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**14. ABSTRACT**
Type I (IFN-α) and type II (IFN-γ) interferons are important mediators of autoimmunity. Our group recently showed a strong association of IFN-γ receptor 1 (*Ifngr1*) expression and of IFN-γ receptor 2 (*Ifngr2*) expression in peripheral blood mononuclear cells (PBMC) with the presence of RA and its radiographic severity, respectively (*Arthritis Rheumatol*. 2015 67:1165). IL-2 has essential regulatory function in inflammatory diseases and is considered as a potential therapy for autoimmune disease. We tested the hypothesis that RA is associated with alterations in IFN-γ and IL-2 STAT signaling within certain subsets of PBMCs. We used a high-definition phospho-flow approach to evaluate the activation of STAT1, STAT3 and STAT5 after IFN-γ or IL-2 stimulation. We analyzed PBMCs from 37 RA patients and 12 healthy controls (HC) for activation of STATs in specific CD4 and CD8 T cells subpopulations, B cells and monocytes. We found that IFN-γ induced STAT1 activation was significantly greater in RA naïve, central memory, Tfh and Treg subsets of CD4+ T cell populations compared to HC ($p<0.05$). IL-2 very efficiently activated STAT5 in all T and B cell populations in RA and HC. The activation of STAT5 in RA was significantly greater than HC in only one population: effector memory CD4 T cells ($p<0.01$). Our studies revealed the presence of a STAT5 phosphatase in RA T cell subsets that likely counteracts IL-2 regulator activity and contribute to the pathogenesis of RA.

**15. SUBJECT TERMS**
Rheumatoid arthritis; Autoimmunity; T lymphocyte subsets; Cell Signaling; Interferon-gamma; STAT1; STAT3; STAT5: Interleukin-2

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## TABLE OF CONTENTS


| | Page No. |
|---|---|
| 1. Introduction | 4 |
| 2. Keywords | 4 |
| 3. Accomplishments | 4 |
| 4. Impact | 14 |
| 5. Changes/Problems | 15 |
| 6. Products | 16 |
| 7. Participants & Other Collaborating Organizations | 18 |
| 8. Special Reporting Requirements | 21 |
| 9. Appendices | N.A. |

## 1. INTRODUCTION:

This project addresses the hypothesis that elevated and/or altered IFN-γ signaling within selective subsets of mononuclear cells promotes disease severity in RA. This study developed from our novel observation that in peripheral blood the expression levels of interferon gamma receptor 1 (IFNGR1) is associated with RA and the expression levels of IFNGR2 correlates significantly with the degree of radiographic damage in RA patients. The aims of this proposal are: (1) To identify the specific circulating cell type in which IFNGR expression is elevated in RA. Using a combination of molecular biological and immunological approaches, we will analyze the expression levels of IFNGR1 and IFNGR2 in monocytes, naïve and memory B cell populations, naïve and memory T cell populations including T-follicular helper cells, Treg cells and T helper effector subpopulations (Th1, Th17 and Th17/1). (2) To determine the outcome of IFNGR signals by assaying the activation of IFN-γ induced STAT1 and changes in activation of STAT3 and STAT5 in RA versus healthy controls, at basal level and following stimulation with cytokines such as IL-2, IL6 etc. (3) To determine the molecular mechanism and outcome of attenuated IL-2 induced activation of STAT5 in specific subpopulations of T cells in RA. The information to be gained can potentially help to identify new cell signaling targets, perhaps cell-type specific, for RA and other autoimmune diseases, and perhaps malignancies. This in turn may help to develop new drugs that are more targeted, either to particular cell types or patients in whom these cell types are most important to the disease. Ultimately, this may lead to more effective, and safer drugs with fewer adverse effects.

## 2. KEYWORDS:

Rheumatoid arthritis; Autoimmunity; T lymphocyte subsets; Cell Signaling; Interferon-gamma; STAT1; STAT3; STAT5: Interleukin-2

## 3. ACCOMPLISHMENTS:

The PI is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction.

**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.*

| Specific Aim 1 (specified in proposal) | Timeline | Status |
|---|---|---|
| **Major Task 1 - To identify the circulating cell types in which IFNGR expression is upregulated in RA and determine how it relates to disease activity.** | Months | **Completed, % complete, or Future Work** |
| Subtask 1 – To recruit 250 participants for Major Tasks 1, 2, and 3. This includes 150 with RA (50 each with low disease activity/remission; moderate disease activity; high disease activity); 50 with multiple sclerosis; 50 healthy controls. Collect data, | Begin Month 4 (after IRB approval); end Month 27 | We have recruited and collected samples from 126 RA (84%), 43 RRMS (86%) and 20 HC (40%). We are on |

| | | |
|---|---|---|
| including disease activity, medications, demographics, etc. | | track to meet objective by month 27. |
| Subtask 2 – Perform FACS and quantitative real-time PCR (qRT-PCR) to measure IFNGR1 and IFNGR2 expression in multiple T cell and B cell populations and monocytes. | Begin Month 4 and proceed in batches; end Month 27 | Strategy for determining IFNGR1 and IFNGR2 expression in 12 samples optimized (see details below). Cell populations from 39 RA, 19 MS and 2 HC have been sorted and RNA prepared. We are on target to complete objective by month 27 |
| Subtask 3 - Assess IFN-γ receptor protein levels in cell subsets (including Th1, Th17, Th17/1, etc.) in RA with different disease activity (remission/low; moderate; high), MS, and controls. | Begin Month 4 and proceed in batches; end Month 27 | These studies have been initiated and will be completed on target. We have developed a refined barcoding approach to facilitate this and other studies for this proposal. See details below. |
| Subtask 4 - We will compare results among patients with RA with different disease activity (remission/low; moderate; high), MS, and controls. | Begin Month 7 and proceed throughout the funding period | Analyses will begin month 27 when enough data on IFNGR expression collected. |
| *Milestone(s) Achieved* | | |
| Local IRB renewed | 3 | 6-5-18 |
| HRPO Approval | 6 | HRPO Log Number A-19648 - approved on August 1, 2016 |
| Present results at scientific meetings | 18, 24 | Two national scientific meetings: ACR 2017, AAI 2018 |
| Publish results in scientific journals | 24, 30 | Manuscripts in preparation |
| **Specific Aim 2 (specified in proposal)** | | |
| **Major Task 2 - To determine the effect of upregulated IFNGR expression on IFN-γ-induced activation of STAT1, STAT3, and STAT5 signaling in peripheral blood cell subsets in RA.** | | |
| Subtask 1 - Compare the level of activation of STATs (as assessed by the degree of phosphorylation) in peripheral blood naïve and memory CD4+ T cells, Th effector populations, | Begin Month 4 and proceed in batches; end Month 27 | This task is ongoing. Preliminary data is presented below. Majority of the data |

| | | |
|---|---|---|
| Treg, naïve and memory B cells, and monocytes at baseline and following stimulation with IFN-γ in RA (n=150) using phospho-flow cytometry. | | collection will be completed by month 27. |
| Subtask 2 - Determine if altered STAT1 (or STAT3 or STAT5) activation leads to differences in nuclear localization of STAT1 (or STAT3 or STAT5) followed by changes in cellular morphology in different mononuclear subpopulations using quantitative image analysis and flow cytometry (Imagestream). | Begin Month 4 and proceed in batches; end Month 27 | This task was delayed to develop the barcoding approach for greater specificity with limited variation. These experiments will be begin and completed by month 30. |
| Subtask 3 - Determine if IFN-γ signals alter the ability of other cytokines (IL-2, GM-CSF, IL-6, IL-23) to activate their respective STATs. | Begin Month 4 and proceed in batches; end Month 27 | This task has been initiated. Analyses will be performed during the next 4 months. |
| Present results at scientific meetings | 18, 24 | Two national scientific meetings: ACR 2017, AAI 2018 |
| Publish results in scientific journals | 24, 30 | Manuscripts in preparation |
| **Specific Aim 3 (specified in proposal)** | | |
| **Major Task 3 - To determine the molecular mechanism and outcome of attenuated IL-2 induced activation of STAT5 in specific subpopulations of T cells in RA.** | | |
| Subtask 1 – Determine whether altered IL-2 mediated activation of STAT5 in subpopulations of T cells in RA contributes to disease pathogenesis. | Begin Month 4 and proceed in batches; end Month 27 | Data from MS (RA comparator group) are shown below. RA and HC data are being analyzed. |
| Subtask 2 – Determine the outcome of attenuated IL-2 mediated activation of STAT5 on Th effector cell and regulatory cell expansion and function. | Begin Month 4 and proceed in batches; end Month 27 | This subtask begun. Initial results indicate that IFN-γ does not attenuate STAT5 signals. However, we find IL2 signals enhance IFN-γ signals in MS. This is being addressed in detail (see details below). |
| Present results at scientific meetings | 18, 24 | Two national scientific meetings: ACR 2017, AAI 2018 |
| Publish results in scientific journals | 24, 30 | Manuscripts in preparation |

**What was accomplished under these goals?**
*For this reporting period describe: 1) major activities; 2) specific objectives; 3) significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative); and/or 4) other achievements. Include a discussion of stated goals not met. Description shall include pertinent data and graphs in sufficient detail to explain any significant results achieved. A succinct description of the methodology used shall be provided. As the project progresses to completion, the emphasis in reporting in this section should shift from reporting activities to reporting accomplishments.*

**1) Major activities**
**I. *Collection of Blood samples from RA, MS (multiple sclerosis) and healthy controls (HC).***
a. Target: 150 RA patients (50 remission/low disease, 50 moderate disease, 50 high disease); collected 126 RA patients.
b. Target: 50 newly diagnosed treatment naïve MS patients; collected peripheral blood cells from 43 MS patients. Three Neurologists, Drs., Bashir, Rinker and Meador provide the heparinized peripheral blood from which peripheral blood mononuclear cells are isolated and cryopreserved.
c. Target: 50 HC; collected 20 HC.

**II. *Recruitment and training of graduate students*:**
Two graduate students, Mr. Vishal Sharma (Ph.D. Immunology program) and Mr. Brandon Pope (MD/Ph.D. program) were recruited in March 2017 for the studies in this proposal. They now have the necessary proficiency in all of the tools necessary for this project. Both of these graduates have completed their qualifying examination and admitted to candidacy. Mr. Sharma has developed a refined barcoding approach that now allows to interrogate signaling pathways in 16 different individuals simultaneously (Fig 1). This approach now enables us to very rapidly and with high precision analyze all patient samples. Mr. Brandon has developed skills for unbiased computational analysis of flow cytometry data using tools such as T-SNE and SPADE (see below). These novel approaches enhance our ability to interrogate our data within the grant period.

**2) Specific objectives.**
***Aim 1. To identify the circulating cell types in which IFNGR expression is upregulated in RA and determine how it relates to disease activity.***
Mr. Vishal Sharma and Mr. Brandon Pope are performing a 12-way sort to obtain the following cell populations: CD4 (naïve, effector, central memory, effector memory), CD8 (naïve, effector, central memory, effector memory), Treg cells, Tfh cells, B cells and monocyte. We have so far sorted 11HC, 24RA and 13 MS. Our sort rate is now 7 individuals in 2.5 hrs to obtain enough cells for definitive quantitation of IFNGR1, IFNGR2, IL2RA, IL2RB, γc and 18S (control). We currently sort 21 patients/controls a week. At this rate we will complete all sorts in 10 weeks and one additional week for all gene expression quantitation. We therefore anticipate data acquisition will be completed by week 26. Data analysis will begin immediately after data acquisition as outlined in the original proposal.

