapeutic targeting" examines basic mechanisms for loss of tolerance to lupus related autoantigens using novel reagents and technologies.
The Principal Project (Dr. Betty Diamond) will use a novel fluorescence-labeled autoantigen reagent to isolate and characterize autoreactive B cells from patients with lupus and to ask about their origins and transcriptional profile, specific to autoreactive B cells, compared with cells that protect against microbial antigens.
The Collaborative Project (Dr. Anne Davidson) will ask how TNF inhibitors that are widely used to treat inflammation in autoimmune diseases break B cell tolerance to induce non-specific and specific lupus related autoantibodies.
The Pilot Project (Dr. Sun Jung Kim) will address the transcriptional, metabolic and functional diversity of circulating T follicular helper cells in patients with lupus and ask whether it is possible to restore normal B cell helper function of these cells by altering cell metabolism.

A better understanding of how the autoreactive lupus B cells become activated to produce lupus-related autoantibodies is needed in order to design therapies for lupus that are more effective and less globally immunosuppressive. We expect to collaborate with other ACEs that have similar scientific interests and complementary technologies; this should lead to synergistic interactions that will move us forward faster.

The principal project is focused on understanding the protective antibody response to vaccine in SLE patients and to the study of ABCs. Therefore there is no overlap.

GMS Diomaris Gonzalez Tel
Lupus Research Alliance (Mackay) 11/01/19 -10/30/22 0.4 cal mons
Investigators-Initiated Clinical Trials Co-PI Diamond
A novel Phase 2 double-blind, randomized, controlled clinical trial to evaluate the efficacy of centrally acting, non-toxic ACE inhibition in cognitive impairment associated with SLE
This is a clinical trial of centrally acting ACE inhibitors in NPSLE.
No overlap

Rationale

Tissue injury in SLE results from multiple and often redundant inflammatory pathways and mediators, therefore, a therapeutic approach that modulates multiple inflammatory mediators or pathways rather than ablating single pathways will be associated with greater clinical efficacy and less toxicity. We are also oriented towards the development of non-immunosuppressive treatments for SLE. To this end, the proposed clinical trial tests the efficacy of centrally acting Angiotensin Converting Enzyme Inhibitors (CA-ACEi), FDA-approved medication for hypertension with a highly favorable safety profile, compared to non-centrally acting ACEI (nonCA-ACEi) for improving abnormal resting brain metabolism and cognitive function in patients with SLE.

GMS Theresa Do Tel
NIH R01 AR074565 (Diamond/Kim) 07/05/19 – 06/30/24 0.96 cal mons
Alteration of function and specificity of T_{FH} in SLE
This proposal examines the T follicular helper cells in a mouse model of SLE.

No overlap

Specific Aims

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with a complex pathogenesis 1. Recent studies show that genetic predisposition is involved in both the initiation and propagation of disease 2. While there is an insufficient understanding of disease mechanisms, it is clear that there is a breakdown in B cell tolerance as autoantibodies are present in all patients. These autoantibodies often appear to arisein a T cell dependent manner, suggesting the existence of autoreactive T cells 3, 4, 5. *PRDM1* (the gene encoding BLIMP1) was identified as a risk factor for SLE by genome wide association studies (GWAS) 6, 7, and dendritic cells (DCs) of healthy individuals harboring the *PRDM1* SLE risk allele phenocopy murine BLIMP1-deficient DCs 8. Thus, mice with a conditional knockout of BLIMP1 in DCs (*Prdm1* CKO; *CD11c-CRE*; *Prdm1flox / flox* on C57BL/6 background) were generated. These mice develop a lupus-like pathology in a T cell dependent fashion 9.

CD4+ follicular helper T (TFH) cells are pivotal for formation of the germinal center (GC), and an increased frequency of TFH has been observed in various autoinflammatory models 10, 11 and in active SLE patients 12, 13. DCs of *Prdm1* CKO mice skew to TFH differentiation, and the repertoire of TFH cells from these mice differs from the repertoire of TFH cells from control mice 14. The disease phenotype is observed only in female *Prdm1* CKO mice, suggesting gender dependent mechanisms are critical factors for this disease model. We have, Moreover, shown that autoimmunity does not develop in female *Prdm1* CKO mice that have been ovariectomized, but does develop when exogenous estrogen is administered to ovariectomized mice, demonstrating that hormone, rather than sex chromosome, regulates the autoimmunity. Based on these observations, we hypothesize that the fate and repertoire of self-reactive CD4+ T cells is established by aberrant antigen presentation by DCs in the thymus of *Prdm1* CKO mice. Estrogen and estrogen receptor signaling is critical to the altered repertoire of TFH cells, and to the skewing of effector T cells to the TFH subset. Finally, we propose that the fate of CD4+ T cells is epigenetically determined in the thymus and skewed to TFH differentiation in *Prdm1* CKO mice. We will test our hypotheses in three aims:

Aim 1: Determine the origin and function of CD4+ TFH cells in *Prdm1* CKO lupus prone mice. (A) We will compare the TCR repertoire of CD4+ T cells from the thymus of *Prdm1* CKO mice and control mice. If we observe a difference in the repertoire of CD4+ thymocytes from female *Prdm1* CKO mice compared to female control mice, we will determine if this is influenced by strength of TCR signaling, using TCR signaling reporter mice, *Nur77*-GFP. In vitro co-culture of thymocytes from *Nur77*-GFP with thymic DCs isolated from female control or female *Prdm1* CKO mice will tell us whether BLIMP1-deficient DCs induce a different TCR signal strength in thymocytes. **(B)** We will determine the B cell activation capacity of TFH cells from female *Prdm1* CKO mice compared to female control mice, and if TFH cells from *Prdm1* CKO mice will induce autoreactive B cells to become antibody secreting cells. Finally, we will compare the gene expression profile of TFH cells in spleens of female *Prdm1* CKO and female control mice.

Aim 2: Determine the mechanism of estradiol regulation of T cell selection and differentiation in female *Prdm1* CKO mice. (A) We will investigate the functional changes induced by estrogen in DCs and the responsible estrogen receptor. We will focus on alterations in the expression of genes that are involved in antigen processing and antigen presentation in DCs, especially *Ctss* and *Il6*. We will further investigate how these changes contribute to the preferential differentiation of TFH in female *Prdm1* CKO mice. We will assess whether the estrogen receptor (ER) signaling skews T cells to TFH differentiation in vivo and in vitro by modulation of ER1 or ER2. **(B)** We will investigate hormonal regulation of repertoire and function of TFH cells in *Prdm1* CKO mice.

Aim 3: Investigate epigenetic modification of CD4+ T cells by DCs in the thymus. We will test the hypothesis that the epigenetic marks in CD4+ T cells are regulated by DCs in the thymus, and influence effector T cell differentiation in the periphery. To do this, we will **(a)** characterize epigenetic marks of CD4+ thymocytes, and **(b)** investigate how epigenetic marks influence T cell polarization.

DOD Lupus – Impact Award (Diamond) 09/15/2020 – 09/14/2023 1.2 cal mons
Understanding plasma cell differentiation in SLE
This is a study to distinguish plasma cells of germinal center origin from plasma cells of extrafollicular origin.
No overlap

Impact statement

This proposal will address the focus area "Understanding lupus disease heterogeneity. We have developed a novel method to isolate and characterize ANA+ B cells and plasma cells in SLE. This method revealed two distinct clusters of SLE patients, based on the relative frequencies of ANA+ memory B cells and IgM and IgG ANA+ plasma cells. In the proposed research, we aim to develop this strategy to subtype patients and to further increase our understanding of whether this stratification scheme reflects different plasma cell differentiation pathways. We will address whether the clustering relates to a dominant extrafollicular or germinal center pathway for differentiation of ANA+ plasma cells. In addition, we will study the expression profiles of ANA+ plasma cells from both groups of patients and will determine what governs the differentiation of ANA+ plasma cells in SLE.

We believe that with the proposed research we will develop a stratification system that will facilitate the assessment of therapeutic agents, and we will learn much more about B cell biology in SLE, with the possibility to discover new therapeutic targets. No current therapies for SLE specifically target the autoreactive plasma cells. As most current therapies are immunosuppressive, thereby leading to increased susceptibility to infection, more specifically targeted therapies would be highly beneficial.

Our research will address this in two ways: First of all, our RNA-sequencing studies combined with repertoire studies will reveal if the stratification of patients based on their pattern of ANA+ antigen-experienced cells reflects their plasma cell differentiation pathway and will also reveal differential expression of therapeutic targets by the plasma cells. In this case, our research can be used to develop personalized medicine with therapeutics that can specifically alter one of these pathways. This will likely result in fewer side effects compared to targeting the entire plasma cell or B cell compartment, which is associated with immunosuppression; leaving one plasma cell differentiation pathways intact may result in reduced immunosuppression. We will also learn the triggers for plasma cell differentiation in SLE. This will lead to a better understanding of the tolerance failure that leads to the emergence of ANA+ plasma cells, and will reveal how to prevent plasma cell differentiation.

The short-term impact of our research project is that it will provide us with insight into the mechanisms that lead to differentiation of ANA+ plasma cells in SLE. The results of these studies may enable us to stratify patients for clinical trials. In the short-term, our research can be the foundation to study the efficiency of existing therapies in the two subgroups of SLE patients, such as Belimumab, which may be more efficacious in targeting extrafollicular plasma cell differentiation, or Mycophenolate, which may be more efficacious in targeting T cells and a germinal center path to plasma cell differentiation. In addition, our research may reveal targets in either differentiation pathway for which drugs already exist and have been proven safe in other diseases. In both of these cases our research will allow for development of stratification methods to more specifically target the plasma cell differentiation pathways in a precision manner. In the long-term, we may learn how to block the enhanced plasma cell differentiation seen in SLE patients.

