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PRESTIGIOUS NIH GRANT AWARDED TO UNIVERSITY OF MASSACHUSETTS MEDICAL SCHOOL RESEARCHERS

$2.5 million awarded for promising research into ME/CFS, often a post-viral disease, that disables millions of Americans

This research has implications for millions of additional people now experiencing long-term post-viral illness from COVID-19

Boston, MA, March 16, 2021 — On March 8th, the National Institutes of Health (NIH) announced a prestigious grant awarded to a two-woman research team at the University of Massachusetts Medical School (UMMS), in Worcester, Massachusetts. The RO1 grant (AI159314) of $2.5 million is administered by NIH's National Institute of Allergy and Infectious Diseases (NIAID) and is awarded to researchers Liisa Selin, MD, PhD, and Anna Gil, PhD, for their work on the highly disabling disease ME/CFS (Myalgic Encephalomyelitis / Chronic Fatigue Syndrome).

The Massachusetts ME/CFS & FM Association (MassME) is pleased to have supported this research team over the years, and now releases the following statement applauding the grant:

> "Historically, NIH has dedicated little money towards researching this disease. That has had devastating consequences: few researchers drawn to the field, little research conducted, no biomarker found, no treatments found, no cause or cure found. So this grant to Liisa Selin's lab is a welcome infusion of NIH resources."

In 2015, the Institute of Medicine (now the National Academy of Medicine) stated: "**Remarkably little research funding** has been made available to study the etiology, pathophysiology, and effective treatment of this disease, especially given the number of people afflicted… **There is an urgent need for more research**…"

This NIH RO1 grant, titled "Altered T cell Responses in ME/CFS" allows the researchers to examine the role of aberrant T cell responses in the immunopathogenesis of ME/CFS patients. Selin and Gil's recent research findings could point to potential biomarkers, treatments and ways of tracking response to therapy for the disease, things that have been sorely missing. To date, there is no FDA approved treatment for ME/CFS, a devastating disease with neurological and immunological characteristics, afflicting up to 2.5 million Americans.

Key symptoms of ME/CFS include extreme exhaustion, energy depletion, cognitive dysfunction ('brain fog') and a worsening of all symptoms after any type of physical or cognitive exertion. Patients experience the disease on a spectrum, from mild to very severe; 70% of patients are too sick to work, 25% are homebound and bedridden, often unable to care for themselves for decades. Some are too weak to read, talk or eat. There is no cure.

This debilitating chronic disease often comes as a result of a post-viral illness. About 80% of those with ME/CFS first get a viral or bacterial infection, such as acute infectious mononucleosis caused by Epstein Barr Virus. They get sick, never fully recover, and then, six months later, are eligible for a diagnosis of

ME/CFS.

Post-Acute Sequelae of COVID-19 (PASC), or Long COVID, is also a lingering post-viral illness affecting at least 10% of those who have had SARS-CoV-2. NIH's Dr. Anthony Fauci has said on multiple occasions that the symptoms COVID 'Long Haulers' experience are similar to those of ME/CFS; leading ME/CFS doctors and researchers agree. Now they, including Selin and Gil, are concerned this could lead to millions of Long COVID patients who will not get better, and who may soon be eligible for an ME/CFS diagnosis. Because of this, Selin and Gil are also studying Long COVID patients.

Researcher Liisa Selin, MD, PhD, who was also previously awarded a Solve ME/CFS Initiative Ramsey award for this same research, states:

> "We are grateful to NIH for this award. And we so appreciate the support we have received from MassME. We hope our research translates into real help for the patient community, perhaps even a biomarker and treatments. There are almost 60,000 people in Massachusetts living with ME/CFS, and millions in the US, 75% of whom are women. We will be happy if our work can offer them tangible help."

Nancy Klimas, MD, Director of Nova Southeastern University's Institute for Neuro-Immune Medicine, recently awarded a $4 million grant from the Centers for Disease Control to study ME/CFS and Long COVID, says:

> "It's exciting to see Liisa Selin's work move to the next level. Her focus on immune exhaustion is right on target. Immune restoration as a treatment focus will be important to ME/CFS, and also to the post-COVID illness that is being called Long COVID or Post-Acute Sequelae of SARS CoV-2 Infection (PASC)."

For years, Selin and Gil have studied the role of T cells in viral immunopathogenesis in ME/CFS, in heterologous immunity and cross-reactive T cell responses to Epstein Barr Virus and their role in infectious mononucleosis, and more recently in multiple sclerosis. Liisa Selin has received 12 NIH grant awards to date, totaling $20 million, funded to UMMS. Five of those grant awards were part of large, highly-prestigious collaborative research projects, which altogether brought $78 million to UMMS.

To learn more about ME/CFS, visit www.MassMECFS.org and https://solvecfs.org/

For more information about Selin and Gil's research, including a video, a scientific poster and abstracts, please see the accompanying material found below, or see here (https://www.massmecfs.org/images/pdf/Selin_MassME_Press_Release_03162021.pdf)

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Accompanying Material

MASSACHUSETTS ME/CFS & FM ASSOCIATION, RESEARCH CLUB 2020
Video of guest speakers: Liisa Selin, MD, PhD, and Anna Gil, PhD (Sunday, Sept 27, 2020)
https://vimeo.com/524080450

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ADDITIONAL INFORMATION ABOUT NIH ROI (AI159314)
Written by Anna Gil and Liisa K. Selin

ALTERED T CELL RESPONSES IN ME/CFS
NIH NIAD RO1 (AI159314)

Narrative
This proposal will examine the ME/CFS from the perspective that an aberrant response to an immunological trigger like infection results in a dysregulated immune system that is partially immunosuppressed due to CD8 T cell exhaustion. These studies will identify potential biomarkers and mechanisms driving the immunopathogenesis of ME/CFS leading to future therapies.