***Aim 2. To determine the effect of upregulated IFNGR expression on IFN-γ-induced activation of STAT1, STAT3, and STAT5 signaling in peripheral blood cell subsets in RA.***

We continue to make the greatest progress in objectives of Aim 2. We have developed a refined fluorescent barcoding approach (described in greater detail below) that now allows to interrogate the activation of STAT1, STAT3 and STAT5 induced by IFN-γ in sixteen samples simultaneously. This also enable mixing of RA and controls (MS and HC) to overcome any variability in staining. To determine if activation of STATS leads to translocation to nucleus, we will use the ImageStream. These experiments are underway.

***Aim 3. To determine the molecular mechanism and outcome of attenuated IL-2 induced activation of STAT5 in specific subpopulations of T cells in RA.***

We have analyzed IL-2 induced STAT5 activation in 17 RA patients and 10 HC. We initially observed enhanced IL-2 induced STAT5 activation only in RA effector memory CD4 T cells compared to HC. The expected result was enhanced IL-2 induced activation of STAT5 in RA Treg cells and Tfh cells, as regulatory feedback to disease. We therefore hypothesized that a phosphatase in RA T cells dephosphorylates active STAT5 (phospho-STAT5). To test for this, PBMC were pretreated with phosphatase inhibitors before stimulation with IL-2. Remarkably, our results reveal the existence of a phosphatase that selectively acts on p-STAT5 in RA T cells.

**3) Significant results or key outcomes, including major findings, developments, or conclusions (both positive and negative)**

Aim 1. The main objective of this Aim is to determine the expression of IFNGR1 and IFNGR2 in different cell subpopulations from RA, MS and HC. The expression of the receptors will be compared to disease activity and activation of STATs (Aim 2). We have optimized an approach that allows us to efficiently sort 12 different mononuclear cell populations with high purity from each individual at a rate of 22 minutes sort time per patient/control. We have further optimized our ability to detect IFNGR gene expression in as few as 200 cells by qRT PCR. Development of this throughput is necessary for meeting the objective of this task in a timely manner. Based on our ability to sort 21 patient/controls per week, we expect to complete data acquisition for this Aim in three months.

Aim 2. *Fluorescent cell barcoding*: Based on our preliminary findings, we identified a potential concern, namely variability in staining between samples when a large number of samples are stained in the same experiment. This was specifically a concern since our staining strategy involved up 16 different fluorescent parameters to simultaneously interrogate the activation of STATs multiple cell populations. To overcome this issue, we refined a fluorescent barcoding approach originally developed by Nolan and colleagues (Stanford University). The original approach reported by Nolan's group required "harsh" denaturing conditions for barcode labeling and resulted in loss of many epitopes recognized by cell surface marking antibodies. We refined the technique such that epitopes are not affected allowing for unrestricted multi-dimensional flow cytometry. In this strategy, PBMC stimulated or unstimulated with IFN-γ, are labelled with different concentrations of amine reactive brilliant violet (BV) 450 and/or BV500 (BD Biosciences) (Fig. 1). A diagrammatic representation of the flow cytometry plot of such labeling is shown in the upper left corner of Fig 1. In the plot each circle represents cells from a different individual. An actual experiment is also depicted in Fig 1. Each cluster in the dot plot labeled "barcode" represents a different sample. To validate the fluorescent barcoding strategy, we stimulated or unstimulated PBMC with IFN-γ from the same individual and determined the

proportion CD4+ T cells and levels of pSTAT1 (Fig. 2). We found that the proportion of CD4+ T cells and activation of STAT1 in each cluster was the same. Similar data was obtained for all epitopes/cell surface markers tested (data not shown). This refined barcoding approach will enable us to interrogate 16 individuals each experiment. All of the planned 300 individuals will be completed in three months.

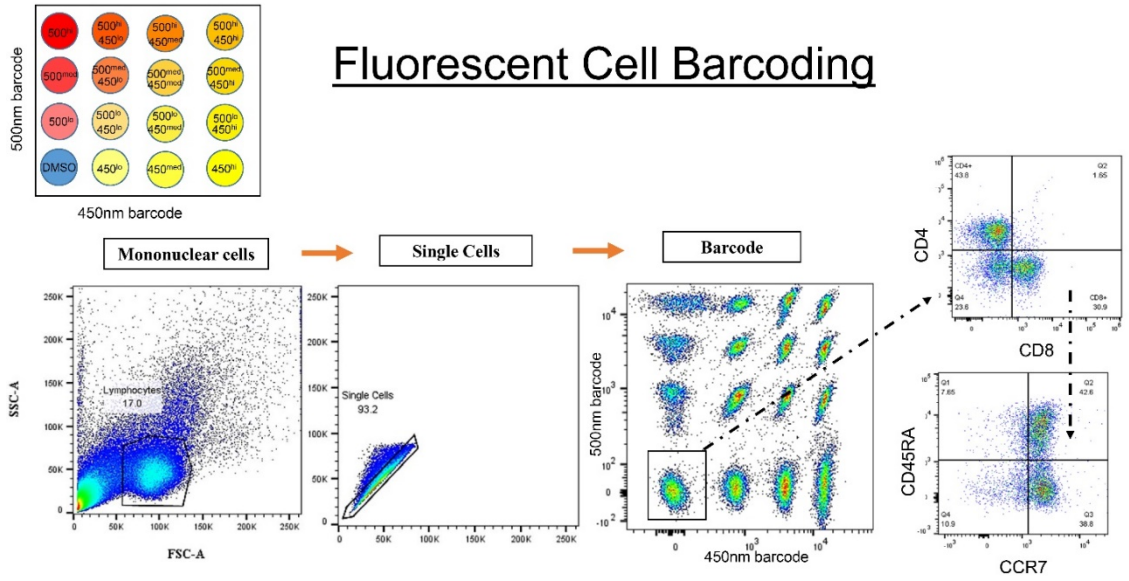


**Fig. 1.** Fluorescent barcoding strategy. PBMCs from 16 different individuals are labeled with different concentrations of amine reactive BV450 and/or BV500 dye. Upper left corner is a diagrammatic representation of flow cytometry dot plot where each circle represents a PBMC sample that can be distinguished from another based on fluorescent intensity of BV450 and/or BV500. The lower panels from left to right represent analysis strategy of an actual pooled sample of barcoded PBMCs.

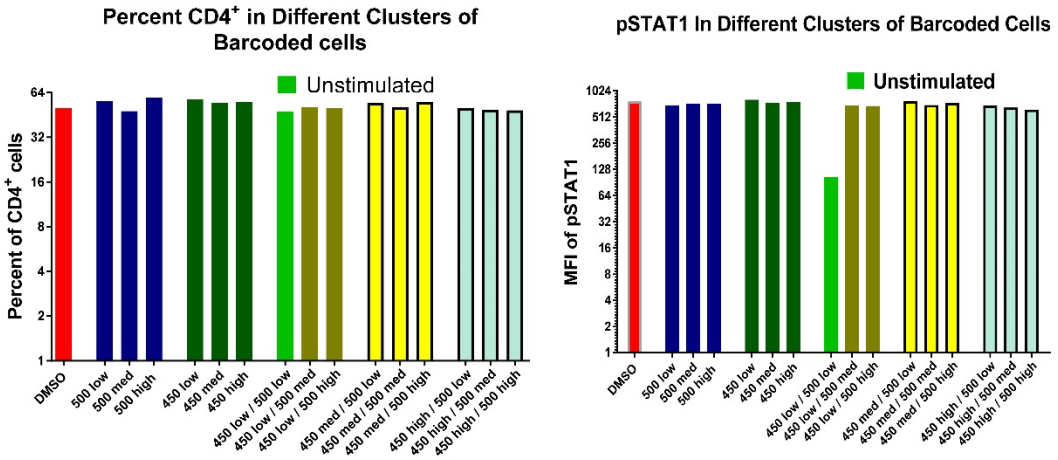


**Fig. 2.** Validation of fluorescent barcoding strategy. PBMCs from a one patient was unstimulated (green) or stimulated (all the rest) with IFN-γ for 15 min and distributed into 16 pools and labeled with barcoding dyes. The proportion of CD4 T cells in each cluster (Fig. 1) is shown in left panel. Right panel shows MFI of pSTAT1 in each cluster. The data shows that each cluster contains equal proportion of CD4 T cells and equal levels of pSTAT1.

*IFN-γ induced activation of STAT1, STAT3 and STAT5.* We interrogated IFN-γ induced activation of STAT1 (pY701), STAT3 (pY705) and STAT5 (pY694) in peripheral blood T cell subpopulations from HC, RA patients of varying severity and newly diagnosed treatment naïve MS patients using phospho-flow cytometry. IFN-γ did not activate STAT3 in any sub-population of T cells, B cells and monocytes (Fig. 4 and data not shown). In RA, IFN-γ induced activation of STAT1 was greatest in remission (CDAI ≤2.8), and lowest in individuals with moderate disease. In fact, in CD4 naïve and central memory T cells, we observe a trend towards increased IFNγ-induced STAT1 activation with decrease in disease severity (Fig. 3). Such differences were not observed in CD8 T cell populations, Tregs and Tfh (Fig. 3 and data not shown). CD4 T cell populations from MS patients had the higher IFN-γ induced STAT1 activation than RA and HC (Fig. 3). Unlike in RA and HC, IFN-γ induced activation of STAT1 in naïve CD8 T cells.

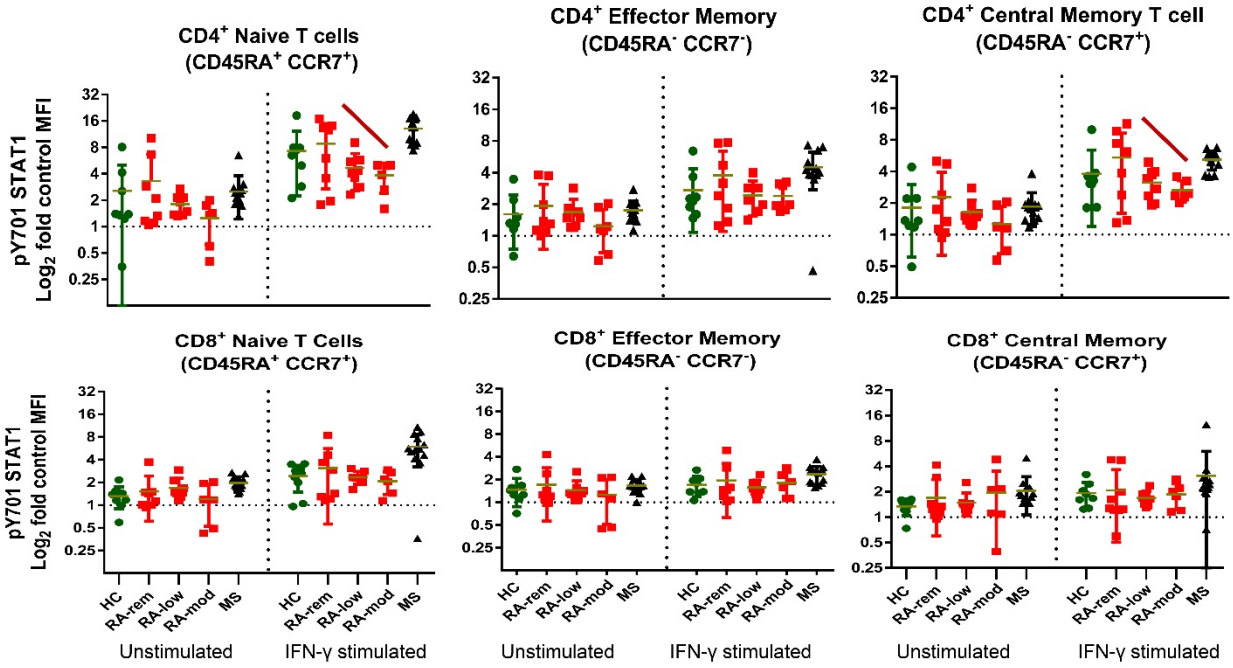


**Fig. 3.** IFN-γ induced STAT1 activation (pY701-STAT1) in RA increases with disease activity in CD4 T cell populations. pY701-STAT1 at basal and following IFN-γ (50 ng/ml) stimulation in naïve CD4 (CD45RA+CCR7+), effector memory CD4 (CD45RA-CCR7-) and central memory CD4 (CD45RA-CCR7+), *upper plots* and naïve CD8 (CD45RA+CCR7+), effector memory CD8 (CD45RA-CCR7-), central memory CD8 (CD45RA-CCr7+), *lower panels.* Data is from healthy controls (HC), remission RA (CDAI≤2.8), low RA (CDAI >2.8≤10), moderate RA (CDAI>10<22) and treatment naïve newly diagnosed MS. Each dot represents an individual patient or control. Data is mean ± 95% confidence interval.

