

**The Harold S. Geneen Charitable Trust**

**Awards Program for Coronary Heart Disease Research**

HRiA Progress Report

December 2020

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The Medical Foundation at Health Resources in Action

Awardees from 2019 Grant Cycle

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| **Francis Alenghat, M.D., Ph.D.**  University of Chicago  *Serum Amyloid A Inhibition of Macrophage Lipoprotein Lipase and its Impact on Synthesis of Specialized Pro-resolving Mediators* | **2019 Cycle Awardee**  Project Dates:  12/31/2019 – 12/30/2021 |  | **Page 2** |
| **Frank Brozovich, M.D., Ph.D.**  Mayo Clinic  *The Vascular Phenotype and Novel Targets for Heart Failure with Preserved Ejection Fraction (HFpEF)* | **2019 Cycle Awardee**  Project Dates:  12/31/2019 – 12/30/2021 |  | **Page 4** |
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**2019 Awardees**

**Francis Alenghat, M.D., Ph.D.**

Professor of Medicine and Physiology

University of Chicago

**Project Title:** “*Serum Amyloid A Inhibition of Macrophage Lipoprotein Lipase and its Impact on Synthesis of Specialized Pro-resolving Mediators”*

**Specific Aims:**

1. To determine how a chemical associated with coronary heart disease changes an immune cell’s metabolism and controls an immune cell’s role in promoting or reducing inflammation.
2. To measure the impact of the above-mentioned immune cell changes and chemical on the body’s ability to combat harmful inflammation.

**Summary of Research Progress to Date:**

Dr. Alenghat has made progress across both aims described in the original proposal, and merits of continued funding. The investigator sought to determine how a chemical associated with coronary heart disease both causes and exacerbates this disease, with the hope that answering such questions would lead to the identification of new therapeutic targets for patients. In conducting experiments associated with AIM 1, Dr. Alenghat found that the chemical associated with coronary heart disease prevents the ability for immune cells to breakdown fat. The breakdown of fat is important, as it is needed to help the body combat harmful inflammation through the conversion of fat into chemicals similar to omega-3 fatty acids (fish oil), which have well known anti-inflammatory properties. The Dr. Alenghat predicts that this anti-inflammatory response by cells is prevented by the presence of this chemical associated with coronary heart disease. Working on experiments associated with AIM 2, Dr. Alenghat has optimized cell culture conditions needed for immune cells to produce these anti-inflammatory chemicals. Dr. Alenghat is poised to conduct the remainder of the experiments to address how these cells important for anti-inflammatory responses are affected by the chemical associated with heart disease, and why this chemical may be an important driver of this disease.

Overall, Dr. Alenghat has made good progress towards completion of the aims. As stated in the progress report, there was significant delays encountered due to closer of the laboratory from March through June 2020 due to COVID-19. During this time, other work associated with the projects could be completed so that once operational, experiments could proceed. Dr. Alenghat acknowledges that there has been some slow down to enhance and create ideal experimental conditions for the cell-culture work, but this is an important foundation for the experiments that required careful completion. It is anticipated that Dr. Alenghat will likely request a no-cost extension at the end of the project period due to the disrupted research activity due to COVID-19.

**Summary of Fiscal Reports to Date:**

All of the expenditures to date are due to personnel costs. There do not appear to be any expenditures associated with supplies or other costs. Based upon the report submitted by Dr. Alenghat, this aligns with most of the work associated with basic cell culture costs and optimizing experimental conditions. The carry-over amount is larger than anticipated for a typical year, however, due to COVID-19 related delays this is acceptable.

**Award related honors, submitted and/or accepted presentations and publications, and current and/or pending funding:**

1. **Honors:**

2020: Cardiovascular Director, Kidney Transplant Program, University of Chicago

2020: Associate Program Director, Cardiovascular Fellowship, University of Chicago

1. **Presentations:**

2019: Inflammation and Coronary Artery Disease, Postgraduate Institute of Medical Education and Research, Chadigarh, India

2020: Inflammation and Coronary Artery Disease, Pritzker School of Medicine, Chicago, IL

2020: Inflammation and Coronary Artery Disease, University of Chicago Medicine, Chicago, IL

1. **Publications:**

Arnold, K.A., J.E. Blair, J.D. Paul, A.P. Shah, S. Nathan, and **F.J. Alenghat** (2019). Monocyte and Macrophage Subtypes as Paired Cell Biomarkers for Coronary Artery Disease. *Experimental Physiology*; doi: 10.1113/EP087827.