GMS Heather Sewell Tel: Leidos Biomedical Research, Inc. (Gregersen) **Serological Sciences Network** 10/01/2020 – 09/30/2023 1.2 cal mons
This is a study of Covid convalescent serum.
No overlap

Background:
In light of the emergence of the novel coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), and the urgent need to mitigate the pathogen's spread, the National Cancer Institute (NCI) and the National Institute of Allergy and Infectious Disease (NIAID) are establishing a Serological Sciences Network of Excellence to mobilize collaborative efforts to develop serological assays of high specificity and high sensitivity

for deployment to test for SARS-CoV-2 induced immune responses and to rapidly expand national serological testing capacity. The proposed Serological Sciences Network for SARS-CoV-2 (SeroNet) will contain several components. The Serological Capacity Building Centers are a critical component of the SeroNet. The Capacity Building Centers (CBC) shall focus on the rapid deployment and expansion of SARS- CoV-2 serological testing capacity and practice. In addition to the CBCs, the SeroNet includes the Centers of Excellence, Research Projects, and the Frederick National Laboratory for Cancer Research (FNLCR) Serology Laboratory. Serological Sciences Centers of Excellence and Serological Sciences Research Projects will be grant funded to understand the mechanisms driving serological, humoral, and cellular immune responses to SARS-CoV-2 viral infection to inform the development of novel serological tests. Each SeroNet component is expected to interact closely, collaborate, share data, resources, and samples. The Serological Sciences Network Coordinating Center (SSNCC) at FNLCR will manage and coordinate data and communications across SeroNet, and a SeroNet Steering Committee (SSC) comprised of members from each component, including NCI and NIAID, will provide scientific oversight and guidance.

NIH P01AI148102-01A (Co-Investigator- Diamond)(Brenner) 12/1/2020 – 11/30/2025 1.2 cal mons
Differentiation of immune cells and fibroblasts in inflamed tissue in RA and SLE
Role: Co-investigator Project 1 My role in this proposal is to perform cell isolations and single cell analyses of SLE tissue and blood, focusing on B cells.
No overlap

Project 1: Origin and function of atypical lymphoid populations in inflamed tissue in SLE and RA
Clinicians have considered systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) to be related diseases for decades as the two diseases are often present in the same family and, indeed, some patients appear to have both diseases simultaneously in a syndrome termed Rhupus (1, 2). Lymphocyte populations expanded in these chronic autoimmune diseases can possess phenotypes and functions that diverge from those described in established immunologic paradigms (3, 4). In particular, SLE and RA patients exhibit an expanded population of CD11c+, CD21, CXCR5- B cells termed age- or autoimmunity-associated B cells (ABCs).

Studies of ABCs in SLE kidney and RA synovium suggest functional differences from blood ABCs. Several challenges remain to understand the derivation and function of ABCs. First, different definitions have been used to characterize ABC-like cells, resulting in analyses of partially overlapping cell populations. A clear delineation of the heterogeneity in phenotype and transcriptome among putative ABC populations is critical to establish their functional heterogeneity.
Second, an understanding of how ABCs accumulate in tissues is required to design strategies to interfere with this process. Transcriptomic analyses indicate that ABCs may differentiate *in situ* in nephritic kidneys and in rheumatoid synovium. Third, the cellular interactions that promote ABC development and function within tissues remain unclear.
Mass cytometric analysis of circulating lymphocytes reveals a strong and specific correlation between the frequency of circulating ABCs and the frequency of T peripheral helper (Tph) cells, a tissue-homing B cell-helper T cell population, similar to but distinct T follicular helper (Tfh) cells suggesting potential interactions between these 2 lymphocyte populations, both of which are present in inflamed tissue (5).

Here we propose 3 complementary aims to evaluate ABC phenotypes and function, differentiation pathways, cellular interactions, and localization in SLE and RA tissue. Aims 1 and 2 will be performed in SLE kidney and blood and RA synovium synovial fluid and blood. Aim 3 will be performed in both RA and SLE tissue.

Aim 1 Define the heterogeneity, developmental pathway, and antigenic specificity of tissue ABCs.
We hypothesize that ABC populations differentiate locally within inflamed tissues and produce disease-associated autoantibodies. We will define the heterogeneity of tissue ABCs and compare tissue to blood ABCs. Using high
throughput repertoire sequencing, we will compare B cell receptor (BCR) repertoires of tissue ABCs with other tissue B cells, blood ABCs, blood plasmablasts and potential B cell precursor populations, naïve and memory

B cells, to determine differentiation pathways. We will also evaluate which disease-associated antigens are recognized by blood and tissue ABCs and if plasma cells and ABCs in tissue recognize the same antigenic targets.

Aim 2 Determine the functional interactions between blood ABCs and T cells.
We hypothesize that ABCs and Tph cells interact with ABCs functioning as antigen presenting cells to drive Tph differentiation. We will evaluate the ability of ABCs to promote differentiation of naïve CD4+ T cells into IL-21 producing Tfh or Tph cells, or to activate established Tfh/Tph cells. We will evaluate the ability of Tph and Tfh cells to enhance ABC survival, antibody secretion, and cytokine production and to induce differentiation of naïve B cells into ABCs.

Aim 3 Determine the major cellular partners interacting with ABCs in inflamed tissues in SLE and RA.
We hypothesize that ABCs and Tph cells will cluster near tissue DCs within inflamed tissues. We will map the localization of ABCs in SLE kidneys and RA synovium. We will specifically address the co-localization of ABCs with Tph cells and Tfh cells, as well as with NK cells, CD8+ T cells, myeloid cells, and also with proinflammatory stromal cells such as CD90+ fibroblasts. We will then evaluate expression of chemokine/chemokine receptor pairs in ABCs and closely co-localizing cell populations to identify candidate mediators of co-localization.

Impact: These studies derive from recent observations on tissue infiltrating cells in RA and SLE. They extend our knowledge of a recently identified B cell population and determine how they interact with Tfh and Tph cells, lymphocyte populations that are expanded in autoimmune disease, and will inform how these cells can be targeted therapeutically.

Synergy with other projects: All projects in this PPG are designed to understand the derivation and function of cell states unique to or highly enriched in inflamed tissue.
Use of cores: We will work closely with the Computational Systems Immunology Core for aims 1 and 3.

GMS Alison Bemis Tel: NIAID 1UM1AI09565
(Nepom) 02/01/2014 – 01/30/2023 1.2 cal mons
ITN-Targeting CD40L (VIB4920) in Lupus Nephritis-VIBRANT

There are data from mouse models and from clinical studies suggesting that similar cytokines are present in lupus lesional skin and in lupus nephritis kidneys. Similar cells and molecules are present in lesional skin and kidney from patients.

There are, however, no high-resolution studies to assess the gene expression profile of tissue-infiltrating cells, endothelial cells and tissue-resident cells. If the activation patterns appear similar among cellular subsets in both kidney and skin, it may be possible to use skin disease to perform proof of mechanism studies of therapeutic agents for lupus nephritis.

Kidney tissue, blood, urine, and lesional and non lesional skin of lupus patients will simultaneously be studied in the context of the Accelerating Medicines Partnership for Rheumatoid Arthritis and SLE (AMP RA/SLE). The proposed ITN component of the project will be to assess mechanistic correlates of efficacy and immune tolerance of lesional and non lesional skin in lupus nephritis patients with skin disease. The AMP RA/SLE data base on kidney disease will be available to compare mechanisms of pathogenesis between kidney and skin and biomarkers of clinical efficacy and tolerance.

Our approach will be to perform RNA seq on subsets of hematopoietic cells, endothelial cells in both kidney and skin, epithelial cells in the kidney, and keratinocytes in the skin. The AMP RA/SLE study is a longitudinal study of patients with new onset or exacerbatican of lupus nephritis. A kidney biopsy, blood and urine will be obtained at the time of initiation of therapy for nephritis. Patients will be followed longitudinally with repeat blood and urine samples to identify patterns of gene expression in particular cell types that associate with favorable or poor clinical response. In some patients repat kidney biopsies will be obtained. We anticipate enrolling 200 patients with nephritis. We anticipate at least 40% will have some form of cutaneous lupus and 10% having a form of cutaneous lupus other than malar rash. Thus, we anticipate obtaining biopsies of lesional and from lesional skin form at least 60 subjects. The data from this study will be correlated with the

data from the parent AMP RA/SLE study to determine if pathogenic mechanisms are similar in kidney and skin and if response to therapy is similar. We propose to obtain and analyze biopsies of lesional and non lesional skin from enrolled patients. The study of skin would allow for a within patient comparison of mechanisms of action in skin and kidney. We would include biopsies of non lesional tissue to address the possibility that an early indication of injury in lupus may be seen in endothelial cell function. The AMP RA/SLE will cover the cost of the analysis of blood, kidney and urine. The AMP RA/SLE will, likewise, cover the cast of enrolling patients. of data analysis and data storage, while all data will be shared with the ITN.

Lupus Research Alliance (Mackay) 03/01/19 -02/28/23 0.24 cal mons
Investigators-Initiated Clinical Trials Co-PI Diamond *no cost extension

ACE inhibition, cognition and resting brain glucose metabolism in SLE

This is a clinical trial of centrally acting ACE inhibitors in NPSLE.

Rationale

Tissue injury in SLE results from multiple and often redundant inflammatory pathways and mediators, therefore, a therapeutic approach that modulates multiple inflammatory mediators or pathways rather than ablating single pathways will be associated with greater clinical efficacy and less toxicity. We are also oriented towards the development of non-immunosuppressive treatments for SLE. To this end, the proposed clinical trial tests the efficacy of centrally acting Angiotensin Converting Enzyme Inhibitors (CA-ACEi), FDA-approved medication for hypertension with a highly favorable safety profile, compared to non-centrally acting ACEI (nonCA-ACEi) for improving abnormal resting brain metabolism and cognitive function in patients with SLE.

Cognitive impairment (CI) is one of the most common manifestations of neuropsychiatric SLE (NPSLE) with reported prevalence ranging from 3-80% and significant impact on quality of life [1-3]. Although cognition is impacted by many factors; mood disturbances, medication, infection, hormonal and metabolic imbalances, attribution to SLE-related immune mechanisms has been increasingly recognized. We and others have proposed SLE-associated mechanisms that contribute to CI including autoantibody-mediated neuronal toxicity and central nervous system (CNS) effects of inflammatory cytokines, chemokines and other small molecules [4-7]. A central, downstream target of many of these proposed pathways are microglia; resident macrophage- like cells responsible for routine surveillance and phagocytosis in the CNS. Under inflammatory conditions, activated microglia produce neurotoxic inflammatory cytokines, chemokines and reactive oxygen species [8] and are also associated with synaptic pruning, thereby directly affecting neuronal synaptic transmission [9].