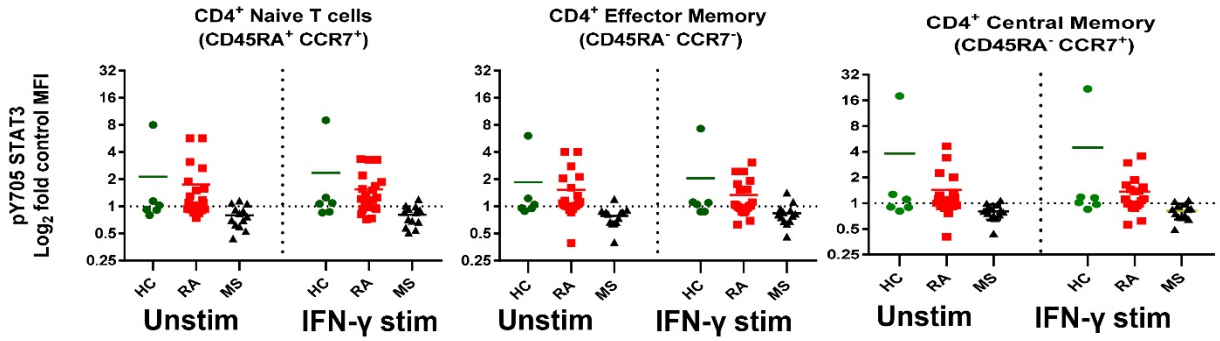


**Fig. 4.** IFN-γ does not induce STAT3 activation in CD4 T cell populations from HC, RA and MS.

A pairwise analysis of pSTAT1 in CD4 T cell populations from RA patients stratified on disease activity was performed between before and after IFN-γ stimulation (Fig 5). The preliminary data reveals greatest heterogeneity in disease remission RA patients. The implication of this finding will be clearer as we complete analysis of all recruited paptients. Overall the data suggest a gain in IFN-γ resposne with decrease in disease severity.

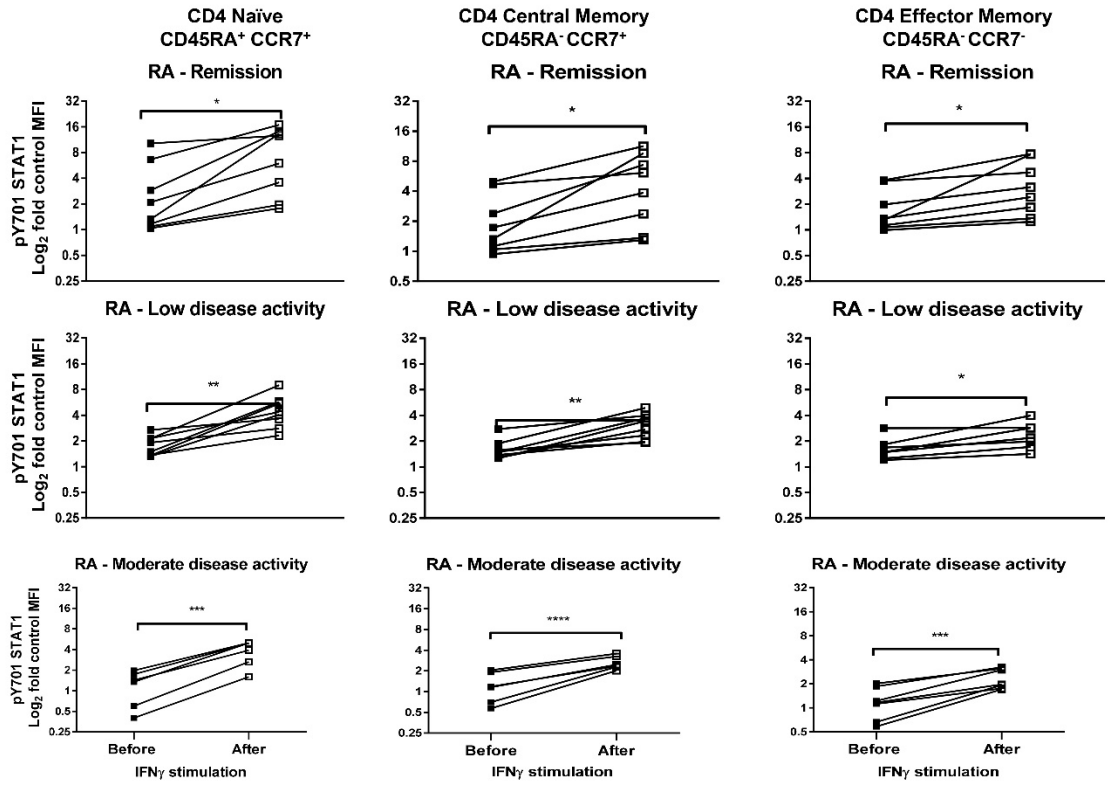


**Fig. 5.** Pairwise analysis of IFN-γ induced STAT1 activation in CD4 T cell populations from RA patients with different disease activity. Data shows that patients in remission show the greatest variation in IFN-γ response. *p<0.05, **p<0.01 and ***p<0.001 based on two-tailed student's T-test.

Aim 3. *IL-2 enhances IFN-γ induced STAT1 activation*: A key goal of Aim 3 is to determine the outcome of co-stimulation IFN-γ and IL-2 with respect to activation of their respective canonical STAT activation pathways. In preliminary data we show that in MS (disease control), co-stimulation of several CD4 T cell populations (naïve, central memory, effector, and effector memory) with IFN-γ and IL-2 enhanced activation of STAT1 to levels greater than that with IFN-γ alone (Fig. 6). Within CD8 T cell populations, this effect of co-stimulation was observed in naïve, central memory and effector T cells. IL-2 alone did not activate STAT1 and IFN-γ did not by itself activate STAT5 (Fig. 5 and data not shown). In addition, we observed no effect of IFN-γ on IL-2 induced STAT5 activation in any T cell population (data not shown). We also observed IL-2 enhanced IFN-γ induced STAT1 activation in Tregs but not in T follicular helper cells (Tfh) (Fig. 7). The data with RA and HC is currently preliminary. If this result persists, the finding suggests a novel mechanism for IL-2 to enhance inflammation and thereby pathogenesis in autoimmunity.

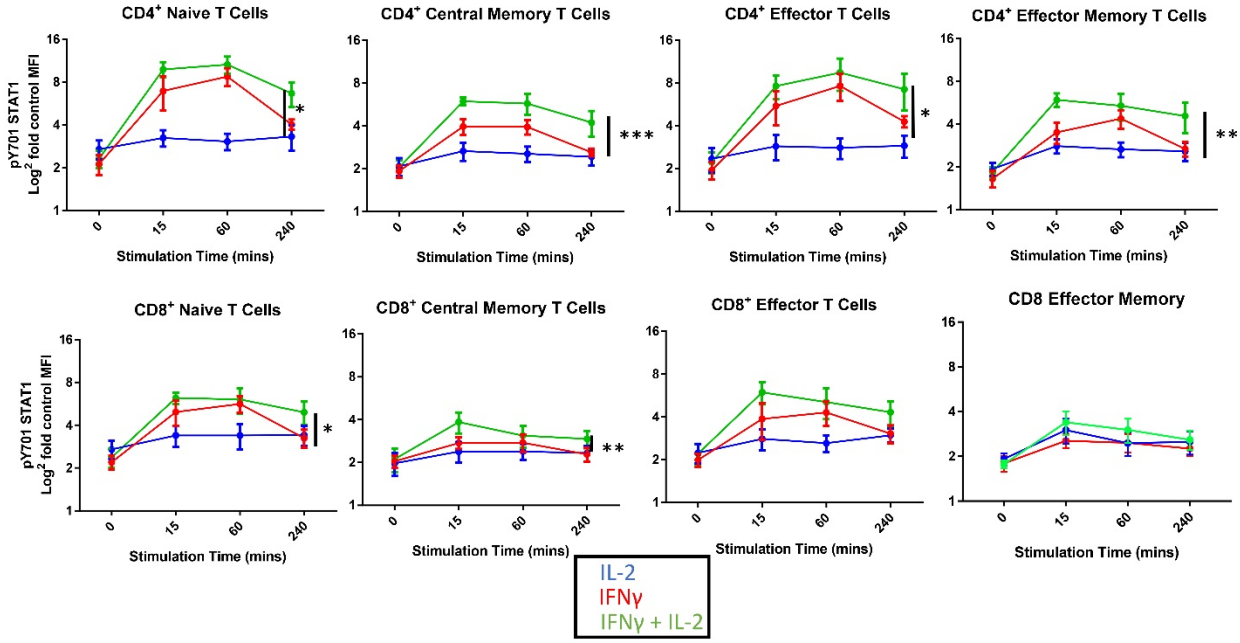


**Fig. 6.** IL-2 enhances IFN-γ induced STAT1 activation in CD4 T cell populations and selected subpopulations of CD8 T cells from treatment naïve RRMS. PBMC were unstimulated or stimulated with IFN-γ (50 ng/ml), IL-2 (10 ng/ml) or both for time points indicated. *p<0.05, **p<0.01 – two way Anova.

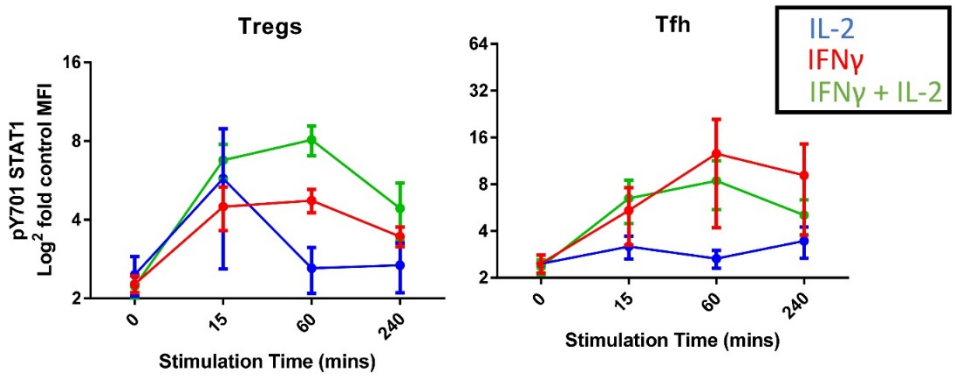


**Fig. 7.** IL-2 enhances IFN-γ induced STAT1 activation in Tregs but not Tfh cells. *Please see Fig 6 for other details.*

**What opportunities for training and professional development has the project provided?**
*If the project was not intended to provide training and professional development opportunities or there is nothing significant to report during this reporting period, state "Nothing to Report."*

*Describe opportunities for training and professional development provided to anyone who worked on the project or anyone who was involved in the activities supported by the project. "Training" activities are those in which individuals with advanced professional skills and experience assist others in attaining greater proficiency. Training activities may include, for example, courses or one-on-one work with a mentor. "Professional development" activities result in increased knowledge or skill in one's area of expertise and may include workshops, conferences, seminars, study groups, and individual study. Include participation in conferences, workshops, and seminars not listed under major activities.*

While this project was not intended to provide training and professional development opportunities, it has been an excellent training vehicle for several learners. This project provided opportunities for training for two PhD students, Vishal Sharma, and Brandon Pope, who each joined the Bridges/Raman group in March 2017 and have each developed significant expertise in techniques required for this project and are generating high quality data. Mr. Sharma is a PhD student in the UAB Immunology theme of the UAB Graduate Biomedical Sciences program, and Mr. Pope is an MD/PhD student in the UAB Medical Scientist Training Program (MD/PhD training program). Mr. Brandon Pope and Mr. Vishal Sharma successfully completed their qualifying examinations in April and June 2018, respectively. These trainees have benefited from mentorship from Drs. Raman and Bridges.

