The Solve ME/CFS
CHRONICLE

WINTER 2017

SMCI's Comprehensive Research Program Improves the ME/CFS Ecosystem and Spans Every Phase of the Discovery Process

THE DISCOVERY PROCESS

Discovery requires not just "bench science," but also a healthy ecosystem in which research can thrive.

At the Solve ME/CFS Initiative (SMCI), the comprehensive nature of our research program is underscored by **two core components**:

1) We initiate and support high-quality research across every phase of the discovery process (as shown above and described on page 4).

2) We work to improve the overall ME/CFS ecosystem through the following key functions:

- **DEBUNKING** fallacies and misinformation about ME/CFS
- **CREATING** opportunities for young investigators
- **FACILITATING** patients' participation in research
- **ADVOCATING** for effective policies and federal actions
- **PUBLICIZING** current scientific and medical developments
- **PROMOTING** cross-pollination of ideas through think tanks

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SMCI's Comprehensive Research Program Improves the ME/CFS Ecosystem and Spans Every Phase of the Discovery Process (cont.)

While our methods of improving the overall ME/CFS research ecosystem are straightforward, allow us to elaborate on the overall discovery process. Dr. Nahle clarifies that this non-linear process can be broken down into six phases:

1. **Capacity building**: Includes the development of human capital, infrastructure, tools, and resources to drive ME/CFS research forward
2. **Target discovery**: Encompasses the identification of reliable biomarkers, indicators, or other biological culprits that can be therapeutically targeted or manipulated
3. **Repurposing opportunities**: The retooling of existing FDA-approved drugs for other uses; when possible, it can bypass several time-consuming steps toward drug approval
4. **Preclinical research**: Denotes research in the basic sciences using biological specimens (e.g., patient samples, cultured cells, tissues) or model systems (e.g., animal models) to understand the mechanisms and signaling pathways that will have applications in clinical trials; this step is fundamental for targeted therapy design
5. **Clinical research**: Involves experimentation with human participants done in a clinical or laboratory setting; this includes clinical trials, natural history studies, clinical effectiveness, and outcome research as well as the development and improvement of clinical criteria updates
6. **Therapeutic discovery**: This is the goal and includes the identification and development of treatments and, eventually, a cure

2016/2017 SMCI RESEARCH DASHBOARD

1 Capacity Building → 2 Target Discovery → Repurposing Opportunities → 3 Preclinical Research → 4 Clinical Research → Therapeutic Discovery

Ramsay Award Program projects awarded through rigorous peer review

TEAM 1 Brain inflammation - Diagnostics - Neuroimaging	1			4
TEAM 2 B-Cell function - Metabolomics - Rituximab	1	2	3	4
TEAM 3 Bioenergetics - Natural Killer cells - Mitochondria	1	2	3	
TEAM 4 Autoimmunity - genetic screening	1			4
TEAM 5 Viral infection - HHV6 - Immunity - Energetics	1	2	3	

SMCI-Directed Research Studies addressing severe knowledge gaps

Group 1 Metabolomics - Bioenergetics (Cornell/Metab/Levine)	1	2		
Group 2 Immune-senescence - cell cycle energetics (Wash U)	1	2	3	
Group 3 Dug screening platforms - Therapeutics (MSKCC)	1	2	3	4

Collaborative project through our Cathleen J. Gleeson PhD Fund

CJG Diagnostics – Metabolic Imaging (U of Washington)	1		3	4

BIOBANK

Resources in support of studies

- NIH
- University of Vermont
- University of Toronto
- Washington University in St. Louis

Dr. Nahle notes that "By creating environments in which real and durable research and advocacy collaborations develop and flourish, we reframe the discussion so that all voices in ME/CFS can be heard and respected. Through unity and cross-pollination, we are affecting change and deconstructing stubborn medical challenges in ME/CFS."

We act as agents for change and unity: we meet with government officials and science leaders to advocate for policies and federal action; we author dozens of opinion and technical pieces addressing current ME/CFS affairs across the science, research, and policy landscapes; we debunk fallacies and misinformation through our No Spin Zone; we create opportunity for young investigators through our MeetME Travel Awards; and we bring scientific and current information to our community through webinars and opinion pieces. In addition, we participate in conferences and convene some of the top minds in ME/CFS clinical care and research to collaborate on the key issues facing ME/CFS.