Summary
Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a complex disorder affecting numerous organ systems and biological processes. Published data seems to suggest that ME/CFS may be preceded by infection, and the chronic manifestation of illness may represent an altered host response to infection, or an inability to resolve inflammation. Previous studies focused on perturbation in cytokines and metabolism have also shown that CD8 T responses are decreased in ME/CFS. In preliminary studies we examined the frequency, functional and phenotypic status of CD8 T cells to determine whether they were altered in chronic ME/CFS donors as compared to healthy donors. We observed an increased CD4:CD8 ratio, altered expression of exhaustion/activation markers like CTLA4 and 2B4 on CD8 T cells, and decreased production of IFN□, TNF□ and CD107a/b upregulation following PMA stimulation, all suggesting CD8 T cell exhaustion. This was associated with a, perhaps compensatory increased frequency of activated $CD4^+CD8^+$ T cells in the ME/CFS donors as compared to healthy controls. Notably, a subset of the CD8 and the $CD4^+CD8^+$ T cell populations were spontaneously producing atypical cytokines, subdividing ME/CFS donors into two subsets: type 1 had an increased frequency of $FoxP3^+helios^+$ Treg-like cells producing IL9 (female donors); type 2 had $FoxP3^+helios^-$ cells producing IL17 (male donors). When we examined the T-cell receptor (TCR) repertoire of the $CD4^+CD8^+$ T cell population we found evidence of antigen driven clonal expansions to an unknown antigen at this time, whether it will be a viral or auto-antigen. *We hypothesize that the common theme in ME/CFS is an aberrant response to an immunological trigger like infection, which results in a permanently dysregulated immune system as a result of CD8 T cell exhaustion.* These studies will identify potential biomarkers and mechanisms driving the immunopathogenesis of ME/CFS leading to future therapies. We will explore this hypothesis in the following Aims. Aim 1 we will examine altered CD8 and $CD4^+CD8^+$ T-cell responses in ME/CFS: 1) we will determine if the level of CD8 T cell exhaustion varies with ME/CFS type 1 (female) and Type 2 (male) response and with the severity of ME/CFS symptoms using a larger ME/CFS cohort; 2) we will examine EBV antigen-specific responses in ME/CFS donors to determine if a common persistent virus response is altered by the immunosuppressive state of CD8 T cell exhaustion and further contributing to the disease state of ME/CFS; 3) microarray analyses will be done on sorted activated T cell subsets to assist in understanding the alterations in the functionality of the exhausted and activated CD8 and $CD4^+CD8^+$ T cell subsets in ME/CFS donors. In Aim 2 we will

examine TCR repertoire of CD8 and $CD4^+CD8^+$ T-cell subsets for evidence of antigen driven clonal expansion. Defining the characteristics of the activated clonally expanded CD8 and $CD4^+CD8^+$ T cells would be a major step in the field potentially leading to the identification a specific infectious or auto-antigen response that could be the main driver of CD8 T cell exhaustion and the immunological basis of ME/CFS.

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FOCIS SCIENTIFIC POSTER 2020
Federation of Clinical Immunology Societies
https://www.massmecfs.org/images/pdf/MECFS_FOCIS_poster_2020.pdf

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FOCIS 2020 ABSTRACT
Immune dysregulation in myalgic encephalomyelitis/chronic fatigue (ME/CFS) and long COVID-19 syndromes: CD8 T-cell over activation and exhaustion, increased CD4+CD8+ T-cells and aberrant cytokines.

By Anna Gil and Liisa K. Selin

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a complex disorder affecting numerous organ systems and biological processes. ME/CFS may be preceded by infection, and the chronic manifestation of illness may represent an altered host response to infection, or an inability to resolve inflammation. Here, we hypothesize that in ME/CFS an aberrant response to an immunological trigger like infection may result in a dysregulated immune system, leading to immunosuppression. Long COVID-19 syndrome patients have symptoms similar to ME/CFS. In both patient groups we observed altered expression of exhaustion markers like CTLA4 and 2B4, decrease in CD8 T-cell number, and function, particularly IFNg/TNF production. The long COVID-19 patients had evidence of sustained activation of both T-cell populations with increased CD38 and HLA-DR. This was associated with a compensatory increased frequency of activated CD4+CD8+ T-cells. In chronic ME/CFS donors both T-cell populations were spontaneously producing cytokines, subdividing into two types: (1) FoxP3+ cells producing IL9 (female donors), (2) IL17-producing cells (male donors). The long COVID-19 patients showed the type 1 aberrant cytokine profile. These results are consistent with immune dysregulation with over activation and exhaustion of CD8 T-cells as observed either in chronic viral infections or tumor environments. The observed exhaustion was associated with a compensatory increase in activated CD4+CD8+ that make unusual cytokines known to interact with the nervous system. These findings identify potential biomarkers and mechanisms driving the immunopathogenesis of ME/CFS leading to future therapies and suggest long COVID-19 may be ME/CFS (Funding: Ramsay Award, Solve ME/CFS Initiative; NIH R01AI159314).