Mr. Sharma and Mr. Pope have been integral parts of the training and educational activities (seminars, lectures, workshops, etc.) of the UAB Division of Clinical Immunology and Rheumatology, and the UAB Comprehensive Arthritis, Musculoskeletal, Bone, and Autoimmunity Center (CAMBAC), one of ~20 university-wide interdisciplinary research centers at UAB. Mr. Sharma and Pope presented their studies at ACR annual meeting (Nov 3-8, 2017, San Diego), American Association of Immunologists annual meeting (May 4-8, 2018, Austin

TX) and the Southeastern Immunology Conference, June 17-18 (UAB, Birmingham). Mr. Pope was awarded a poster award for his abstract at the AAI annual meeting.

**How were the results disseminated to communities of interest?**
*If there is nothing significant to report during this reporting period, state "Nothing to Report."*

*Describe how the results were disseminated to communities of interest. Include any outreach activities that were undertaken to reach members of communities who are not usually aware of these project activities, for the purpose of enhancing public understanding and increasing interest in learning and careers in science, technology, and the humanities.*

Nothing to report

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

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

***Goals***

1. We anticipate meeting the target for patient recruitment, i.e. 150 RA, 50 MS and 50 HC.
2. Aim 1 studies will be completed. This represents two objectives (i) expression of IFNGR1 and IFNGR2 in unstimulated T cell and B cell populations and monocytes and (ii) expression of IFNGR1 and IFNGR2 in CD4 T cells differentiated to Th1, Th17 and Th17/1 (expresses both IFN-γ and IL-17).
3. Complete studies proposed in Aim 2, subtask 1, and 3. The barcoding strategy will allow us to analyze 32 samples (two experiments) per week. For data analysis will use a combination of standard flow cytometric analysis using FlowJo combined with t-SNE and SPADE. This approach offers us the opportunity to analyze the data to determine activation changes in subpopulations of T cells that are present in low frequency.
4. In a subset of patients, we will utilize imaging flow cytometry (ImageStream) to quantitate translocation of activated STATs into the nucleus (objective of Aim 2 – subtask 2).
5. We will interrogate if activation of T cells by IL-2 are affected by IFN-γ stimulation.
6. Experiments to determine outcome of IL-2 induced activation of STAT5 in RA and controls will performed along with IFN-γ stimulation. We therefore expect to analyze majority of the patient samples by end of year 3.
7. Data analysis with the statistical help of Dr. Reynolds (Co-Investigator) will be performed continuously during year 3. We expect to submit three manuscripts for publication during year 3, one of which will be a methods paper describing the barcoding technology.

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

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

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

Nothing to report.

**What was the impact on other disciplines?**
*If there is nothing significant to report during this reporting period, state "Nothing to Report."*

*Describe how the findings, results, or techniques that were developed or improved, or other products from the project made an impact or are likely to make an impact on other disciplines.*

The fluorescent bar coding strategy described above has broad applicability to analysis of relatively large numbers of samples in an efficient manner. Thus, research involving phosphoflow cytometry is likely to be advanced. This applies to the field of immunology and includes host defense, autoimmunity, transplantation, etc.

**What was the impact on technology transfer?**
*If there is nothing significant to report during this reporting period, state "Nothing to Report."*

*Describe ways in which the project made an impact, or is likely to make an impact, on commercial technology or public use, including:*

- *transfer of results to entities in government or industry;*
- *instances where the research has led to the initiation of a start-up company; or*
- *adoption of new practices.*

Nothing to report.

**What was the impact on society beyond science and technology?**
*If there is nothing significant to report during this reporting period, state "Nothing to Report."*

*Describe how results from the project made an impact, or are likely to make an impact, beyond the bounds of science, engineering, and the academic world on areas such as:*

- *improving public knowledge, attitudes, skills, and abilities;*
- *changing behavior, practices, decision making, policies (including regulatory policies), or social actions; or*
- *improving social, economic, civic, or environmental conditions.*

Nothing to report.

5. **CHANGES/PROBLEMS:** The Project Director/Principal Investigator (PD/PI) is reminded that the recipient organization is required to obtain prior written approval from the awarding agency Grants Officer whenever there are significant changes in the project or its direction. If not previously reported in writing, provide the following additional information or state, "Nothing to Report," if applicable:

**Changes in approach and reasons for change**
*Describe any changes in approach during the reporting period and reasons for these changes. Remember that significant changes in objectives and scope require prior approval of the agency.*

There were no significant changes to the approach during this reporting period.

**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.*

Specific Aim 2, Subtask 2 was delayed by ~3 months in order to develop the barcoding approach for greater specificity with limited variation. This approach has now been fully developed (Fig. 1) and we anticipate that this new technique will save significant time for analyses in the future. We anticipate the project to be completed as proposed within the original time frame. There were no other problems or delays encountered during this reporting period.

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

There were no changes during the reporting period that had a significant impact on expenditures.

**Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**
*Describe significant deviations, unexpected outcomes, or changes in approved protocols for the use or care of human subjects, vertebrate animals, biohazards, and/or select agents during the reporting period. If required, were these changes approved by the applicable institution committee (or equivalent) and reported to the agency? Also specify the applicable Institutional Review Board/Institutional Animal Care and Use Committee approval dates.*

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

No significant changes.

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

No significant changes.

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

No significant changes.

**6. PRODUCTS:** List any products resulting from the project during the reporting period. If there is nothing to report under a particular item, state "Nothing to Report."

- **Publications, conference papers, and presentations**
  Report only the major publication(s) resulting from the work under this award.

  **Journal publications.** *List peer-reviewed articles or papers appearing in scientific, technical, or professional journals. Identify for each publication: Author(s); title; journal; volume: year; page numbers; status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

  Nothing to report.

  **Books or other non-periodical, one-time publications.** *Report any book, monograph, dissertation, abstract, or the like published as or in a separate publication, rather than a periodical or series. Include any significant publication in the proceedings of a one-time conference or in the report of a one-time study, commission, or the like. Identify for each one-time publication: Author(s); title; editor; title of collection, if applicable; bibliographic information; year; type of publication (e.g., book, thesis or dissertation); status of publication (published; accepted, awaiting publication; submitted, under review; other); acknowledgement of federal support (yes/no).*

  Nothing to report.

  **Other publications, conference papers, and presentations**. *Identify any other publications, conference papers and/or presentations not reported above. Specify the status of the publication as noted above. List presentations made during the last year (international, national, local societies, military meetings, etc.). Use an asterisk (*) if presentation produced a manuscript.*

  Pope, B. J., Sharma, V, Boland, M, Reynolds, R., Bridges, S.L. Jr., and Raman, C. Enhanced IFN-γ STAT1 signaling in CD4 T cell populations and attenuated IL-2 STAT5 signaling contribute to the pathogenesis of rheumatoid arthritis (RA). *Presented at the annual meeting of the American College of Rheumatology, San Diego, November 3-8, 2017.*

  Pope, B.J., Sharma, V., Boland, M., Meador, W.S., Bridges, S.L. and Raman, C. IL-2 enhances IFNγ signals in subpopulations of T and B lymphocytes from treatment naïve relapsing remitting multiple sclerosis (RRMS) patients. *Presented at the annual meeting of the American Association of Immunologists, Austin, May 4-8, 2018.*

  Sharma, V., Pope, B. J., Boland, M., Reynolds, R., Sun, D., Bridges, S. L. and Raman, C. Enhanced interferon gamma response contributes to disease remission in rheumatoid arthritis. *Presented at the annual meeting of the American Association of Immunologists, Austin, May 4-8, 2018.*

- **Website(s) or other Internet site(s)**
  *List the URL for any Internet site(s) that disseminates the results of the research activities. A short description of each site should be provided. It is not necessary to include the publications already specified above in this section.*

  Nothing to report.

- **Technologies or techniques**
  *Identify technologies or techniques that resulted from the research activities. In addition to a description of the technologies or techniques, describe how they will be shared.*

  Nothing to report.

- **Inventions, patent applications, and/or licenses**
  *Identify inventions, patent applications with date, and/or licenses that have resulted from the research. State whether an application is provisional or non-provisional and indicate the application number. Submission of this information as part of an interim research performance progress report is not a substitute for any other invention reporting required under the terms and conditions of an award.*

  Nothing to report.

- **Other Products**
  *Identify any other reportable outcomes that were developed under this project. Reportable outcomes are defined as a research result that is or relates to a product, scientific advance, or research tool that makes a meaningful contribution toward the understanding, prevention, diagnosis, prognosis, treatment, and/or rehabilitation of a disease, injury or condition, or to improve the quality of life. Examples include:*
  - *data or databases;*
  - *biospecimen collections;*
  - *audio or video products;*
  - *software;*
  - *models;*
  - *educational aids or curricula;*
  - *instruments or equipment;*
  - *research material (e.g., Germplasm; cell lines, DNA probes, animal models);*
  - *clinical interventions;*
  - *new business creation; and*
  - *other.*

  Nothing to report.

## 7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

**What individuals have worked on the project?**

*Provide the following information for: (1) PDs/PIs; and (2) each person who has worked at least one person month per year on the project during the reporting period, regardless of the source of compensation (a person month equals approximately 160 hours of effort). If information is unchanged from a previous submission, provide the name only and indicate "no change."*

| | |
|---|---|
| *Name:* | *S. Louis Bridges, Jr., MD, PhD* |
| *Project Role:* | *Principal Investigator* |
| *Researcher Identifier:* | *ORCID ID: 0000-0003-3785-1389* |
| *Nearest person month worked:* | *1.2 calendar months* |
| *Contribution to Project:* | *Dr. Bridges has provided overall guidance for this project. He leads the effort to identify patients to be enrolled, oversees all studies in Aim 1 and works closely with Dr. Raman on all lab-based studies in the project. He supervises the Laboratory Manager (Mr. Wanzeck) and all non-lab based study personnel. He oversees the collection of clinical data, processing of blood samples, and all data management aspects of the project.* |

| | |
|---|---|
| *Name:* | *Chander Raman, PhD* |
| *Project Role:* | *Co-Investigator* |
| *Nearest person month worked:* | *4.8 calendar months* |
| *Contribution to Project:* | *Dr. Raman is critical to the success of this project. He directs and oversee the functional/mechanistic studies. He directly oversees all lab-based research personnel except for Mr. Wanzeck. Dr. Raman works closely with the PI on all three Aims of this project and is key to data analysis, manuscript preparation and submission.* |

| | |
|---|---|
| *Name:* | *Richard Reynolds, PhD* |
| *Project Role:* | *Co-Investigator* |
| *Nearest person month worked:* | *1.2 calendar months* |
| *Contribution to Project:* | *Dr. Reynolds has provided direct into the study design, overall analysis plan, and statistical analyses for the project.* |

| | |
|---|---|
| *Name:* | *Keith Wanzeck, BS* |
| *Project Role:* | *Laboratory Manager* |
| *Nearest person month worked:* | *1.2 calendar months* |
| *Contribution to Project:* | *Mr. Wanzeck is responsible for coordination of blood draws, and processing and routing of blood samples and biospecimens. He serves as a liaison between Dr. Bridges' lab and Dr. Raman's lab.* |

| | |
|---|---|
| *Name:* | *Stephanie Ledbetter, MS* |

| | |
|---|---|
| *Project Role:* | *Program Manager* |
| *Nearest person month worked:* | *1.2 calendar months* |
| *Contribution to Project:* | *Ms. Ledbetter is responsible for all regulatory issues, including the UAB IRB submissions and renewals, as well as HRPO issues. She also coordinates other aspects of the study such as laboratory meetings, and other logistic issues.* |

| | |
|---|---|
| *Name:* | *Jinyi Wang* |
| *Project Role:* | *Research Associate* |
| *Nearest person month worked:* | *12 calendar months* |
| *Contribution to Project:* | *Ms. Wang is responsible for performing isolation of PBMCs, and plays a large role in all the experiments done in all aims. She helps to guide and supervise the graduate students and other trainees in the lab-based research procedures performed as part of this study.* |

| | |
|---|---|
| *Name:* | *Vishal Sharma* |
| *Project Role:* | *Graduate student* |
| *Nearest person month worked:* | *4 calendar months* |
| *Contribution to Project:* | *As part of his PhD studies, Mr. Sharma is performing dissertation research on this project. He works on performing the assays, data analysis, and presentation of results from this project, and beginning to plan follow up studies.* |

| | |
|---|---|
| *Name:* | *Brandon Pope* |
| *Project Role:* | *MD/PhD student* |
| *Nearest person month worked:* | *4 calendar months* |
| *Contribution to Project:* | *As part of his MD/PhD program, Mr. Pope is performing dissertation research on this project. He works on performing the assays, data analysis, and presentation of results from this project, and beginning to plan follow up studies.* |
| *Funding Support:* | *Medical Scientist Training Program grant* |

**Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**
*If there is nothing significant to report during this reporting period, state "Nothing to Report."*

*If the active support has changed for the PD/PI(s) or senior/key personnel, then describe what the change has been. Changes may occur, for example, if a previously active grant has closed and/or if a previously pending grant is now active. Annotate this information so it is clear what has changed from the previous submission. Submission of other support information is not*

*necessary for pending changes or for changes in the level of effort for active support reported previously. The awarding agency may require prior written approval if a change in active other support significantly impacts the effort on the project that is the subject of the project report.*

See attached Other Support documents for Drs. Bridges, Raman, and Reynolds.

**What other organizations were involved as partners?**
*If there is nothing significant to report during this reporting period, state "Nothing to Report."*

*Describe partner organizations – academic institutions, other nonprofits, industrial or commercial firms, state or local governments, schools or school systems, or other organizations (foreign or domestic) – that were involved with the project. Partner organizations may have provided financial or in-kind support, supplied facilities or equipment, collaborated in the research, exchanged personnel, or otherwise contributed.*
*Provide the following information for each partnership:*

*Organization Name:*
*Location of Organization: (if foreign location list country)*
*Partner's contribution to the project (identify one or more)*

- *Financial support;*
- *In-kind support (e.g., partner makes software, computers, equipment, etc., available to project staff);*
- *Facilities (e.g., project staff use the partner's facilities for project activities);*
- *Collaboration (e.g., partner's staff work with project staff on the project);*
- *Personnel exchanges (e.g., project staff and/or partner's staff use each other's facilities, work at each other's site); and*
- *Other.*

Nothing to report

## 8. SPECIAL REPORTING REQUIREMENTS

### COLLABORATIVE AWARDS:

Not applicable.

### QUAD CHARTS:

Not applicable.

**9. APPENDICES:** Attach all appendices that contain information that supplements, clarifies or supports the text. Examples include original copies of journal articles, reprints of manuscripts and abstracts, a curriculum vitae, patent applications, study questionnaires, and surveys, etc.

None.

**BRIDGES, JR., S. LOUIS**

**Summary of Changes:**
New Active: P50 AR060772 (Saag, PD/PI) Investigations in Gout, Hyperuricemia, and ComorbidiTies (INSIGHT) Center of Research Translation (CORT) - Administrative Core (Saag, Core Director);
ACE Protocol ARA08 (K. Deane, PI)
Changes in Effort: W81XWH-16-1-0537 (Bridges)
New Pending: P30 AR0739755 (Bridges); R01 (Pope); U19 AI142737 (Lund); R01 AI143994 (Bridges and Ippolito); R01 AR0740796 (Reynolds)
Completed: P50 AR060772 Administrative Core and Project 3; Centers of Research Translation (CoRT): Gout and Hyperuricemia: from Bench to Backyard

ACTIVE

W81XWH-16-1-0537 (PI: Bridges, SL Jr.) 09/01/16 - 08/31/19 1.8 CM Dept of Defense Congressionally Directed Medical Research Programs
The Role of the Interferon-Gamma-Jak/STAT Pathway in Rheumatoid Arthritis
To achieve the goal of this proposal, the specific aims are: (1) To identify the specific circulating cell type in which IFNGR expression is elevated in RA. Using a combination of molecular biological and immunological approaches, we will analyze the expression levels of IFNGR1 and IFNGR2 in monocytes, naïve and memory B cell populations, naïve and memory T cell populations including T-follicular helper cells, Treg cells and T helper effector subpopulations (Th1, Th17 and Th17/1). (2) To determine the outcome of IFNGR signals by assaying the activation of IFN-γ induced STAT1 and changes in activation of STAT3 and STAT5 in RA versus healthy controls, at basal level and following stimulation with cytokines such as IL-2, IL6 etc. (3) To determine the molecular mechanism and outcome of attenuated IL-2 induced activation of STAT5 in specific subpopulations of T cells in RA. For this prospective, clinical study, we will analyze PBMCs and clinical data collected from 250 subjects: 150 with RA (50 each with remission/low disease activity; moderate disease activity; high disease activity); 50 with relapsing remitting multiple sclerosis; and 50 healthy controls. We will use cutting edge techniques, including high-resolution phospho-flow cytometry complemented with single cell image analysis of T cell populations and others, to address critical questions on the pathogenesis of RA.

P2C HD086851 (PI: Bamman, MM) 09/17/15 – 06/30/20 0.6 CM NIH/ NICHD
Costs National Resource Center for High-Impact Clinical Trials in Medical Rehabilitation
Role: Member, Executive Committee; Director of the Pilot Studies Component
The P2C National Resource Center for High-Impact Clinical Trials in Medical Rehabilitation (High-Impact Trials Center, HITC) will serve as a catalyst for the design and implementation of rigorous, high-impact clinical trials to advance medical rehabilitation research. Assisting the Director and Associate Directors on Center oversight will be three Executive Committee members: SL Bridges, Jr., MD, PhD, KG Saag, MD, MSc, and DG Standaert, MD, PhD. The central goal of Pilot Component (Pilot-C), directed by Dr. Bridges, is to catalyze the success of medical rehabilitation researchers and interdisciplinary teams by providing consultation, seed funds, key expertise and resources, and ultimately feedback, to medical rehabilitation researchers for the conduct of innovative pilot projects, early-stage proof-of-concept studies, and futility studies needed to shape more definitive clinical trials. The central goal will be met by achieving the following aims: Aim 1. To work closely with the Collab-C, providing consultation to medical rehabilitation research teams on how to: 1) Formulate and refine strong and impactful research questions; 2) Identify the goals and aims needed to achieve future clinical outcome trials. Aim 2. To identify and prioritize the most competitive proposals for both pilot studies and voucher funding via an annual peer review process. Aim 3. To provide expertise, resources, and/or mentorship to selected pilot study awardees with ongoing availability during the planning and implementation phases in order to: 1) Bolster the scientific yield of each pilot study; and 2) Position each awardee for a subsequent, highly competitive clinical trial application. Aim 4. To provide constructive and substantive

feedback to applicants not selected for funding, and to direct those applicants toward other programs and opportunities within the Center that can strengthen future applications. The Pilot-C will award four $40K pilot studies per year.
**NIH/NICHD Grants Management Officer**: Hong Cao, 6100 Executive Blvd, Rm. 8A07F, Bethesda, MD 20892

P30 AR048311 (PI: Mountz, JD) 09/28/01 - 08/31/19 1.2 CM
NIH/NIAMS NCE
Rheumatic Diseases Core Centers: Administrative Core
Role: Associate Director of the RDCC
The overall goal of the UAB-RDCC is to stimulate collaborative and innovative interdisciplinary research in order to enhance our fundamental understanding of disease mechanisms and their application to human rheumatic diseases. Through this understanding, the UAB-RDCC's goal is to improve the diagnosis and treatment of patients with arthritis and musculoskeletal diseases. The strategy of the UAB-RDCC is to draw on the strengths of the UAB research community, including the Hudson Alpha Institute of Biotechnology and Southern Research, to provide essential scientific tools and technologies, to enlist new investigators, to foster the sharing of knowledge and to nurture collaborations among translational and basic science investigators in the fight against rheumatic diseases through the creation and support of a vibrant scientific culture of discovery and innovation. Accordingly, our specific aims are 1) to facilitate rheumatic disease research through Research Core facilities, which provide scientifically rigorous, state-of-the-art techniques necessary for improved understanding of disease pathogenesis and the development of new treatments; 2) to support outstanding Pilot & Feasibility research projects drawing on the unique strengths of the RDCC research base and using innovative tools and approaches in biomedical science; and 3) to provide career development and career enrichment activities to enhance both the mentorship of talented investigators as independent researchers and the continuing education of all of our investigators. To achieve its specific aims, the UAB-RDCC has worked continuously with its Research Core facilities to develop technical capacities, to assess user needs and to provide a variety of formats for outreach and enrichment, including our IDEAs program (individualized design and experimental analyses sessions). The RDCC leadership team has worked to support the continued development of available tools and technologies for rheumatic diseases research, and through these efforts the UAB-RDCC provides the opportunity for investigators to commit their programs to the mission of NIAMS.
**Contracting / Grants Officer**: Su-yau Mao, PhD, maos2@mail.nih.gov, (301) 594-5032, Program Director, Arthritis Biology Program, Division of Skin and Rheumatic Diseases, NIAMS, NIH, DHHS, One Democracy Plaza, 6701 Democracy Blvd., Ste. 800, Bethesda, MD 20892-4872

P60 AR064172 (Contact PI: Bridges, SL Jr.; PI: Saag, KG) 09/16/13 - 07/31/19 2.4 CM
NIH/NIAMS UAB Multidisciplinary Clinical Research Center NCE
The UAB MCRC is a multidisciplinary program uniquely positioned to promote research related to the causes, diagnoses, treatments and improved care of patients with arthritis and musculoskeletal diseases. The MCRC builds on the capabilities of the UAB Comprehensive Arthritis, Musculoskeletal, and Autoimmunity Center (CAMAC) and its thematic workgroups (Experimental Therapeutics & Biomarkers; Neurobehavioral Medicine; Epidemiology, Prevention, & Outcomes; Genetics and Functional Genomics; Immunology, Autoimmunity & Inflammation; Bone, Cartilage and Connective Tissue). An outstanding MCRC Methodology Core is comprised of experts in biostatistics (Redden, Howard, McGwin, Aslibekyan), data management (Westfall), statistical genetics and bioinformatics (Cui, Lefkowitz, Liu) and health services research (Kilgore). All have a proven record of collaborative clinical investigation in musculoskeletal diseases. This proposal includes 2 innovative projects: 1. Facilitating Treat-to-Target Strategies Using Novel Health Technology with Decision Support (Curtis); 2. Adaptive Immune Responses to Gut Microbiota in Juvenile & Adult Spondyloarthritis (Elson). Project 2 focuses on populations for which there is a paucity of clinical research: (juvenile spondyloarthritis). Both projects leverage and expand upon substantial existing resources, including ongoing cohorts. The Administrative Core coordinates MCRC activities, sets the strategic agenda, facilitates interactions and collaborations, promotes scientific development, and performs evaluation of MCRC programs. Four advisory groups have been established to assist the MCRC Director and Associate Director in maximizing the strengths

of the MCRC's projects, as well as in identifying and correcting weaknesses: 1. Executive Committee; 2. Internal Advisory Committee; 3. External Advisory Committee; 4. Data Safety Monitoring Committee. The Scientific Development Program, which promotes the introduction and development of new techniques and nurtures young and new faculty in arthritis and musculoskeletal disease research, ensures the continued energy and vitality of this MCRC.
**Contracting / Grants Officer**: Yan Z. Wang, MD, PhD, wangy1@mail.nih.gov, (301) 594-5032, Rheumatic Diseases Genetics and Translational Research Program, Division of Skin and Rheumatic Diseases, NIAMS, NIH, DHHS, One Democracy Plaza, 6701 Democracy Blvd., Ste. 800, Bethesda, MD 20892-4872