The role of activated microglia in CNS pathology associated with neurodegenerative diseases such as Alzheimers Dementia is well established [10-12] and there is substantial evidence in murine and ex-vivo cell culture models and autopsy findings from SLE patients to suggest that microglia may be downstream mediators of several inflammatory processes contributing to CNS disease in SLE [13-19].

The renin angiotensin system, a known regulator of systemic hemodynamic and mineralocorticoid homeostasis, is also implicated in neuroinflammatory responses through effects of angiotensin II (pro-inflammatory) and bradykinin (anti-inflammatory) on microglia activation [20, 21]. ACE inhibition *in vitro* and in mouse models ameliorates the microglia response to inflammatory stimuli [22, 23] and treatment with CA-ACEi has been shown to reverse or prevent progression of cognitive decline in some neurodegenerative diseases [24-26]. Our mouse model of a cross-reactive anti-dsDNA/NMDA receptor antibody (DNRAb) that targets CA-1 hippocampal neurons resulting in impaired spatial memory [27] also demonstrates microglia-mediated synaptic pruning in response to neurotoxic effects of DNRAb that is inhibited by CA-ACEi (Nestor J, JEM, *in press*). We have used a multimodal neuroimaging approach to study effects of DNRAb in SLE patients with no history of CNS disease and demonstrated abnormally increased resting glucose metabolism in the hippocampus, orbitofrontal cortex and posterior putamen/globus pallidus/thalamus (putamen/GP/thalamus) [28, 29] that correlates with impaired performance on cognitive testing. Post hoc analysis of our data demonstrates improvement in regional resting hypermetabolism over time in SLE patients concurrently taking CA-ACEi.

This Phase 2, randomized, double blind, controlled clinical trial is designed to evaluate the neuro-protective effects of CA-ACEi in SLE using imaging and functional outcome measures. As it is a Phase 2 trial with a

limited number of subjects, an imaging biomarker was chosen as the primary endpoint rather than cognitive testing due to the large number of subjects that would be required to show a between-group difference in cognitive function. The proposed trial and mechanistic studies derive from and will extend the previous work of our team of scientists at the Feinstein Institute for Medical Research (FIMR) who have successfully collaborated on the characterization of CI in SLE for the past 10 years. Our combined expertise is unique and includes Rheumatology, Immunology, Neurology, Neuroscience, Neuropsychology, Biostatistics and Neuroimaging. Our overall hypothesis is that treatment with CA-ACEi will have beneficial effects on cognition in SLE as measured by decreased resting regional glucose metabolism, stable or improved performance on cognitive testing, and reduced microglia activation compared to treatment with a nonCA-ACEi.

Lupus Research Alliance (Diamond) 06/01/2016 – 12/30/2022 0.6 cal mons
LuCin Lupus Clinical Investigators Network Award LuCIN is a network of 58 North American lupus research centers whose objective is to identify novel therapies and conduct focused clinical trials.

NIH 1UM1AI110494 (Aranow) 05/01/2014 – 04/30/2024 0.24 cal mons
Proposal for The Feinstein Center for Clinical Research in Autoimmune Disease
This is a proposal to establish an Autoimmunity Centers of Excellence Basic Science Center (Diamond-Mechanistic Investigator)
Specific Aims:
The specific aims of the proposal to establish The Feinstein Institute for Medical Research Center for Clinical Research in Autoimmune
Disease are:
1.To conduct collaborative innovative clinical trials in autoimmune disease that will promote improved patient outcomes through control of
inflammatory disease and a reduction of organ damage and dysfunction;
2.To conduct collaborative innovative clinical trials accompanied by mechanistic studies that will result in a better understanding of the
pathogenesis of autoimmune diseases and mechanisms for therapeutic responses;
3.To conduct collaborative innovative clinical trials that will lead to a personalized medicine approach to treatment of autoimmune
disease;
4.To conduct collaborative innovative clinical trials evaluating agents those do not cause clinically significant immunosuppression.
5.To conduct collaborative innovative clinical trials accompanied by mechanist studies that would not be pursued by the pharmaceutical
industry

Connie Murphy Tel:
NIGMS 5R25GM139082 (Davidson) 09/01/2020 – 08/30/2025 0.3 cal mons
MAVEN: Developing diverse senior scientists leaders
The MAVEN long-term objective is to expand the national pool of qualified women and minority candidates for senior scientist positions across all NIGMS areas of science. We will do so by adapting best education practices from other industries in executive leadership, strategic career planning, and institution culture change, to create a sustainable, but intensive program with objective evaluation metrics.

Tedora Staeva Tel:
Lupus Research Alliance (Diamond) 09/01/2022 – 08/31/2023 0.60 cal mons
Probing Remission in SLE: Blood and Brain (PRISE)

It is very clear that we need to understand the heterogeneity that exists among SLE patients. Patients respond differently to medications. There is widespread concern that we are rejecting good therapeutic options for SLE because only a subset of patients enrolled in a clinical trial will respond to the particular drug being tested; this interferes with our ability to detect a strong beneficial response that may only occur in a subset of individuals.

Most studies that have tried to assess the heterogeneity that exists among patients have looked at patients with active disease. These studies are confounded by immunosuppressive medication use and the ongoing inflammatory response. We propose to study patients in drug free clinical remission who previously had active disease requiring corticosteroids or immunosuppressive medication. Our patient population comes from London, Mexico City, Los Angeles and New York City. Its racial and ethnic diversity reflects that of SLE patients. These patients do not have the confounding challenges of powerful drugs being prescribed or ongoing disease activity. We will explore the immune cells of these patients to understand heterogeneity in a stable patient population not on these drugs. We will compare them to active patients and healthy individuals. These studies should help us learn what the goals of therapy might be and to match patients to particular medications (precision medicine). These studies also will also allow us to understand the mechanisms by which the immune system is kept in balance in patients that are in remission.

The definition of clinical remission does not adequately account for brain health, specifically cognitive impairment which patients identify as a major impediment to a good quality of life. We propose to study brain function in patients in remission by neuroimaging and neuropsychological testing to determine the extent to which patients who appear to be in clinical remission do or do not have SLE-related activity in their brain. We will thus learn the spectrum of brain abnormalities that persist and whether these associate with particular abnormalities in cells of the immune system. We anticipate that we will identify some patients who by conventional assessment appear to be in full remission but whose brains are not functioning normally and might need further therapy to restore brain health.

Pending

None

Other Support

GEORGIOU, GEORGE

Previous (Project Period Ending within the past 5 years)

Title: Molecular and Immunologic Analysis of Influenza Vaccine Response
Effort: 4.2%
Supporting Agency: CDC 75D30119C06088 (Co-I, PI: Kennedy)
Address:1600 Clifton Road, NE, Atlanta, GA
Contracting/Grants Officer: Ronnie Williams, oga3@cdc.gov,
Performance Period: 09/2019-08/2021
Project Goals: The major goal for UT Austin's subaward on this proposal is the comprehensive analyses of the human humoral anti-HA repertoire elicited by three seasonal influenza vaccines.
Overlap: None

Title: Human-Enzyme Mediated, Systemic Depletion of Cystine for Cancer Treatment
Effort: 3%
Supporting Agency: NIH: R01CA189623 (MPI: Georgiou, DiGiovanni, Stone)
Grants Officer: Michael C. Alley, 9000 Rockville Pike, Bethesda, MD
Funding Amount: Total Direct/yr NCE- no additional funds
Project Goals: The major goal of this project is to determine that prolonged, systemic depletion of the serum L-Cys/CSSC pool using engineered human enzymes may constitute a potent cancer therapeutic avenue either as a monotherapy or as a sensitizer (due to the ensuing redox balance perturbation) for combination therapy with minimal toxicity.
Overlap: None

Title: Molecular, Functional and Structural Analyses of Anti-PAD Antibodies in Rheumatoid Arthritis
Effort: 1%
Supporting Agency: 1 R56AI143994-01 (Co-I, PI: Bridges)
Grants Officer: John Peyman, peymanj@niaid.nih.gov
Performance Period: 04/12/2019-03/31/2020
Project Goals: The major goal of UT Austin's portion of this project is molecular identification and structure determination of the monoclonal antibodies that comprise serum IgG antibody repertoires.
Overlap: None

Title: HIV bNAbs
Effort: 1%
Supporting Agency: Leidos Biomedical Research Inc.: 15X219 (PI)
Grants Officer: Chris Case, PO Box B, Frederick, MD 21702-1201
Performance Period: 11/1/2015-03/15/2020
Project Goals: The major goal of this project is to adapt novel technologies for the analysis of humoral immune responses.
Overlap: None

Title: RSV IgSEQ
Effort: 1%
Supporting Agency: Sanofi Pasteur Biologics (Co-I, PI: Ippolito)
Address: 38 Cambridge, MA 02139
Contracting/Grants Officer: Joshua DiNapoli

Performance Period: 12/01/2018-06/30/2020
Project Goals: The major goals of this project are a molecular-level comparison of baseline repertoires (cellular and serological) in RSV-immune study subjects with their activated repertoires elicited by RSV.
Overlap: None

Title: Development of an engineered & pharmacologically optimized human methionine-gamma-lyase drug candidate for the treatment of prostate cancer and glioblastoma.
Effort: 2%
Supporting Agency: CPRIT RP180590 (Co-I, PI: Stone)
Performance Period: 03/01/2018-08/31/2021 (NCE)
Project Goals: The major goals of this project are to make further improvements in the potency of this drug, understand the mechanism of action and identify biomarkers for selecting patients most likely to benefit from this therapy.
Overlap: None

Title: Molecular Analysis of Serum Antibody Constituents in Zika Virus Infection
Effort: 1%
Supporting Agency: NIH: R21AI135682 (MPI: Georgiou, Baric)
Contracting/Grants Officer: Donna R Sullivan
Performance Period: 09/01/2017-01/31/2020
Project Goals: The major goal of this project is to assess and quantify the persistence of specific and protective antibodies as well as cross-reactive (possible pathogenic) antibodies in Zika-infected patient blood.
Overlap: None