To be specific, SMCI manages the following programs to facilitate research work for all who join us in the fight for a cure, while creating and collaborating on projects that emphasize the role of patients as partners—not subjects:

SMCI'S NATIONAL PATIENT REGISTRY

Our new, state-of-the-art national registry for ME/CFS will enable clinical trials, further understanding of the natural history of this disease, and includes built-in options for data sharing and collaboration among patients, researchers, and other disease organizations.

SMCI'S BIOBANK

Our biobank is a repository of physical samples from patients to support the work of qualified researchers and accelerate the discovery process. This important aspect of the services we provide also links patients with researchers and facilitates the use of human samples for ME/CFS research. Studies using samples from our biobank have been used in phases 1, 2, and 3 of the discovery process.

SMCI'S RESEARCH WEBINAR SERIES

The medical webinars we produce, featuring influencers in science, medicine, and policy, are the go-to source of trusted, up-to-date medical information, current research, and policy development. On-demand video from SMCI's 2016 Webinar Series, moderated by Dr. Zaher Nahle, is offered free of charge on our website at SolveCFS.org/2016-webinar-series.

SMCI'S RESEARCH ADVISORY COUNCIL

The SMCI Research Advisory Council (RAC) consists of world-class leaders and provides great depth to our work. The RAC includes foremost experts on ME/CFS like Anthony Komaroff, MD (Harvard); Susan Levine, MD (CFSAC, The Levine Clinic); Jose Montoya, MD (Stanford); Peter Rowe, MD (Johns Hopkins); Cindy Bateman, MD (Bateman Horne Center); and Andreas Kogelnik, PhD, MD (OMI) as well as a number of scientific leaders like Sheila Stewart, PhD (Washington University) and Michel Silvestri (Sweden).

SMCI'S RAMSAY AWARD PROGRAM

This program supports and promotes original, bold, quality research work through seed grants. Grant recipients are selected via a peer-review competition with three primary objectives: to **INVEST** in original ideas that could clarify the onset, progression, root causes, and natural history of ME/CFS; to **CREATE** environments to attract, support, and retain talent in the ME/CFS community and help awardees generate relevant data to compete for long-term federal funding; and to **FACILITATE** collaboration and cross-pollination among dedicated researchers through the sharing of resources and access to additional programming and the organization's network.

In 2016, SMCI's Ramsay Award Program supported studies in gut microbiome, autoimmunity, bioenergetics, pathogenic interaction, inflammation, brain imaging, and metabolomics research. Peer-reviewed selection criteria included significance, quality, feasibility, innovation, novelty, and research environment among other factors.

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SMCI's Comprehensive Research Program Improves the ME/CFS Ecosystem and Spans Every Phase of the Discovery Process (cont.)

SMCI's Ramsay Award Program grant winners selected in 2016 are as follows:

Research Team 1's study, entitled "Advanced Non-Invasive Analysis in ME/CFS Diagnosis and Treatment Decisions," will use a **magnetic resonance spectroscopic thermometry** (MRSt) technique to assess absolute temperature across the entire brain, allowing researchers to investigate the **pathophysiology** of ME/CFS (in other words, the functional changes that accompany the disease).

Research Team 2's study, entitled "Metabolic Analysis of B-Cell Maturation in Myalgic Encephalomyelitis/Chronic Fatigue Syndrome," theorizes that "a single agent is not responsible and that **chronic changes to the normal functioning** of immune and other body cells caused by **stressors such as infections** more likely underlie this disease."

Research Team 3's study, entitled "The Bioenergetic Health Index of NK Cells as a Diagnostic Tool for Chronic Fatigue Syndrome," takes a look at **natural killer (NK) lymphocytes** (a type of white blood cell), a critical first defense against viruses and cancers. NK cell dysfunction is a **pathological hallmark** in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

Research Team 4's study, entitled "Autoimmune Signature in CFS/ME," **combines in-depth genetic screening** methodologies with the study of **autoimmune factors** regulating a specific type of surface receptors important in cellular signaling and function.