R01 HD084124 (Contact PI: Bamman, MM; PI: Bridges, SL Jr.) 04/15/15-03/31/20 1.65 CM NIH/ NIA

Role: Multiple PI
Overcoming TWEAK Signaling to Restore Muscle and Mobility after Joint Replacement
Elective total hip (THA) and knee (TKA) arthroplasty relieve pain and improve mobility function for osteoarthritis (OA), up to 35% of patients endure persistent muscle atrophy and mobility limitations that impact quality of life, increase morbidity, and burden the healthcare system. Our preliminary findings in THA/TKA patients strongly suggest the TNF-like weak inducer of apoptosis (TWEAK) signaling pathway may be central to muscle inflammation susceptibility (MuIS) and impaired THA/TKA recovery. These findings raise the hypothesis that progressive resistance exercise training plus adjunctive functional mobility training (PRT+FM) after THA/TKA will more effectively restore muscle mass and mobility function to healthy standards than usual care and, because MuIS(+) are predicted to suffer failed muscle recovery and persistent dismobility under usual care, the impact of PRT+FM will be greatest in MuIS(+). We will test this hypothesis in a randomized controlled trial of 88 THA/TKA patients with the following aims: 1: To determine the effects of 16 wk of PRT+FM vs. usual care after elective THA/TKA on muscle mass, performance, and mobility function. 2: To determine whether MuIS status modifies the effects of PRT+FM or usual care after THA/TKA. Cellular and molecular mechanisms of muscle mass regulation will be studied in detail. 3. To determine the long-term impact of 16 wk PRT+FM by re- assessing outcomes at 6 mo and 1 year.
**Contracting / Grants Officer**: Susan F. Marden, mardens@mail.nih.gov, (301) 435-6838, NICHD, Nation Center for Medical Rehabilitation Research, 6710B Rockledge Drive, Room 2161C, MSC 7002
Bethesda, MD 20817

UM1 AR065705 (PI: Curtis, JR) 09/01/14 - 08/30/19 0.24 CM NIH/ NIAMS
Safety and Effectiveness of Live Zoster Vaccine in Anti-TNF Users (VERVE)
Role: Investigator
Herpes zoster (HZ) risk is elevated by various states of immunosuppression including rheumatoid arthritis (RA), so prevention of HZ in this setting has major potential public health impact. A live attenuated vaccine (Zostavax®) reduces HZ morbidity by nearly 70%, but it is contraindicated in patients receiving some immunosuppressive medications such as biologic therapies. This is due to theoretical concern that these individuals could develop local or disseminated varicella infection from the vaccine-strain virus, but there are no published data to suggest that these safety concerns are warranted, and a growing body of observational data suggest that vaccinating such patients might be safe. We will conduct the Varicella zostER VaccinE (VERVE) trial, a randomized, double-blind, placebo-controlled large pragmatic trial to evaluate the immunogenicity, safety, and longer-term effectiveness of the live HZ vaccine in arthritis patients receiving anti- TNF therapy.
**Contracting / Grants Officer**: James Witter, MD, PhD, witterj@mail.nih.gov, (301) 594-5032, Rheumatic Diseases Clinical Program, Division of Skin and Rheumatic Diseases, NIAMS, NIH, DHHS, One Democracy Plaza, 6701 Democracy Boulevard, Suite 800, Bethesda, MD 20892-4872
T32 AR069516 (PI: Bridges, SL Jr.) 05/01/16 - 04/30/21 0.24 CM NIH/NIAMS
Training Program in Rheumatic and Musculoskeletal Diseases Research

The UAB Training Program in Rheumatic and Musculoskeletal Disease Research builds on established strengths in adult and pediatric rheumatology, immunology, musculoskeletal medicine, and clinical/translational investigation. To provide a vibrant and effective interdisciplinary training environment, this program brings together the Divisions of Clinical Immunology and Rheumatology and Pediatric Rheumatology, the Comprehensive Arthritis, Musculoskeletal, Bone, and Autoimmunity Center (CAMBAC), and the Center for Outcomes and Effectiveness Research and Education (COERE). This training program also builds on trans-departmental initiatives in autoimmunity and inflammation, genetics, and state of the art translational clinical and outcomes research. The members of the UAB training faculty are fully committed to continuing to provide mentorship, support, and guidance to young investigators to help them develop the tools and skills necessary to advance the diagnosis, treatment, and prevention of rheumatic and musculoskeletal diseases.
**Contracting / Grants Officer**: Su-yau Mao, PhD, maos2@mail.nih.gov, (301) 594-5032, Program Director, Arthritis Biology Program, Division of Skin and Rheumatic Diseases, NIAMS, NIH, DHHS, One Democracy Plaza, 6701 Democracy Blvd., Ste. 800, Bethesda, MD 20892-4872

P50 AR060772 (Saag, PD/PI) 08/01/17 – 07/31/22 1.2 CM NIH/ NIAMS

Investigations in Gout, Hyperuricemia, and ComorbidiTies (INSIGHT) Center of Research Translation (CORT) - Administrative Core (Saag, Core Director)
Our INSIGHT CORT includes 4 research projects and an Administrative Core focused on the theme, “Gout, Hyperuricemia, and Associated Comorbidities”. This CORT aims to: (1) Conduct four outstanding, innovative, and synergistic translational research projects drawing on the unique strengths of multidisciplinary research teams at our three major centers: University of Alabama at Birmingham, Harvard University, and University of California San Diego. (2) Foster the development of pilot and feasibility projects and the development and application of new translational methods to research in gout and hyperuricemia and their associated major comorbidities, particularly chronic kidney disease and metabolic syndrome. (3) Promote training of translational investigators in current methods of research applicable to gout and hyperuricemia through enrichment activities overseen by our Administrative Core. CORT projects will include studies to: determine if innovative peripheral blood leukocyte adenosine monophosphate-activated protein kinase (AMPK) activity metabolomics have promise as gout flare biomarkers independent of serum urate (Project 1), examine the influence of key gene-environment interactions within an internet case-crossover study of gout flares (Project 2), unravel the functional genomics of urate transporters genes identified in previously reported genome wide association studies (Project 3), and investigate the mechanism of urate lowering therapy on renal function within the soon to begin comparative study of gout therapies (VA STOP-GOUT) (Project 4).
**Contracting / Grants Officer**: James Witter, MD, PhD, witterj@mail.nih.gov, (301) 594-5032, Rheumatic Diseases Clinical Program, Division of Skin and Rheumatic Diseases, NIAMS, NIH, DHHS, One Democracy Plaza, 6701 Democracy Boulevard, Suite 800, Bethesda, MD 20892-4872

ACE Protocol ARA08 (K. Deane, PI) 02/01/15 - 11/30/19 0.42 CM NIH/ NIAID/UCSF
Strategy to Prevent the Onset of Clinically-Apparent Rheumatoid Arthritis (StopRA)
The primary objective is to determine the efficacy of a 12-month course of hydroxychloroquine (HCQ) to prevent the development of clinically-apparent rheumatoid arthritis (RA). Primary objective at 36 months in subjects at high-risk for future RA due to high titer elevations of anti-cyclic citrullinated peptide-3 (anti-CCP3) (>40 units) but who are without history or clinical findings of inflammatory arthritis (IA) at Baseline
Role: Recruitment Site PI

PENDING
P30 AR073755 (Bridges) 07/01/18 – 06/30/23 1.8 CM

NIH/NIAMS
UAB Translational Research Center for Rheumatic Diseases
The overall objective of the UAB Translational Research Center for Rheumatic Diseases is to stimulate innovative interdisciplinary research to make important discoveries and apply this new knowledge to patients with rheumatic diseases. Our Cores are focused on both basic and translational research (Patient Data and Sample Core-PDSC; Flow Cytometry and Imaging Core-FCIC; and Single Cell, Genetics/Genomics Core-SCGC). The UAB RDRRC has several goals: 1. We will improve the excellence of our programs and promote innovative research by sharing the scientific, clinical, intellectual, data, and specimen resources at UAB. 2. We will develop technical capacities, assess user needs, and have flexibility to adapt as the research milieu changes. 3. Through an innovative Catalyst Award Program, we will attract young investigators as well as established, talented investigators from other disciplines into rheumatic diseases research. Catalyst Awards will provide seed money for innovative projects using the resource Cores or nano-sabbaticals to bring new technologies, analyses, or methods into our resource Cores. 4. As a way of developing the next generation of translational researchers in rheumatic disease, we will expand a robust Scientific Enrichment Program and perform outreach, training, and mentoring.
Role: PD/PI

P30 AR073755 (Bridges) 07/01/18 – 06/30/23 0.6 CM
NIH/NIAMS
UAB Translational Research Center for Rheumatic Diseases
Patient Data and Sample Core
The UAB RDRRC Patient Data and Sample Core (PDSC) will accelerate improvements in diagnosis, treatment, or prevention of rheumatic diseases through enhancement of innovative translational research studies by leveraging multiple resources at the UAB. Resources to be provided to investigators at UAB and nationally include guidance and assistance in identifying existing high-quality clinical data (demographic, disease activity, etc.), research data (genotypes, detailed autoantibody profiles, etc.) and accompanying biospecimens (DNA, serum, etc.) from large, previously/currently funded (NIAMS, etc.) clinical studies of RA, SLE, lupus, juvenile arthritis, OA, gout, etc. The PDSC will also assist investigators in the identification of prospectively collected customized disease-specific clinical data and accompanying custom-processed biospecimens (blood, synovial fluid, synovial tissue) from adult and pediatric (blood only) rheumatic disease patients. The data and samples will be collected from the large, robust, clinical practices of the UAB Division of Clinical Immunology and Rheumatology, the UAB Division of Pediatric Rheumatology, and the UAB Division of Orthopaedic Surgery. The PDSC, in collaboration with the UAB Informatics Institute and Health System Information Services, will guide and assist the acquisition of unique data such as external data from health plans claims (CMS, etc.) and mobile health data (fitness trackers, smartphones), that will be linked to biospecimen and EHR data and searchable through i2b2. And finally, the PDSC, in conjunction with the Admin Core, will shepherd investigators to customized services, including study design, methodology, biostatistics, etc.; regulatory support (IRB, MTAs); cutting-edge research resources through the other RDRRC cores; and data analysis and interpretation.
Role: Core Leader

No Number (Pope) 12/01/18 – 11/30/23 0.24 CM
Northwestern University/NIAMS
Synovial Macrophage Transcriptional Signatures for Predicting Therapeutic Efficacy
Role: Co-Investigator

U19 AI142737 (Lund, PD/PI) 04/01/19 – 03/31/24 0.6 CM NIH/ NIAID
Cooperative Centers on Human Immunology: Tissue and organ specific human B cell immunity
Core B: The Human Tissue Collection, Processing and Repository Core (Tector and Bridges, Co-Core Lead)
The overarching goal of this U19 Project is to advance understanding of humoral immunity by evaluating B cells in eight different human tissues. In Specific Aim 1, we will collect tissues from deceased organ donors via

the Alabama Organ Center. The objective of Specific Aim 2 is to isolate and cryopreserve leukocytes from the tissues. Lastly, Specific Aim 3 will establish a searchable biorepository of these samples with which to support the research objectives of the U19.
Role: Co-Core Lead