Title: Duke DARPA Pandemic Prevention Platform (P3)
Effort: 16.6%
Supporting Agency: DOD/DARPA (Co-PI: Georgiou, PI: Sempowski)
Grants Officer: Colonel Matt Hepburn, 675 North Randolph Street, Arlington, VA 22203, Matt.Hepburn@darpa.mil
Performance Period: 10/01/2017-09/25/2019
Project Goals: The major goal of this project is to develop an integrated technology platform that gives public health officials the capability to halt the spread of any viral disease outbreak before it can escalate to pandemic status.
Overlap: None

Title: Neutralizing Antibody Evolution Following Sessional Flu Vaccination or Infection
The major goal of this project is to study the neutralizing antibody evolution following seasonal flu vaccination.
Effort: 1%
Supporting Agency: Harvard/Children's Hospital
Grants Officer: Karen Lee, 250 Longwood Ave, Boston, MA
Performance Period: 8/1/2014-07/31/2018
Project Goals: Neutralizing Antibody Evolution Following Sessional Flu Vaccination or Infection
The major goal of this project is to study the neutralizing antibody evolution following seasonal flu vaccination.
Overlap: None

Title: Preclinical Development of a Therapeutic Enzyme for Immune Checkpoint Inhibition in Cancer.
Effort: 8.3%
Supporting Agency: CPRIT: DP150061
Address: 1701 North Congress Ave, Austin, TX 78701
Contracting/Grants Officer: Wilfredo Ruiz

Performance Period: 12/1/2014-05/31/2018
Project Goals: The major goal of this project is to expand and execute the product development and preclinical studies needed to deliver a powerful immune checkpoint inhibitor into the clinic for cancer therapy.
Overlap: None

Title: Therapeutic Enzyme Development
Effort: 1%
Supporting Agency: KYN Therapeutics, LLC: Sponsored Research Agreement
Address: 400 Technology Square, 10th floor, Cambridge, MA 02139
Grants Officer: Mark Manfredi
Performance Period: 04/01/2016-05/31/2018 renewed annually
Project Goals: The major goal of this project is the development of a therapeutic enzyme that can reverse immunosuppression caused by metabolites produced by tumors.
Overlap: None

Title: Engineering, Optimization, and Validation of Novel Human Therapeutics
Effort: 8.3%
Supporting Agency: Aeglea BioTherapeutics, LLC: Sponsored Research Agreement
Address: 815-A Brazos, Suite 101, Austin, TX
Grants Officer: David Lowe
Performance Period: 12/01/2013-08/31/2018
Project Goals: The major goal of this project is to engineer and characterize therapeutic arginine & methionine degrading enzymes and their initial preclinical testing in vitro and in vivo animal models.
Overlap: None

Title: High-throughput sequencing of the human paired T cell receptor α -β repertoire in identical twin pairs
Effort: 2.1%
Supporting Agency: NIH Cooperative Centers for Translational Research in Human Immunology (CCHI)
Address: 3172 Porter Drive, Palo Alto, CA,
Grants Officer: Bach-Hong Tran
Performance Period: 04/01/2017-03/31/2018
Project Goals: Development and validation of the high throughput TCR paired sequencing technology, carry out the paired repertoire sequencing of twins and perform the data analysis.
Overlap: None

Current
Funding is listed in Total Award Amount (including Indirect costs)

Title: Serum IgOME profiling of polyclonal sera
Effort: 6.5%
Supporting Agency: Bill and Melinda Gates Foundation (INV-004956)
Address: P.O. Box 23350, Seattle, WA 98102, USA
Contracting Officer: Harry Kleanthous, harry.kleanthous@gatesfoundation.org
Performance Period: 11/2021-08/31/2024
Funding Amount:
Project Goals: Serum proteome analysis of immune sera to characterize dominant antibody clonotypes following vaccination with different platforms or following natural infection.
Overlap: None

Title: Pan-B-coronavirus S2 vaccine
Effort: 4%
Supporting Agency: Bill and Melinda Gates Foundation (Co-I, INV-031624- subaward to Ippolito, G.C.)
Address: P.O. Box 23350, Seattle, WA 98102, USA
Contracting Officer: Harry Kleanthous, harry.kleanthous@gatesfoundation.org
Project Period: 8/2021-7/2023
Funding Amount:
Project Goals: characterize the B cell receptor (BCR) repertoire and the plasma immunoglobulin G (IgG) repertoires directed to the S2 subunit that are elicited by licensed spike-based vaccines, next-generation S2 antigens, or by natural infection.
Overlap: None

Title: North Carolina Seronet Center for Excellence: Research Core C
Effort: 8.3%
Supporting Agency: NIH 5U54CA260543 (Co-I, PI: Baric; subaward 5119501 to Ippolito, G.C.)
Address: 37 Convent Dr., Bethesda, MD 20814
Contracting/Grants Officer: Elizabeth Lee Read-connole, bconnole@mail.nih.gov, Performance Period: 09/2020-08/2023
Funding Amount:
Project Goals: The major goals of this project are to 1) characterize the immune responses elicited to SARS-CoV2 infection, 2) understand the mechanisms driving the serological, humoral and cellular immune responses, 3) determine modifiers of the serologic memory and 4) determine the serological correlates of disease pathogenesis, and protection against future infection. Research Core C will be integral to the examination of serological antibody repertoires in COVID-19 study subjects as well as in convalescent plasmas obtained from survivors.
Overlap: None

Title: Etiology and outcome of MIS-C
Effort: 4.2%
Supporting Agency: NIAID 3U19AI144306-02S1 (Co-I, PI: Diamond)
Address: 37 Convent Dr., Bethesda, MD 20814
Contracting/Grants Officer: David R. Johnson, drjohnson@niaid.nih.gov, Performance Period: 08/2020-08/2025
Funding Amount:
Project Goals: The major goal of this project is to test two hypotheses regarding the Multisystem Inflammatory Syndrome (MIS-C) recently identified in children and young adults infected with SARS-CoV-2.
Overlap: None

Title: Antibody Landscape following Human Norovirus Infection and Vaccination
Effort: 2%
Supporting Agency: NIH 1R01AI148260-01 (Co-I, PI: Baric)
Address: 37 Convent Dr., Bethesda, MD 20814
Contracting/Grants Officer: Rodolfo M. Alarcon, Rodolfo.alarcon@nih.gov, Performance Period: 03/2020-02/2025
Funding Amount:
Project Goals: The major goals of this project are to critically inform the development of broadly effective HuNoV vaccine.
Overlap: None

Title: Systematic, molecular level analysis of the Fc receptor ligation on antibody effector functions.
Effort: 8.3%
Supporting Agency: NIH U01AI148118 (PI: Georgiou)

Address: 37 Convent Dr., Bethesda, MD 20814
Contracting/Grants Officer: Kevin Roy Heath, kevin.heath@nih.gov,
Performance Period: 12/2019-11/2024
Funding Amount:
Project Goals: The major goal of this project is to delineate, in unprecedented detail, the cytotoxic mechanisms and signaling events triggered by each receptor on myeloid cells and thus provide a rational framework for the engineering of therapeutic antibodies having more potent effector functions and improved clinical efficacy.
Overlap: None

Title: Center for Influenza Vaccine Research in High-Risk Populations
Effort: 8.3%
Supporting Agency: NIH 75N93019C00052 (Co-I, PI: Ross)
Address: 37 Convent Dr., Bethesda, MD 20814
Contracting/Grants Officer: Erin Felent, Erin.Felent@nih.gov,
Performance Period: 09/2019 – 09/2026
Funding Amount:
Project Goals: The major goal for UT Austin's subaward on this proposal is to delineate the B-cell and serological antibody repertoires elicited by influenza virus, including a molecular-level assessment of influenza vaccine candidates through preclinical animal studies, early phase clinical trials, and healthy volunteer human challenge studies.
Overlap: None

Title: CIVICs A
Effort: 4.2%
Supporting Agency: NIH 75N93019C00050 (Co-I, PI: Moody)
Address: 37 Convent Dr., Bethesda, MD 20814
Contracting/Grants Officer: Erin Felent, Erin.Felent@nih.gov,
Performance Period: 09/2019-09/2026
Funding Amount:
Project Goals: The major goal for UT Austin's subaward on this proposal is to delineate the B-cell and serological antibody repertoires elicited by influenza virus, including a molecular-level assessment of influenza vaccine candidates through preclinical animal studies, early phase clinical trials, and healthy volunteer human challenge studies.
Overlap: None

Title: Alteration of function and specificity of TFH in SLE
Effort: 4.2%
Supporting Agency: NIH R01 AR074565-01 (Co-I, PI: Diamond)
Address: 37 Convent Dr., Bethesda, MD 20814
Contracting/Grants Officer: Marie Mancini, mancinim2@mail.nih.gov
Performance Period: 09/2019 – 08/2024
Funding Amount:
Project Goals: The major goals of this project are to study how BLIMP1-deficient DCs allow self-reactive T cells to escape central tolerance mechanisms in the thymus.
Overlap: None

Title: Development and Mechanistic Studies of an Engineered Human Therapeutic to Abrogate Immune Suppression due to Elevated Methylthioadenosine (MTA) by MTAP null/low Tumors.
Effort: 1%
Supporting Agency: NIH/NCI 1R01CA240700 (Co-I, PI: Stone)
Address: 37 Convent Dr., Bethesda, MD 20814
Contracting/Grants Officer: Leslie Hickman
Performance Period: 07/2019-06/2024

Funding Amount:
Project Goals: The major goals of this project are development of a novel biologic cancer therapeutic, to reverse the immunosuppressive effects of MTA and aid in the treatment of patients with MTAPnull/low tumors as a key biomarker
Overlap: None

Title: Heterogeneous pathways to autoantibody production: implications for prognosis and therapeutic targeting
Effort: 4.2%
Supporting Agency: NIH/NIAID 1 U19AI144306 (Co-I, PI: Diamond)
Address: 5601 Fishers Ln, Rockville, MD 20852
Contracting/Grants Officer: Regina Kitsoulis
Performance Period: 04/2019-03/2024
Funding Amount:
Project Goals: The major goals of this project are to compare vaccine responses in SLE patients and healthy subjects with respect to clonality and cross-reactivity with autoantigen.
Overlap: None

Title: Mechanism of DNA-specific Autoimmunity in Systemic Lupus Erythematosus
Effort: 1%
Supporting Agency: NIH/NIAMS 2 R01AR071703 (Co-I, PI: Reizis)
Contracting/Grants Officer: Marina Mancini
Performance Period: 04/2018-03/2024
Funding Amount:
Project Goals: The major goals of this project are to delineate the B-cell antibody repertoire in autoimmune DNASE1L3-deficient mice.
Overlap: None

Title: Antibody Discovery and Optimization using the Eclonal Technology
Effort: 8.3%
Supporting Agency: Clayton Foundation for Research (PI)
Grants Officer: Jarred Sloan, 1 River Way, Houston, TX 77056,
Performance Period: 1/2013-12/2022(renewed annually)
Funding Amount: Total Direct/yr
Project Goals: The major goal of this project is the development of new technologies for IgG discovery and production for cancer therapy.
Overlap: None

Pending
None

DOD OTHER SUPPORT – Nir Hacohen, PhD

Active - The Broad Institute, Inc.