Karunakaran, D., M. Nguyen, M. Geoffrion, Z. Lister, H.S. Cheng, H. Wyatt, J.W. Kandiah, R. Jung, **F.J. Alenghat**, A. Mompeon, R. Lee, C. Pan, A.J. Lusis, P. Liu, L.P. Matic, U. Hedin, J.E. Fish, L.Guo, F. Kolodgie, R. Virmani, K.J. Rayner. Therapeutic knockdown of RIPK1 gene expression reduces NF-κB inflammation in macrophages and prevents atherosclerotic lesion development. (accepted, *Circulation*).

Hyatt, D., A.E. Schroeder, A. Bhatnagar, D.E. Golan, K.D. Swanson, and **F.J. Alenghat** (2019). Skap2 Regulates Atherosclerosis through Macrophage Polarization and Efferocytosis. *bioRxiv* doi.org/10.1101/857649 - preprint, in revision for publication

Holzhauser, L., K.J. Clerkin, T. Fujino, **F.J. Alenghat**, J. Raikhelkar, G. Kim, G. Sayer, N. Uriel. Donor-Derived Cell-Free DNA is Associated with Cardiac Allograft Vasculopathy - in review

1. **Current and Pending Funding:**

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| --- | --- | --- | --- | --- | --- |
| **Funding Source and Project Title** | **Funding Period** | **Approved** | **Total Amount** | **Annual Direct Costs** | **Role of Awardee** |
| NIH/NHLBI/ Title: Determinants of Regulatory Macrophage Function in Coronary Artery Disease | 08/01/20-07/31/22 | Funded | $162,000.00 | $50,000.00 | Principal Investigator |
| AHA/ Title: Regulatory Macrophage Function in Coronary Artery Disease and the Impact of Inflammatory Connective Tissue Diseases | 07/01/20-06/30/23 | Funded (in process) | $300,000.00 | $90,909.00 | Principal Investigator |

**Frank Brozovich, M.D., Ph.D.**

Professor of Medicine and Physiology

Mayo Clinic

**Project Title:** “*The Vascular Phenotype and Novel Targets for Heart Failure with Preserved Ejection Fraction (HFpEF)”*

**Specific Aims:**

Aim 1: To determine if chemicals that increase inflammation cause the cells within the heart to become stressed which lead to changes in heart muscle function associated with heart failure with preserved ejection fraction (HFpEF – diastolic heart failure).

Aim 2: To determine if HFpEF associated contractile changes in heart muscle are due to altered cellular signaling and/or changes in structures involved in muscle contraction.

**Summary of Research Progress to Date:**

Dr. Brozovich has made significant progress towards achieving the proposed project goals, and merits continued funding. The project seeks to examine what causes changes in cardiac function associated with HFpEF, for which there is no evidence-based treatment. The application uses two models of HFpEF, pig and rodent. Dr. Brozovich has successfully created a rat model of HFpEF through providing the rat with a high fat diet and drug treatment. This is a necessary first step in the overall project plan and an important contribution for other investigators interested in this topic. The investigators have yet to start experimentation associated with AIM 1.

Work associated with AIM 2 has focused on examining how structures involved with muscle contraction associated with HFpEF are altered. There are some known structural and cell signaling changes that occur in heart failure with reduced ejection fraction (HFrER – systolic heart failure). Initial findings indicate that there are multiple changes that occur that contribute to the heart muscle contractile abnormalities that are different between individuals that have HFpEF and heart failure with reduced ejection fraction (HFrEF).

Because of the COVID-19 pandemic, Dr. Brozovich was not able to work (both care for animal and perform experiments) for over 3 months. Additionally, it was indicated that the institution’s policies resulted in decreased productivity to help ensure decreased likelihood of COVID-19 transmission. Despite these set-backs, Dr. Brozovich has made good progress towards the proposed work. It is anticipated that this awardee will likely request an extension at the conclusion of the project to account for this delay.

**Summary of Fiscal Reports to Date:**

Dr. Brozovich has spent a significant portion of the funds on personnel costs. There have been a few expenses accrued associated with animal care. More funds than would be expected during a typical year are anticipated to be carried into year 2. However, due to the unforeseen circumstances surrounding COVID-19 and the progress made towards the studies, this is thought to be acceptable.

**Award related honors, submitted and/or accepted presentations and publications, and current and/or pending funding:**

1. **Honors:**

None disclosed.

1. **Presentations:**

None disclosed.

1. **Publications:**

None disclosed.

1. **Current or Pending Funding**

None disclosed.