U19 AI142737 (Lund, PD/PI) 04/01/19 – 03/31/24 0.48 CM NIH/ NIAID

Cooperative Centers on Human Immunology: Tissue and organ specific human B cell immunity
Project 1: Development and Maintenance of Human Glycan and Phospholipid Antibody Repertoires (Kearney and King, Co-Project Lead)
The overarching goal of this U19 Project is to advance understanding of humoral immunity by evaluating B cells in eight different human tissues The goal of this project is to define
mechanisms controlling maturation of the human natural B lymphocyte repertoire and its tissue distribution. We will achieve this goal by completing a targeted analysis of B cells reactive with conserved carbohydrate and phospholipid T lymphocyte-independent antigens associated with clinically relevant bacteria and xenoantigens.
Role: Co-Investigator

R01 AI143994 (Bridges, Ippolito, MPIs) 04/01/19 – 03/31/24 2.4 CM NIH
Molecular, Functional and Structural Analyses of Anti-PAD Antibodies in Rheumatoid Arthritis
Our Specific Aims are: 1. Characterize, at the molecular level, the circulating anti-PAD IgG profiles in RA patients. We will use a combination of mass spectrometric analysis of affinity-purified anti-PAD IgG and Next-Gen sequencing of B cells (plasmablasts or PAD4-specific) from the same patients; 2. Functionally characterize anti-PAD mAbs produced by RA patients. Monoclonal antibodies will be generated from the most abundant serum IgG clonotypes in Aim 1. 3. Molecularly and functionally characterize the serum anti-PAD antibodies of RA patients who sero-convert from anti-PAD4+ to anti-PAD4/3 cross reactive antibodies.
R01 AR074796 (Reynolds, PI) 12/01/18 – 11/30/22 0.6 CM NIH
Functional and Integrative Omlcs of Incident Gout and Recurrent Gout Flares

P30 AR072583 (Curtis, PD/PI) 09/01/17 – 08/31/22 0.6 CM NIH/ NIAMS
Direct Costs UAB Mobile hEalth and MEthodologic (MEME) Core Center – Administrative Core (Curtis, Core Director) The UAB Mobile hEalth and MEthodologic (MEME) Core Center encompasses three distinct and synergistic cores (mHealth, Methodologic, and Administrative), all aligned around the theme of mobile health data, health informatics, real-world data and advanced analytics. The goal of the MEME CCCR is to bring innovative health information technology tools and methods to the research community to advance effectively the NIAMS mission, and to embrace research and technology necessary to transform healthcare in the 21st century.
Role: Associate Director
Role: Associate Director
No Number (Perlman, PI) 10/01/16 – 09/30/19 0.6 CM
Northwestern University/Arthritis Foundation
Precision Medicine for Patients with RA

<u>PAST</u>

P50 AR060772 (Contact PI: Saag, KG; PI: Bridges, SL Jr.) 09/01/12 - 08/31/18 1.2 CM
NIH/NIAMS NCE
Centers of Research Translation (CoRT): Gout and Hyperuricemia: from Bench to Bedside to Backyard

Role: Multiple PI; Administrative Core
Gout affects ~1-2% of the U.S. population. With an aging population, the societal burden of gout will likely grow. The role of genetic factors on gout and hyperuricemia among different races/ethnicities and the mechanisms by which treatment of hyperuricemia may impact vascular disease remain poorly understood. While the causes of hyperuricemia are known, and efficacious treatments for gout are available, there are large gaps in the quality of care of gout patients. These care gaps, the societal impact of gout, and rising concerns about deleterious effects of hyperuricemia make these conditions ideal targets for translational research. Our multi-disciplinary UAB CORT includes 3 research projects and an administrative core focused on the theme of "Gout and Hyperuricemia: from Bench to Bedside to Backyard. We will characterize biomarkers of inflammation (CRP), vascular disease (endothelial function), and blood pressure changes associated with the ULT allopurinol (Project 1); examine factors associated with suboptimal gout care and factors influencing effective and safer dosing of allopurinol and colchicine in African-Americans and Caucasians (Project 2); and compare the effectiveness of a novel pharmacy-based "virtual" Gout Clinic that includes protocol-driven care to usual care in the treatment of chronic gout (Project 3). The overall goal of our CORT is to improve the health of patients with gout and hyperuricemia by applying scientifically rigorous, state-of-the-art methodology to clinically important questions in translational investigation and to educate clinical investigators through an enrichment program.
**Contracting / Grants Officer**: James Witter, MD, PhD, witterj@mail.nih.gov, (301) 594-5032, Rheumatic Diseases Clinical Program, Division of Skin and Rheumatic Diseases, NIAMS, NIH, DHHS, One Democracy Plaza, 6701 Democracy Boulevard, Suite 800, Bethesda, MD 20892-4872

P50 AR060772 09/01/12 - 08/31/17 0.3 CM NIH/ NIAMS

Centers of Research Translation (CoRT): Gout and Hyperuricemia: from Bench to Bedside to Backyard
Project 3: Determinants of Achieving Target Serum Urate in Gout and Safety of Gout Treatments (Singh, PI)
Role: Investigator
The aims of this project are: 1) To identify key patient, provider, and health system factors associated with achieving and maintaining serum urate below 6 mg/dl ("target") in gout patients taking allopurinol; 2) To characterize the epidemiology and risk factors for major adverse events (AEs) associated with the use of allopurinol and colchicine for treatment of gout. We will use natural language processing (NLP) algorithm that incorporates the rich information from national VA EHR and nationally available laboratory results in addition to lCD-9 codes to more accurately identify gout patients. With a similar approach, we will identify a validated cohort of gout patients with major AEs. We will examine association of key (patient, physician, healthcare) factors with ability to achieve target serum urate and with risk of major AEs.
**Contracting / Grants Officer**: James Witter, MD, PhD, witterj@mail.nih.gov, (301) 594-5032, Rheumatic Diseases Clinical Program, Division of Skin and Rheumatic Diseases, NIAMS, NIH, DHHS, One Democracy Plaza, 6701 Democracy Boulevard, Suite 800, Bethesda, MD 20892-4872

OVERLAP

No Overlap

**RAMAN, CHANDER**

**Summary of Changes:**
New Active:
Changes in Effort:
New Pending: R01 AR070744 (Szalai); R01 AR074796 (Reynolds); R21 AI142627 (Raman); LR170037 Lupus Research Program (Szalai); R01 DK119118 (Szalai)
Completed: R21 AI107748 (Raman)

ACTIVE

W81XWH-16-1-0537 (PI: Bridges, SL Jr.) 09/01/16 - 08/31/19 4.8
CM Dept of Defense Congressionally Directed Medical Research Programs
The Role of the Interferon-Gamma-Jak/STAT Pathway in Rheumatoid Arthritis
To achieve the goal of this proposal, the specific aims are: (1) To identify the specific circulating cell type in which IFNGR expression is elevated in RA. Using a combination of molecular biological and immunological approaches, we will analyze the expression levels of IFNGR1 and IFNGR2 in monocytes, naïve and memory B cell populations, naïve and memory T cell populations including T-follicular helper cells, Treg cells and T helper effector subpopulations (Th1, Th17 and Th17/1). (2) To determine the outcome of IFNGR signals by assaying the activation of IFN-γ induced STAT1 and changes in activation of STAT3 and STAT5 in RA versus healthy controls, at basal level and following stimulation with cytokines such as IL-2, IL6 etc. (3) To determine the molecular mechanism and outcome of attenuated IL-2 induced activation of STAT5 in specific subpopulations of T cells in RA. For this prospective, clinical study, we will analyze PBMCs and clinical data collected from 250 subjects: 150 with RA (50 each with remission/low disease activity; moderate disease activity; high disease activity); 50 with relapsing remitting multiple sclerosis; and 50 healthy controls. We will use cutting edge techniques, including high-resolution phospho-flow cytometry complemented with single cell image analysis of T cell populations and others, to address critical questions on the pathogenesis of RA.

R01 AR071157 (Yusuf) 09/01/16 – 08/31/21 1.2 CM
NIH/NIAMS
Mechanisms Elicited by Type I Interferons in Cutaneous Photocarcinogenesis

PENDING

R01 AR070744 (PI: Szalai) 07/01/18 - 06/30/23 0.6 calendar month
NIH/NIAMS
Title: Effects of ITGAM Genetic Variation on Mac-1 Mediated Functions
Aims: The major goals of this project are (i) to establish that 77His and 1146Ser variation in the ITGAM gene alters Mac-1 mediated intracellular signaling, thereby (ii) changing Mac-1 membrane mobility, clustering, and cytoskeletal association in ways that (iii) impact leukocyte functions and renal health.
Role: Co-Investigator

R01 DK099092 (PI: Szalai) 04/01/18 - 03/31/23 0.4 calendar month
NIH/NIDDK
Title: C-reactive protein in acute kidney injury
Aims: The objective of this proposal is to understand the cellular and molecular program triggered by C-reactive protein (CRP) that regulates myeloid-derived suppressor cells (MDSCs) in acute kidney injury (AKI). Aim 1 will map CRP's influence on MDSCs: The *hypothesis* is that CRP promotes MDSC generation, proliferation, subtype differentiation, and/or suppressive function in a manner consistent with CRP elevation during renal ischemia-reperfusion injury (IRI) and exacerbation of AKI. Aim 2 will interrogate the underlying molecular program: The hypothesis is that CRP's influence on MDSCs involves FcγRIIB binding and glycogen synthase kinase-3β (GSK3β) phosphorylation. Aim 3 will ascertain the requirement of this pathway for CRP-

triggered/MDSC-driven AKI: the hypothesis is that a CRP→FcγRIIB→GSK3β cascade is essential. Aim 4 will test if CRP targeting interrupts this cascade in a beneficial way: the hypothesis is that CRP lowering will be as effective as GSK3β inhibition or MDSC depletion at protecting from AKI.
Role: Co-Investigator

R01 AR074796 (Reynolds) 12/01/18 – 11/30/22 0.72 calendar month
NIH/NIAMS
Title: Functional and integrative omics of hyperuricemia to gout and recurrent flares
Aims: In this proposal we ask: 1) Do genes involved in the inflammatory pathogenesis of gout exhibit DNA methylation and gene expression differences in gout patients and asymptomatic hyperuricemia controls, and 2) Do DNA methylation and gene transcription differences explain the propensity for recurrent flares in gout patients undergoing highly controlled urate lowering therapy?
Role: Co-Investigator

R21 AI142627 (Raman) 12/01/18 – 11/30/20 2.4 calendar months
NIH/NIAID
Title: Molecular mechanisms of relapsing remitting multiple sclerosis disease severity in African Americans
Aims: We hypothesize that functional heterogeneity in specific adaptive and innate immune cell populations contribute to the more severe relapsing remitting multiple sclerosis (RRMS) pathogenesis in AA. To elucidate the functional differences in an unbiased manner, we propose to perform high-depth single cell whole genome RNAseq of peripheral blood cells integrated with approaches to facilitate clustering gene expression in defined cell populations.