Title:	Impact of Immunotherapy on Viral Immunity in Humans
Effort:	0.24 (cal)
Supporting Agency	NIH/NIAID, U19AI082630 (Chung)
Grants Officer	Lakshmi Ramachandra ramachandral@mail.nih.gov
Performance Period	06/01/2019-05/31/2024
Funding Amount	(total costs)
Project Goals	The overall goal of the program is to examine how the PD-1 pathway blockade alters immunity in humans with chronic infections or during vaccinations and to dissect the mechanistic role of this pathway in human innate and adaptive immunity. Core D (TCR, BCR and RNA Sequencing) will perform experimental single cell mRNA and TCR/BCR-seq for blood and liver samples from the projects.
Specific Aims	Aim 1: sequence paired tcr chains and bulk bcrs in antigen-specific lymphocytes. Aim 2: sequence tcrs and bcrs in bulk samples of blood or tissue to quantify the repertoire and track b cells and t cells with antigen specificity that was identified in Aim 1. Aim 3: perform droplet-based single-cell rna-sequencing of immune cells, including mrna, tcr and bcr.
Overlap	None

Title:	Genes required for dendritic cell responses to pathogens and T cells
Effort:	.01 (cal)
Supporting Agency	NIH/NIAID, U19AI133524 (Sharpe)
Grants Officer	Chao Jiang 5601 FISHERS LN ROCKVILLE MD 20852 chao.jiang@nih.gov
Performance Period	07/2017-06/2023 (NCE)
Funding Amount	(annual total costs)
Project Goals	The Broad Institute will carry out CRISPR screens to identify genes involved in DC-T interactions in mice.
Specific Aims	In this application, we propose to fill these gaps in our knowledge of DC biology through forward genetic screening for novel regulatory factors in mice. This approach is facilitated by recent advances in genome editing provided by CRISPR-based technologies. A pipeline of gene discovery will be generated through the use of established and emerging FACS-based assays. These assays will be used in vivo and ex vivo to identify DCs that are deficient for regulators of DC interactions with microbes or T cells. All screens will depend on significant interactions between the informatics, mouse perturbation and CRISPR library Cores associated with this U19 application.

	Subsequent functional analysis of candidate regulatory proteins will be performed in collaboration with other investigators on this grant. The cumulative result of these efforts will be a series of novel gene sets that should define pathways and processes that explain numerous aspects of DC biology as they relate to host defense.
Overlap	None

Title:	PEARL: Pathway Exploration and Analysis in Renal Lupus (Diamond)
Effort:	.01 (Cal)
Supporting Agency	NIH, UH2AR067688
Grants Officer	Susana Serrate-Sztein 9000 Rockville Pike Building 31, Room 4C32 Bethesda MD 20892
Performance Period	06/2016-11/2022 (NCE)
Funding Amount	(total costs)
Project Goals	The goal of this project is to apply new technologies for high resolution analyses of gene expression and immunophenotype to kidney, blood and urine of lupus patients with active nephritis in order to develop a better understanding of disease pathogenesis and tissue injury, and stratify patients with respect to therapeutic response for more informed clinical decision making.
Specific Aims	Nephritis is a common and serious manifestation of Systemic Lupus Erythematosus for which there is no adequate therapy. Some patients will exhibit a response to current immunosuppressive regimens while others will not; all are at risk for on and off target toxicities. The current proposal is to apply new technologies for high resolution analyses of gene expression and immunophenotype to kidney, blood and urine of lupus patients with active nephritis in order to develop a better understanding of disease pathogenesis and tissue injury, and stratify patients with respect to therapeutic response for more informed clinical decision making. We will explore blood and urine for less invasive surrogate markers for kidney inflammation. Our plan relies of optimization of analytic approaches, informed choice of cellular subpopulations to analyze, followed by two small studies to refine and validate the approach. In the first, we will study kidneys, blood and urine o 20 patients at a time of renal flare in order to dissect patterns of inflammation. In the second we will study cellular subsets in blood of 40 patients who were part of a clinical trial of lupus nephritis to understand changes from baseline profiles of gene expression and function response in those who experienced a full clinical response to therapy and those who failed to respond. Finally, we will use the information from these studies to design a large scale longitudinal study of patients with lupus nephritis. This unbiased re-examination of this unmet medical challenge should identify novel therapeutic targets, inform the generation of new models of disease, and lead to predictors of response that can then be validated in clinical trials We have unique technology resources and a powerful consortium of clinical investigators in the newly established Lupus Nephritis Trials Network that includes: (i) the infrastructure and expertise for clinical study implementation; (ii) protocols and consents for acquisition of blood, urine, and biopsy specimens; and (3) scalability to move from phase 0 and 1 to phase 2 at the appropriate time.
Overlap	None

Title:	Dissecting the immune landscape in lupus nephritis

Effort:	0.24 (cal)
Supporting Agency	Lupus Research Alliance
Grants Officer	Diomaris Gonzalez 275 Madison Avenue, 10th Floor New York, NY 10016 dgonzalez@lupusresearch.org
Performance Period	2/01/2019 – 6/30/2023
Funding Amount	(total costs)
Project Goals	The goal of the project is to analyze the localization of immune cell types and states in human lupus kidney biopsies, compare them to immune cell infiltrates in the major mouse models of lupus nephritis, and determine association of immune cell states with clinical metrics in lupus nephritis patients.
Specific Aims	Two major challenges in studying lupus kidney disease, a devastating complication of lupus, are that: first, we still do not understand what cells cause kidney damage in people; and second, we do not have good mouse models to study lupus kidney disease. As part of the AMP consortium funded by the National Institutes of Health, our lab recently analyzed the kidneys of patients with lupus kidney disease and discovered the presence 21 cell types of the immune system, which are mostly absent from healthy kidneys. These findings represented an important breakthrough because they provide the first comprehensive view of the cells that contribute to disease or health in the kidneys of patients with lupus. In this LRA proposal, we ask which of these 21 new cell types are related to kidney damage, function, and response to therapy. Pinpointing exactly which cell types contribute to these processes will provide new targets for therapy, as well new tools to predict whether patients will respond to treatment and insight into their future kidney health. To achieve these goals, we will examine tissue biopsies from newly diagnosed patients for the 21 immune cell types to see which are present in patients with the most or least severe kidney damage. We will also determine how we can use mouse models to study lupus, by trying to understand how close the mouse version of lupus nephritis is to the real human disease. If we succeed in our proposal, we will provide new targets for drug development, new approaches for predicting outcome in patients and better understanding of how mouse models can be used to shed light on human lupus kidney disease.
Overlap	None

Title:	Lynch syndrome Colorectal Cancer Immunoprevention using Recurrent Neoantigen Peptide Vaccination
Effort:	0.12 cal
Supporting Agency	Starr Foundation I12-0050 (Lipkin, Getz)
Grants Officer	Sylvie Le Blancq 646 888 3773 leblancs@mskcc.org
Performance Period	01/1/2019-12/31/2021
Funding Amount	(total cost)
Project Goals	We will to establish an approach for an LS CRC immunoprevention vaccine, provide insights into LS premalignant neoantigen immunoediting, and create a novel paradigm of recurrent tumor “hotspot” mutation peptide vaccination for pre-symptomatic patients with increased cancer predisposition.

Specific Aims	AIM1 Delineate Lynch syndrome recurrent colorectal adenoma coding mutations LS tumors are DNA mismatch repair-deficient (MMRD), which is characterized by greatly elevated insertion/deletion (indel) mutation rates in repetitive microsatellites. However, microsatellite mutations can be challenging to detect in short-read sequencing data. We recently developed novel computation tools to more accurately delineate somatic microsatellite indel mutations and MMRD driver genes[13]. We will perform whole exome and RNA-sequencing on 100 LS colorectal adenomas and matching germline control from LS *MLH1* and *MSH2* germline mutation carriers, apply these tools and integrate with existing mutation data from advanced MMRD tumors. Finally, we will nominate the most frequent LS colorectal adenoma recurrent mutations. AIM2 Predict and validate HLA-mediated presentation of Lynch syndrome recurrent neoantigens We will analyze LS patient colon adenoma recurrent mutations in the context of host MHC with state-of-the-art computational tools to predict immunogenic neoantigens. We will then confirm neoantigen presentation by HLA-Immunoprecipitation in primary adenoma and tumor samples. This will reveal recurrent neoantigens that are presented to the immune system, early driver mutations and provide insights into host immunosurveillance. AIM3 Test hypothesis that candidate recurrent neoantigens are immunogenic in Lynch syndrome patients As preliminary data, in LS mouse models we show that recurrent colorectal adenoma neoantigens are immunogenic and that peptide vaccination with as few as 4 recurrent neoantigens enhances T cell immunity, reduces CRC incidence and prolongs survival. Here, for 20 LS patients with colon adenomas we will test whether Aim 2's recurrent and presented neoantigens can be recognized by T cells, and whether patient reactive T-cell lines are cytotoxic against autologous colon adenoma organoids.
Overlap	None

Title:	MAS-seq: end-to-end molecular and software solutions for long-read high-throughput full-length RNA isoform sequencing in bulk and single cell samples
Effort:	0.0 (Internal funds, no effort required)
Supporting Agency	Broad Institute
Grants Officer	John Doench jdoench@broadinstitute.org
Performance Period	09/2020-08/2023
Funding Amount	(total costs)
Project Goals	Our goal is to develop a new method to concatenate full-length transcript from single cells for long-read sequencing to capture isoforms.
Specific Aims	N/A
Overlap	None

Title:	Large-scale nanobody libraries for detecting the surface proteome of human cells
Effort:	0.0 (Internal funds, no effort required)

Supporting Agency	Broad Institute
Grants Officer	John Doench jdoench@broadinstitute.org
Performance Period	04/2021- 03/2023 (NCE)
Funding Amount	(total cost)
Project Goals	Our goal is to create very large-scale libraries of nanobodies using ribosomal display to screen against human proteins.
Specific Aims	N/A
Overlap	None

Title:	Identification of Novel Biomarkers of Neuroimmune Function/Dysfunction
Effort:	0.10 (cal)
Supporting Agency	Alzheimer's Association, ASDF-21-836089-C, (Stevens)
Grants Officer	
Performance Period	11/2020- 10/2022
Funding Amount	(total costs)
Project Goals	We are searching for circulating biomarkers based on transcriptomes of single blood cells to identify genes or cell states associated with Alzheimer's pathology in a cohort of iNPH patients.
Specific Aims	N/A
Overlap	None

Title:	Differentiation of immune cells and fibroblasts in inflamed tissue in RA and SLE
Effort:	1.80 (cal)
Supporting Agency	NIH/NIAID, 5P01AI148102, (Brenner)
Grants Officer	John Peyman
Performance Period	06/15/2021 -03/31/2026
Funding Amount	(total costs)
Project Goals	Project 2. We will study the regulation, function and localization of monocytes in lupus and arthritis
Specific Aims	Rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) are different diseases clinically and the most important tissue damage occurs in joints and kidneys, respectively. Yet, both SLE and RA share a central common theme of adaptive T and B cell interactions that result in autoantibody production. Both tissues develop chronic inflammatory reactions that also include myeloid cell populations, neutrophils and other innate leukocytes. The two diseases cluster in families and share a number of closely related risk alleles suggesting related immune mechanisms. Developing targeted therapies for lupus has been frustrating and while a number of therapies can reduce disease activity in RA, a large unmet need exists in the form of TNF inadequate responders; and there is no cure. Based on the RA/SLE AMP consortium, single cell RNA-seq and CyTOF analysis has phenotypically and transcriptionally identified many unexpected cell types and cell states present in the inflamed kidney in lupus nephritis

	and RA synovitis. Here, we select a set of important cell populations specific to, or highly enriched in, the involved tissues in both diseases. Given the importance of B cells and antibody production, we focus on the novel subset of age (or autoimmunity) associated B cells (ABC B cells) and B helper T cells including both T follicular helper (Tfh) and the recently discovered T peripheral helper (Tph) T cells in Project 1. The project focuses on defining the relationship of ABC to other B cell populations and examines the role of Tph and Tfh cells in driving ABC B cells and their cross-talk. ABC B cells and Tph/Tfh cells are enriched in both lupus kidney and RA synovium allowing their comparison across diseases. Project 2 examines novel macrophage inflammatory states found in lupus kidney and seeks to define the main activating factors and transcription factors that drive cell state changes to achieve the inflammatory CM4 state that predominates in nephritis. Project 3 examines the fibroblastic stroma that drives inflammation in RA. A population of inflammatory sublining CD90+DR+ fibroblasts is profoundly expanded in RA and implicated in perpetuating inflammation. Project 3 examines the role of a Notch gradient and Notch signaling in driving the differentiation and activation of this population in synovium and kidney and its role in inflammatory arthritis. All 3 projects interact to examine the cell types of interest across diseases, to determine which cells are interacting most closely by integrated imaging analysis. By utilizing the synchronized expert pipelines of the Computational Systems Immunology Core for single cell RNA-seq and image analysis, the data gathered from both diseases and tissues can be effectively compared. All 3 projects focus on determining the drivers and transitions that yield the important cell states that have been discovered directly in the involved tissues. Together, the program will provide new insights into the tissue immunopathology in these human autoimmune diseases and help to unfold new avenues for therapeutic intervention.
Overlap	None

Title:	Combining Locally Administered Ipilimumab with a Personalized Neoantigen Cancer Vaccine to Improve T Cell Priming and Anti-Tumor Immunity in High-Risk Renal Cell Carcinoma
Effort:	0.24 (cal)
Supporting Agency	DOD/AMRMC, W81XWH-20-1-0533 (Wu)
Grants Officer	JOSHUA MCKEAN joshua.d.mckean3.civ@mail.mil
Performance Period	09/2020-09/2023
Funding Amount	(total costs)
Project Goals	We will analyze dynamic responses of immune cells to vaccination in a murine model (Aim 1).
Specific Aims	Aim 1: Identify and characterize antigen presenting cells (APCs) that stimulate neoantigen-specific T cells following personal neoantigen vaccine with local IPI. We hypothesize that locally administered IPI will improve antigen presentation and T cell priming by APCs. Utilizing single cell transcriptomic analysis of vaccine site biopsies, we will identify and characterize the transcriptional state of key APCs, to elucidate which cell types may take up and present neoantigens to generate antigen-specific responses following vaccination with or without IPI. These human studies will be integrated with parallel studies in an established mouse model of vaccination to further define the effect of local IPI on APC composition and T cell priming in the draining lymph node. Aim 2: Determine the magnitude and characterize the phenotype, state, and functional avidity of neoantigen- specific T cells following personal neoantigen vaccine with local

	IPI. We hypothesize that the addition of local IPI to neoantigen vaccination, through improved T cell priming and activation, will broaden the T cell repertoire and expand tumor neoantigen-specific T cells, leading to highly specific anti-tumor activity. We plan to utilize established immune assessment pipelines together with novel approaches including single cell transcriptomics, T cell receptor (TCR) reconstruction, and culturing of autologous tumor cells, to comprehensively quantify the breadth, strength, and functional avidity of neoantigen-specific T cell responses in the peripheral blood, during and after vaccination (with or without that addition of local IPI). These correlative studies of this first-in-disease therapeutic trial will provide a deeper understanding of how modulation of antigen presentation and T cell priming affects clinical responses to neoantigen vaccination, and ultimately inform rational therapeutic combinations for future clinical trials in RCC.
Overlap	None

Title:	Factors regulating strength and duration of STING signaling
Effort:	1.20 (cal)
Supporting Agency	NIH/NIAID, R01AI158495
Grants Officer	Nancy Vazquez-Maldonado Scientific Review Officer NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES nv19q@nih.gov
Performance Period	09/2021-08/2026
Funding Amount	(total costs)
Project Goals	We aim to identify and analyze proteins that control STING pathway degradation and transport using genetic, biochemistry and cell biological approaches.
Specific Aims	Aim 1. Ubiquitinated STING as a platform for endosomal microautophagy and control of STING degradation and signaling. We will refine our model of endosomal microautophagy for STING degradation by studying autophagy induction and identifying the E3 ubiquitin ligases required for ubiquitinating STING that in turn recruits ESCRT for autophagosome sealing. We will test whether ubiquitinated STING also induces clearance of viruses through endosomal microautophagy. To deepen our analysis of factors affecting STING trafficking, we will use a new method of optical CRISPR screening to identify genes regulating subcellular STING localization and signaling. Overall, this aim will explore a new mechanism of STING-dependent endosomal microautophagy that provides a consistent model of how STING triggers autophagy. Aim 2. The role of DNAJC13 in restricting STING exit from the ER and STING signaling. We will determine how DNAJC13 blocks STING activity by altering STING trafficking. We will test the roles of DNJAC13 and ERendosomal contacts in limiting STING activation by restricting STING ER exit to the TGN. To define the biochemical mechanisms of STING interactions, we will use deep mutational scanning to find motifs on STING that are responsible for interactions with DNAJC13 and for the effects of DNAJC13 on STING trafficking, as well as motifs that control other aspects of STING localization and signaling. This aim will reveal how ER-endosome contact, a process that has not been previously associated with STING trafficking, contributes to STING biology. Aim 3. Impact of human disease-associated mutations in regulators of STING trafficking. We discovered that a pathogenic mutant of the ESCRT subunit UBAP1, involved in hereditary spastic paraplegia development, leads to STING-dependent type I IFN responses at steady state. We will characterize whether genes studies in Aims 1 and 2 and mutated in human diseases affect innate immune activation and cell death in

	cellular models of the human central nervous system.
Overlap	None

Title:	Prime editing-mediated immunotherapy for fusion protein-driven pediatric cancers resistant to immune checkpoint inhibitors
Effort:	0.1 (cal)
Supporting Agency	Anonymous
Grants Officer	N/A
Performance Period	11/1/2021-10/31/2023
Funding Amount	(total costs)
Project Goals	To develop methods for inducing antigen-specific immunity in tumors
Specific Aims	N/A
Overlap	None