LR170037 Lupus Research Program (PI: Szalai) 10/01/18 – 09/30/21 0.24 calendar month
DoD
Title: Effects of ITGAM genetic variation on Mac-1 mediated functions of B cells
Aims: This functional genomics study will reveal how ITGAM variation affects B cell function. We will 1) Define the impact of the ITGAM 77His and 1146Ser variants on Mac-1 dependent signaling in B cells. 1146Ser should change the extent of phosphorylation of the CD11b cytoplasmic tail and thus impact inside-out signaling whereas 77His should affect Mac-1 outside-in signaling and downstream phosphorylation of signaling molecules; 2) Assess the impact of 77His and 1146Ser on Mac-1 cytoskeletal associations, membrane mobility, and clustering on B cells. Both variants should alter these events following Mac-1, TLR, and BCR activation; and 3) Confirm that ITGAM variation impacts Mac-1 biology in B cells from SLE patients.
Role: Co-Investigator

R01 DK119118 (Szalai) 09/01/18 – 08/31/23 0.12 calendar month
NIH/NIDDK
Title: Role of CRP in The Pathogenesis of Ischemic AKI
Aims: The objective of the current application is to understand the cellular and molecular program triggered by CRP that regulates MDSCs in ischemic AKI. Aim 1 will map CRP's influence on MDSCs: The hypothesis is that CRP promotes MDSC generation, proliferation, subtype differentiation, and/or suppressive function in a manner consistent with CRP elevation during renal ischemia and exacerbation of AKI. Aim 2 will interrogate the underlying molecular program: The hypothesis is that CRP's influence on MDSCs involves FcγRIIB binding and GSK3β phosphorylation. Aim 3 will ascertain the requirement of this pathway for CRP-triggered/MDSC-driven AKI: the hypothesis is that a CRP→FcγRIIB→GSK3β cascade is essential. Aim 4 will test if CRP targeting interrupts this cascade in a beneficial way: the hypothesis is that CRP lowering will be as effective as GSK3β inhibition or MDSC depletion at protecting from AKI. Under each aim evidence for clinical relevance will be sought using humanized mice, human spleen derived MDSCs, and primary human MDSCs from kidney biopsies.
Role: Co-Investigator

Physician-Scientist Award (Scholar, Pope; Mentor, Raman) 07/01/18 – 06/30/20
Rheumatology Research Foundation
Title: IFNγ and IL-2 in the pathogenesis of rheumatoid arthritis
Aims: This proposal will address how enhanced activation of STAT1, as a result of upregulated IFNγ receptor expression, in specific T and B cell subsets modulates key mechanisms of autoimmunity and peripheral tolerance in RA and RRMS patients. I will also test whether dampened IL-2 dependent STAT5 activation plays a role in dysregulated immune signaling in these patients by way of attenuating genes necessary for T regulatory cell (Treg) homeostasis.
Role: Mentor

F31 AR074884 (Trainee, Sharma; Mentor, Raman) 09/01/18 – 08/31/22
NIH/NIAMS
Title: T Cell Intrinsic Interferon Gamma Signaling in The Pathogenesis of Rheumatoid Arthritis
Aims: The overall goal of this project is to elucidate IFNγ signaling in T cells in the pathogenesis of RA. I propose two aims that interrogate the signaling and functionality of IFNγ signaling. I will first address which immune cells upregulate IFNGR as this will allow me to examine which cells contribute to the disease severity. Then, I will determine the pathway by which IFNGR responds to IFNγ signaling in varying RA disease activities
Role: Mentor

F31 AT143251 (Trainee, Pope; Mentor, Raman) 09/01/18 – 08/31/22
NIH/NIAID
Title: Low Dose Interleukin-2 Enhances Interferon Gamma Dependent Signaling in Patients with Relapsing Remitting Multiple Sclerosis
Aims: In Aim 1, I will test the hypothesis that dysregulated IL-2 signaling synergizes with IFNγ signaling and contributes to disease pathogenesis via the dysregulation of PI3K signaling in subpopulations of T and B cells with RRMS. In Aim 2, I will elucidate the role that low dose IL-2 plays in contributing to disease progression by reinforcing effector responses in Th1 and Th17 cells and attenuates regulatory responses in Tregs in treatment of naïve MS.
Role: Mentor

PAST

R21 AI107748 (Raman) 08/01/14 – 07/31/17 1.8 CM
NIH/NIAID NCE
Role of TGFβRIII in T-cell development and immune responses
The goal of the proposal is to determine the mechanistic role of TGFβRIII/betaglycan in development and maturation of T-cells in the thymus and regulation of immune responses in the periphery. For this proposal, the specific aims are: (1) to determine the role of TGFβRIII in T cell development and selection; (2) to determine the role of TGFβRIII in modulating the differentiation of naive T cells to effector cells and autoimmunity.
Program Official: Wolfgang Leitner
Email: wleitner@mail.nih.gov

R01 AI076562 (Raman) 06/01/08 – 05/31/14
NIH/NIAID
Program Official: Stacy Ferguson
Email: fergusonst@mail.nih.gov
The Role of CD5 in B Cell Development and Autoimmunity
The goal of these studies is to use the novel animal models to enable us to resolve CD5 biology in B-cells. An important outcome of the proposed studies will be a major advancement in our understanding of regulatory

pathways in innate B-cell responses to bacterial and viral pathogens and the development of targeting approaches for treatment of autoimmune diseases and leukemia. Specific Aims: (1) determine the role of CD5 in the development of B1a B-cells and its contribution to autoimmunity, (2) elucidate how CD5 regulates B-cell responses to T-independent antigens and T-dependent antigens and (3) dissect the molecular mechanism of CD5-dependent survival and inhibitory signals in normal B-cells.

R01 NS064261 (P. I. De Sarno) 4/01/09 – 03/31/14
NIH/NINDS
Program Official: Ursula Utz
Email: utzu@ninds.nih.gov
Role: Co-Investigator
Title: GSK3: Immunoregulator in experimental autoimmune encephalomyelitis (EAE)
The goal is to test the hypothesis that GSK3 promotes proinflammatory cascades in EAE. Our proposed studies will set the framework for therapeutic targeting of GSK3 for treatment of MS and other neuroinflammatory diseases. Since lithium is already a drug approved by FDA for treatment of psychiatric disorders, the outcome of this proposal can lead to rapid evaluations in human patients. Furthermore, with the availability of more specific GSK3 inhibitors that are being developed, this study is likely to be the basis for their use in the treatment of MS, and other neurodegenerative diseases with inflammatory components.
Specific Aims: 1) expand and follow up our initial findings by examining the consequences of modulating GSK3 in vivo by pharmacological and genetic approaches on the development and progression of acute and relapsing/remitting EAE; 2) perform ex-vivo studies to address the mechanism of lithium-mediated protection to test the hypothesis that the major target of lithium attenuation of EAE in mice are dendritic cells and microglia.

RG 4587-A-1 (DeSilva, T.) 04/01/11 – 03/31/14
National Multiple Sclerosis Society
Role: Co-Investigator
Glutamatergic signaling in demyelination and remyelination in multiple sclerosis
The major goal of the proposal is to determine mechanisms by which glutamate receptor signaling regulates demyelination and remyelination in MS.
Role: Co-Investigator

**REYNOLDS, IV, RICHARD J.**

**Summary of Changes:**
New Active: P50 AR060772 (Saag, PD/PI) Investigations in Gout, Hyperuricemia, and ComorbidiTies (INSIGHT) Center of Research Translation (CORT) - Project 3 (Mount, Director)
Changes in Effort:
New Pending: R01 AR074796 (Reynolds); R01 AI143994 (Bridges and Ippolito); R01 AA027247 (de los Campos); R21 AI142627 (Raman)
Completed: ANRF (Reynolds)

ACTIVE

W81XWH-16-1-0537 (PI: Bridges, SL Jr.) 10/01/16 - 09/30/19 1.2 CM Dept of Defense Congressionally Directed Medical Research Programs
The Role of the Interferon-Gamma-Jak/STAT Pathway in Rheumatoid Arthritis
The goals of the study are 1) to identify T-cell subset populations with IFN differential expression between RA cases and controls, 2) to quantify IFN -mediated differential signaling through STATs, and 3) to assess the molecular mechanism and outcome of attenuated IL-2 induced activation of STAT5 in specific subpopulations of T cells in RA.

P50 AR060772 (Saag, PD/PI) 09/01/17 – 08/31/22 1.8 CM
INvestigations In Gout, Hyperuricemia, and comorbidiTies (INSIGHT) Center of Research Translation (CORT):
Project 3 – Translational Genomics of Hyperuricemia (Mount, Project Lead)
The goal of this project is fill in key knowledge gaps in the functional genomics of hyperuricemia (HU) and its causality with chronic kidney disease (CKD) to yield novel tools for translational urate research, novel insight into shared pathways in CKD and HU, and potential therapeutic targets.
**Contracting / Grants Officer**: James Witter, MD, PhD, witterj@mail.nih.gov, (301) 594-5032, Rheumatic Diseases Clinical Program, Division of Skin and Rheumatic Diseases, NIAMS, NIH, DHHS, One Democracy Plaza, 6701 Democracy Boulevard, Suite 800, Bethesda, MD 20892-4872
Role: Co-Investigator

PENDING

R01 AR074796 (Reynolds) 12/01/18 – 11/30/22 6 calendar months
NIH/NIAMS
Functional and integrative omics of hyperuricemia to gout and recurrent flares

R01 AI143994 (Bridges & Ippolito, MPIs) 04/01/19 – 03/31/24 1.2 calendar months
NIH/NIAID
Molecular, Functional and Structural Analyses of Anti-PAD Antibodies in Rheumatoid Arthritis

R01 AA027240 (de los Campos) 12/01/18 – 11/30/23 3.24 calendar months
NIH/NIAA
Effect of Alcohol Consumption on Chronic Disease Risk: Novel Methods for Mendelian Randomization and Powerful Inference based on Data from the UK-Biobank and two US Cohorts.
Role: Co-Investigator

R21 AI142627 (Raman) 12/01/18 – 11/30/20 0.6 calendar months
NIH
Molecular mechanisms of relapsing remitting multiple sclerosis disease severity in African Americans

COMPLETED

No Number (Reynolds) 06/01/16 – 05/31/18 6.36 CM
Arthritis National Research Foundation

Genetic and Epigenetic Covariance of Gout, Hyperuricemia and Its Comorbidities
The goal of the study is to estimate the genetic and epigenetic overlap of traits related to hyperuricemia, gout and their comorbidities, using whole genome regression.

K01 AR060848 (Reynolds) 04/01/11 – 03/31/16
NIH/NIAMS

Discovering novel genetic and environmental risk factors for RA in African Americans
The goals of the proposal are to implement a mentored career development plan with emphasis on didactic training in the pathobiology of autoimmunity and hands-on training using state-of-the-art statistical models that can accommodate the unique challenges presented by high dimensional genetic data. The project will greatly enhance our understanding of the complex genetic and environmental risk factors for RA in a traditionally understudied population and will provide critical training for Dr. Reynolds' development as an independent scientist.

WS2425009 ASPIRE (Reynolds) 10/01/2012 – 09/30/2014
Pfizer, Inc.

Evaluating genetic heterogeneity of HLA B and HLA DRB1 risk alleles with rheumatoid arthritis in African Americans – Is classical allelic and amino acid sequence level genetic risk conditional on European or African ancestry?
The goals are to estimate the contribution of HLA-B alleles and HLA-B amino acid residues to RA risk in African Americans.

R01 AR062376 (SL Bridges, Jr., PI) 9/01/11 - 8/31/15; subsumed under K award
NIH/NIAMS
Dissection of the ACPA response in African-Americans with Rheumatoid Arthritis
The goals of this proposal are: 1) To examine associations of serum ACPA to a variety of specific citrullinated epitopes and of serum anti-PAD4 Abs with clinical, genetic, and radiographic features in Af-Amer with anti-CCP+ RA. 2) To examine associations of periodontitis and exposure to P. gingivalis with serum ACPA profiles and anti-PAD4 Abs in Af-Amer with anti-CCP+ and anti-CCP-neg RA. 3) To compare the degree of clonality and mutation patterns of peripheral blood B cells from Af-Amer with and without anti-CCP Ab, ACPA, anti-PAD4 Abs; and to assess the reactivity of antibodies from citrullinated protein-specific and PAD4-specific B lymphocytes in RA.