Title:	Personal tumor neoantigens for immunity against chronic lymphocytic leukemia
Effort:	1.20 (cal)
Supporting Agency	NIH, 2R01CA155010-11 (Wu)
Grants Officer	Katarzyna Bourcier katarzyna.bourcier@nih.gov
Performance Period	02/2022 – 01/2027
Funding Amount	(total costs)
Project Goals	We will identify and analyze peptides bound to MHC to develop predictive rules and identify isoforms using long read sequencing to discover novel epitopes based on alterations in splicing.
Specific Aims	Personal neoantigens have been conceptualized as optimal tumor antigens but their broad applicability across cancers has been limited by the variability in mutational burden across tumors. Recent clinical experiences in targeting neoantigens, such as by vaccination, in high and moderate mutation-rate tumors (e.g. melanoma, glioblastoma) have been promising, but such promise for low mutation burden cancers remains under evaluation. Chronic lymphocytic leukemia (CLL) is an example of such a low mutation burden malignancy where improved tumor antigen identification could open new therapeutic opportunities. Indeed, although a growing armamentarium of clinically active therapies is now available for CLL (i.e. targeted inhibitors, CAR-T cells, CPB), CLL remains largely incurable. While inherently immunogenic, as highlighted by evidence of spontaneous regression and its responsiveness to the graft-versus-leukemia (GvL) activity of allogeneic hematopoietic cell transplantation (allo-HCT), CLL patients demonstrate inconsistent ability to mount antigen-specific immunity. Notably, we have achieved several exciting technologic advances over the last 5 years that impact antigen discovery, including: (i) new understanding of the cancer genome and transcriptome, advanced by new sequencing technologies, yielding potential alternative sources of cancer neoantigens; (ii) establishment of a scalable approach to rapidly validate peptide-MHC interactions, providing essential experimental feedback to our prediction efforts; (iii) improvements in the sensitivity, throughput and analysis of immunopeptidome data; (iv) expanded computational infrastructure to rapidly incorporate findings into prediction models for HLA class I. In this application, we

	hypothesize that novel classes of neoantigens are discoverable in CLL and that antigen-specific interactions arising from recognition of these alternative neoantigens could contribute to leukemia control. We propose an integrative strategy for the discovery and validation of novel neoantigen species. This commences with detection analyses of alterations that could encode these alternative CLL neoantigens through long-read and ribosomal sequencing, that can be used to inform improvements on the analysis pipelines. It then proceeds with validation using new high throughput binding assays, immunopeptidome detection and T cell response assessments (Aim 1). Our strategy further involves systematic improvement of our class I prediction tools through generation of experimental data from which we can iteratively correct and refine the epitope predictions. We furthermore incorporate the feature of peptide-MHC stability, which has been increasingly identified as relevant in peptide-MHC immunogenicity (Aim 2). Finally, we propose to confirm the functional relevance of alternative tumor neoantigens through their evaluation in the context of variation in natural history of CLL in a newly-assembled cohort of >1000 molecularly characterized samples, and within the setting of therapeutic response following whole CLL cell vaccination after alloHCT (Aim 3). We thus propose to expand the 'universe' of CLL neoantigens and to define their impact within informative clinically annotated CLL datasets.
Overlap	None

Title:	Single cell and spatial genomic analyses of specimens from patients with autoimmune diseases (AMP AIM Technology Core)
Effort:	.48 (cal)
Supporting Agency	NIH/ NIAMS, 1UC2AR081031-01A1 (Brenner)
Grants Officer	Ricardo Cibotti Health Scientist Administrator NATIONAL INSTITUTE OF ARTHRITIS AND MUSCULOSKELETAL AND SKIN DISEASES cibottirr@mail.nih.gov
Performance Period	03/2022-12/2026
Funding Amount	(total costs)
Project Goals	To carry out single cell RNA-seq, single nucleus RNA-seq, TCR-BCR-seq and spatial transcriptomics on AMP AIM tissue and blood samples.
Specific Aims	To better understand the molecular and cellular pathways driving autoimmune diseases, we propose to deeply profile biological samples from patients with rheumatoid arthritis (RA), psoriasis (Ps), psoriatic arthritis (PsA), primary Sjögren's syndrome (pSS) and systemic lupus erythematosus (SLE). Working closely with the AMP AIM network, we will focus on the cohorts and clinical questions defined by the network of clinicians, biologists and computational biologists together with industry and non-profit partners. For our Technology Core, we selected leading-edge multi-dimensional technologies to deeply profile end organs as well as peripheral blood from patients with autoimmunity. We assembled a team of investigators with expertise in each disease and tissue type, and who have already demonstrated the ability to develop and implement high-throughput pipelines to profile tissue and blood samples. To help us design and interpret the studies, we recruited a team of collaborators and consultants with clinical expertise in each disease, with pathology expertise in each tissue and with technical expertise in spatial profiling methods. In the first year, we will carry out the pilot phase to optimize pipelines for: i) preserving and disaggregating tissues; ii) profiling single cells using scRNA-seq/CITE-seq/TCR-BCR-seq; iii) profiling single nuclei by snRNA-seq/snATAC-seq; iv) preparing tissues for two complementary, leading-edge

	methods for spatial transcriptomics (Visium) and transcript imaging (MERFISH). We will iterate the protocols to optimize cell viability and yield, technical quality metrics specific to each technology and the representation of all cell types. In year 2, we will run the full set of scaled- up technology pipelines using ~50 samples per tissue type, and will assess data quality, site and batch effects and technical artifacts to inform potential modifications for the single-cell pipeline. In Years 3-5, we will profile the remaining ~1000 biopsies and ~1000 blood samples collected by the disease teams. We will develop a computational pipeline for data pre-processing, primary biological analysis and quality metrics (including technical and biological parameters at the scale of genes, cells and tissues) with customized features for each tissue and disease. Our findings will be rapidly communicated within our Technology Core and across the Network to the Disease Teams, Systems Biology Core, network committees overseeing the project, NIH, FNIH and our industry and non-profit partners. We will also respond in real time to advancing changes in technologies and work with the network to pilot and scale up critical methods. The result of the proposed studies will be a set of multi-dimensional datasets that will be shared with the network and the larger community, and provide a basis for cutting edge disease deconstruction and reconstruction across autoimmune end organ pathologies and thus fulfill the vision of AMP-AIM.
Overlap	None

Pending- Broad Institute, Inc.

Title:	PREcision Medicine through IntErrogation of Rna in the kidney (PREMIERE) (Renewal)
Effort:	0.60 (cal)
Supporting Agency	NIH (Kretzler, Hodgin) 2U01DK114907-06
Grants Officer	N/A
Performance Period	07/2022-06/2027
Funding Amount	(Total Costs)
Project Goals	We will develop methods for single cell RNA-seq and in situ hybridization in the human kidney.
Overlap	None

Title:	Dissecting the heterogeneity and function of myeloid cells in lupus nephritis.
Effort:	0.12 (cal)
Supporting Agency	NIH (Davidson)
Grants Officer	N/A
Performance Period	12/2022-11/2027
Funding Amount	(Total Costs)
Project Goals	We will generate and apply CRISPR libraries to target factors controlling macrophage differentiation in mice.
Overlap	None

Active - Massachusetts General Hospital

Title:	An integrated translational approach to overcome drug resistance
Effort:	0.60 (cal)
Supporting Agency	NIH/NCI, U54CA224068 (Corcoran, Flaherty)
Grants Officer	Laurence Doyle 8560 PROGRESS DRIVE FREDERICK MD 21701 doylela@mail.nih.gov
Performance Period	09/30/2017-08/31/2023 (NCE)
Funding Amount	(total costs)
Project Goals	The goal of this project is to define the landscape of acquired mechanisms of resistance to MET inhibition and explore therapeutic strategies to overcome these.
Specific Aims	Drug resistance represents one of the most critical obstacles to clinical benefit for cancer patients. Due to the size and complexity of this challenge, we believe a collaborative team approach is critical and have assembled a team of drug resistance experts from three leading institutions (MGH, the Broad Institute, and MIT/Koch Institute) with an exceptional track record of impactful discoveries in this field. We propose an integrated full-spectrum translational platform—including liquid biopsy, patient-derived tumor models, exome and transcriptome sequencing of tumor tissue, rapid autopsy, functional genomic screens, innovative preclinical mouse models, and a high-throughput combination drug-screening platform covering the CTEP portfolio—to address critical principles of drug resistance across several major cancer types—lung, melanoma and GI cancers, which impact a large percentage of cancer patients. Overall, these three projects will focus on the common theme of bypass resistance mechanisms, a critical and frequent mechanism of therapeutic resistance that can involve both genetic and adaptive resistance mechanisms that “bypass” the effects of therapy, and which can drive both intrinsic and acquired resistance. To maximize the potential impact on cancer patients we will focus projects on three major tumor types—lung, melanoma and GI cancers—with each project integrating at least two tumor types. We will focus our projects on defining and overcoming key bypass resistance mechanisms to three of the most critical classes of cancer therapeutics: MAPK inhibitors, RTK inhibitors, and immune checkpoint inhibitors. While each project will focus on a specific therapy and at least two specific cancer types, we believe the overall program design can be readily applied to additional agents and molecularly-defined cancers, such that the ultimate impact of this work will go beyond the specific studies proposed and will serve as a “blueprint” for critical discoveries related to drug resistance. We anticipate that these efforts will define a new standard in our mechanistic understanding of bypass resistance mechanisms and will lead to novel opportunities to overcome them in the clinic. Our proposed approach will provide a steady stream of novel therapeutic strategies involving CTEP agents and pathways for evaluation in future clinical trials, as well as new potential agents for the CTEP portfolio. We have also integrated cutting-edge strategies for real-time blood-based monitoring of response and resistance to help guide innovative trial design.
Overlap	None

Title:	Abbreviated targeted therapy to improve anti-PD-1 inhibitor efficacy in melanoma
Effort:	0.24 (cal)

Supporting Agency	NIH/NCI, R01CA229851 (Sullivan, Sharpe)
Grants Officer	Min-Kyung Song 9609 MEDICAL CENTER DR ROCKVILLE MD 20850 min.song@nih.gov
Performance Period	05/17/2018 – 04/30/2023
Funding Amount	(total costs)
Project Goals	This project will determine the effectiveness of abbreviated mitogen activated protein kinase (MAPK)-targeted (MTT) therapy combined with anti-PD-1 therapy, identify patients most likely to benefit, determine the effects of this therapy on the tumor microenvironment and immune memory subsets, and identify novel candidate targets to combine with MTT and anti-PD1, based on an in vivo CRISPR screens in melanoma mouse models.
Specific Aims	Mitogen activated protein kinase (MAPK)-targeted therapy (MTT) currently is approved for treating metastatic melanoma patients with tumors harboring an oncogenic mutation in BRAF. Anti-PD-1 antibodies are the standard front-line approach for patients with metastatic melanoma, regardless of genotype, but responses only are seen in 40-45% of patients. To improve outcomes with MTT and anti-PD1, more effective approaches are needed. We recently demonstrated that MTT leads to increased tumor infiltrating lymphocyte (TIL) number, clonality, and effector function, as well as increased immune exhaustion markers such as PD-1, its ligand PD- L1, and TIM3. We hypothesize that these MTT-associated tumor microenvironment changes enhance immune responses in the tumor microenvironment and have the potential to convert an immunologically non-responsive tumor microenvironment into one more responsive to subsequent anti-PD1 therapy. To test our hypothesis, we have opened a trial (NCT031429029) that incorporates a lead-in phase of MTT, a brief period of concomitant MTT and anti-PD-1 therapy with pembrolizumab (pembro), followed by single-agent pembro (Aim 1). We will investigate the clinical benefit rate (CBR) of abbreviated MTT in combination with pembro and determine if MTT-associated effects on the tumor-immune microenvironment are associated with improved CBR at 24 weeks. As part of the trial, serial biopsies (pretreatment, post-MTT lead-in, and on-MTT plus pembro) and peripheral blood will be collected, and our team of clinical, translational, and basic investigators will use these samples to identify biomarkers associated with response and to develop a mechanistic understanding of the effects of MTT alone and in combination with anti-PD-1 antibody therapy on the tumor microenvironment. We also will evaluate the effects of anti-PD-1 and MTT on T cell responses in a GEMM melanoma model and in patients (Aim 2). We will analyze T cell subsets in the mouse melanoma model, assessing the generation of memory T cells in mice that control tumors using tumor rechallenge studies. We will characterize T cell responses in the patients enrolled in the clinical trial in Aim 1, focusing on features of effector, memory, and exhausted T cell subsets. Lastly, we will examine memory populations in melanoma patients who are long- term survivors after treatment with immune checkpoint inhibitors or MTT. Finally, we will pair these translational studies with a complementary mouse melanoma model to determine how this therapy affects the generation, function and maintenance of T cell subsets, and identify new potential therapeutic strategies using in vivo CRISPR screens of mouse melanoma cells. (Aim 3)
Overlap	None

Title:	Developing new Immunotherapies to Enhance CDB+ Tell Cell Killing of Tumors Using Human Melanoma Explants
Effort:	0.6 (cal)
Supporting Agency	V Foundation - T2019-003
Grants Officer	N/A
Performance Period	11/01/2019 – 11/01/2022
Funding Amount	(total costs)
Project Goals	The goal of the project is to enhancer T cell killing of tumors in a human ex vivo melanoma system.
Specific Aims	Aim 1: Harnessing the immune system to treat CRC. Subaims: A. Establish key correlations between genomic features and immune response in CRC. B. Define the molecular determinants of response and resistance to PD-1 inhibition in CRC. C. Develop strategies to enhance the immunogenicity of “cold” immune CRC tumors. D. Conduct clinical trials and correlative studies of novel immune-based strategies for CRC. Aim 2: Optimizing and integrating targeted therapies with immunotherapies in CRC. Subaims: A. Define critical adaptive feedback networks in CRCs with RAS/RAF pathway mutations. B. Evaluate optimized strategies to target RAS/RAF signaling in preclinical patient-derived models. C. Model the effects of targeted therapies on the immune response in CRC. D. Perform clinical trials and correlative studies of new targeted and immune combinations for CRC. Aim 3: Integrating targeted and immune strategies for “precision adjuvant” therapy in CRC. Subaims: A. Evaluate potential adjuvant immune and targeted combinations in preclinical mouse models. B. Perform a ctDNA-guided, genotype-directed “precision adjuvant” trial for Stage III CRC. C. Conduct correlative studies to define predictors of sensitivity to “precision adjuvant” therapy.
Overlap	None

Title:	Mechanisms of Immunity in Human Melanoma
Effort:	0.72 (cal)
Supporting Agency	Adelson Medical Research Foundation
Grants Officer	Steven Garfinkel 300 1st Avenue, Needham, MA 02494
Performance Period	10/2019-09/2023
Funding Amount	(annual total costs)
Project Goals	Our goal is to identify and study mechanisms of melanoma immunity based on patient samples.
Specific Aims	N/A
Overlap	None

Title:	Tumor immunity in response to radiation and checkpoint therapy
Effort:	0.12 (cal)
Supporting Agency	Bristol Myers Squibb, 2020A008293
Grants Officer	N/A

Performance Period	02/05/2021 - 02/04/2024
Funding Amount	
Project Goals	The goal is to study how radiation and anti-PD1 therapy interact to induce immune responses in patients pancreatic adenocarcinoma.
Overlap	None

Title:	Radiation-Induced Lymphopenia: Understanding, Predictive Modeling and Developing Photon and Proton-Based Mitigation Strategies.
Effort:	0.60 (cal)
Supporting Agency	NIH/NIAD, P01CA261669 (Grassberger, Clemens)
Grants Officer	N/A
Performance Period	09/01/2021 -08/31/2026
Funding Amount	(Total Costs)
Project Goals	The goal is to understand how radiation affects T cell survival and repertoire in cancer patients.
Overlap	None

Title:	Single-cell genomic profiling to identify immune signatures of bacterial sepsis in humans
Effort:	0.55 (cal)
Supporting Agency	NIH, R01AI153142 (Goldberg)
Grants Officer	Michael Minnicozzi minnicozzim@niaid.nih.gov
Performance Period	04/01/2021 – 03/31/2026
Funding Amount	(total costs)
Project Goals	The goals of this project are to use single-cell transcriptional profiling to identify human signatures that discriminate sepsis from non-infectious organ dysfunction and investigate the underlying mechanisms of immune dysregulation in sepsis.
Specific Aims	Aim 1. Discover blood single-cell transcriptional signatures that discriminate sepsis from non-infectious organ dysfunction, define unbiased molecular endotypes and associate with clinical outcomes. Aim 2: Identify cell surface markers associated with scRNA-seq-defined cell states, including MS1, that are significantly expanded in sepsis. Aim 3: Define alterations in cellular functions in patients and mice with sepsis and in response to sepsis-induced MS1 cells.
Overlap	None

Title:	High resolution definition of the pathogenic immune response in ARDS during COVID-19 infection
Effort:	0.30 (cal)
Supporting Agency	American Lung Association - ETRA 736415 (Goldberg)
Grants Officer	
Performance Period	07/2020- 12/2022 (NCE)

Funding Amount	(total costs)
Project Goals	We will study the changes in immune responses in COVID-19 infection.
Specific Aims	N/A
Overlap	None

Title:	Single-cell genomics dissection of common immune networks driving autoimmunity
Effort:	0.24 (cal)
Supporting Agency	Juvenile Diabetes Research Fnd Int - 2-SRA-2021-1044-S-B (Villani)
Grants Officer	N/A
Performance Period	01/01/2021 – 12/31/2022
Funding Amount	(total costs)
Project Goals	We will single cell profile blood immune cells from multiple autoimmune diseases and compare to profiles of tissue-derived immune cells.
Specific Aims	N/A
Overlap	None

Title:	Spatially organized multicellular immune hubs in human colorectal cancer
Effort:	0.60 (cal)
Supporting Agency	MGH ECOR Martin Prize
Grants Officer	
Performance Period	04/2022 - 03/2023
Funding Amount	(total costs)
Project Goals	N/A
Specific Aims	N/A
Overlap	None

Pending - Massachusetts General Hospital

Title:	A microscope for ultra-high multiplex spatial imaging of transcripts and proteins in tissues
Effort:	0.00 (cal)
Supporting Agency	MGH
Grants Officer	N/A
Performance Period	02/2023 - 01/2024

Funding Amount	(total costs)
Project Goals	One of our major goals is to dissect spatially resolved transcriptional programs in the placenta. We have applied scRNA-seq and scATAC-seq to discover cell types, states, gene programs in samples from mouse and human.
Specific Aims	N/A
Overlap	None

In-Kind

Title:	"Role of myeloid cells in lupus kidney disease," Paul Hoover, Investigator Award
Effort:	6.72 (cal)
Supporting Agency	Rheumatology Research Foundation
Grants Officer	Damien Smalls Director, Awards and Grants DSmalls@rheumatology.org
Performance Period	10/2019-10/2022
Estimated In-Kind Dollar Value	(total costs)
Project Goals	N/A
Specific Aims	N/A
Overlap	None

Title:	Cancer Research Institute Fellowship, Marc Schwartz, Postdoc
Effort:	12.0 (cal)
Supporting Agency	Cancer Research Institute
Grants Officer	**Ryan Godfrey** Senior Manager, Research Programs Cancer Research Institute 29 Broadway, Floor 4 New York, NY 10006-3111 Tel. www.cancerresearch.org
Performance Period	07/2021-06/2024
Estimated In-Kind Dollar Value	(total costs)
Project Goals	N/A

Specific Aims	N/A
Overlap	None

Title:	Cancer Research Institute Fellowship, Matteo Gentili, Postdoc
Effort:	12.0 (cal)
Supporting Agency	Cancer Research Institute
Grants Officer	**Ryan Godfrey** Senior Manager, Research Programs Cancer Research Institute 29 Broadway, Floor 4 New York, NY 10006-3111 Tel. www.cancerresearch.org
Performance Period	08/2020-07/2023
Estimated In-Kind Dollar Value	(total costs)
Project Goals	N/A
Specific Aims	N/A
Overlap	None

Title:	Cancer Research Institute Fellowship, Rebecca Holden, Postdoc
Effort:	12.0 (cal)
Supporting Agency	Cancer Research Institute
Grants Officer	**Ryan Godfrey** Senior Manager, Research Programs Cancer Research Institute 29 Broadway, Floor 4 New York, NY 10006-3111 Tel. www.cancerresearch.org
Performance Period	11/2020-09/2023
Estimated In-Kind Dollar Value	(total costs)
Project Goals	N/A
Specific Aims	N/A
Overlap	None

Title:	NSF GRFP Fellowship, Rebecca Carlson, Graduate Student

Effort:	4.50 (cal)
Supporting Agency	National Science Foundation
Grants Officer	
Performance Period	09/2018-08/2023
Estimated In-Kind Dollar Value	total costs)
Project Goals	N/A
Specific Aims	N/A
Overlap	None