Research Team 5's study, entitled "HHV-6 Mediated Mitochondrial Modulation and Its Association to ME/CFS," examines the **role of human herpesvirus 6 (HHV-6)** in the development of ME/CFS.

For more information on the studies summarized above, please visit SolveCFS.org/2016-ramsay-award-program-results/ or check out the December issue of *Research 1st* in our SMCI publication archive located at SolveCFS.org/archive.

SMCI-Directed Research Projects

Dr. Zaher Nahle has led the creative scientific work to design and invest aggressively in much-needed projects to further understanding of the pathophysiology of ME/CFS. With a growing number of targeted investments in severe knowledge gaps (such as pathway and biomarker discovery, immuno-senescence and cell-cycle energetics, drug screening and functional genomics, diagnostics and advanced imaging, and metabolomics and big data research), we are creating value across every phase of the discovery process. These are the elements of a growing portfolio of investment in ME/CFS at some of the most prestigious medical centers and research establishments in the country, including Washington University in St. Louis, the University of Washington, Memorial Sloan Kettering Cancer Center, Cornell University, and Metabolon.

Pathway and Biomarker Discovery. Original research in the areas of bioenergetics, metabolomics, and lipidomics using high-throughput technology. Testing completed. Partners in this SMCI-Directed Research Study include Dr. Sue Levine of **The Levine Clinic** in New York, Dr. Maureen Hanson of **Cornell University**, and metabolomics leader **Metabolon**.

- Analysis of same ME/CFS patients characterized for their gut microbiome imbalance using metabolomics and lipidomics methodologies; this is a powerful, integrative approach

- Analysis of well-characterized twins, one with ME/CFS and the other without, to study possible genetic and monogenetic differences in an ideal comparative group
- Analysis of metabolomics profile in patients before and after exercise to characterize the foundation of exertion intolerance in ME/CFS patients in well controlled settings

Immuno-senescence and cell-cycle analysis in the pathophysiology of ME/CFS. Characterization of the disturbances in enzymes and cell-cycle regulators that control cell function using specialized senescence laboratories in collaboration with leaders in the field. Partners in this targeted initiative include Dr. Sheila Stewart of **Washington University in St. Louis** and Dr. Masashi Narita of the Narita Group at **Cambridge University**.

- Analysis of the molecular underpinnings of cellular senescence (a fundamental biological process whose pathophysiology manifestations are reminiscent of aging-related senescence and the arrest of cell function), effects on muscle weakening, dysautonomia, and neurological dysfunction

Drug screening and functional genomics. Studies aiming to uncover potential drug screening targets in ME/CFS. Partners in this targeted initiative include leading experts at **Memorial Sloan Kettering Cancer Center**, namely Drs. Ralf Garippa, Scott Lowe, and Myles Fennell.

- Uses ME/CFS immune cells and chemical libraries of characterized compounds to identify targets for rapid therapeutic application.
- Objectives include promoting immune cells' ability to kill intruders and bolstering ATP production and bioenergetics health using the power of big data and pharmaceutical-grade technologies.

A Collaborative Project through Our Cathleen J. Gleeson PhD Fund

This project, funded by our Cathleen J. Gleeson PhD fund, focuses on **diagnostic testing using non-invasive technology** to measure muscle metabolites in ME/CFS patients for diagnostic testing. This project is led by Kevin Conley, PhD, professor of radiology and co-director of the Translational Center for Metabolic Imaging at the University of Washington and David Maughan, PhD, a professor emeritus of molecular physiology & biophysics at the University of Vermont and visiting scholar in radiology at the **University of Washington**.

SMCI's MeetME Travel Awards

This program enables junior scientists and underrepresented groups to attend ME/CFS conferences and build scientific networks by paying their travel expenses for ME/CFS-focused meetings and conferences around the world.

Per Dr. Nahle, "As you can see, we already have many promising programs and studies under our research umbrella. And you have our steadfast commitment to expand on our efforts in 2017, building on our activities of this past year. Previously, I've borrowed the words of President Lincoln in a time of political uncertainty: 'The dogmas of the quiet past are inadequate to the stormy present. The occasion is piled high with difficulty, and we must rise with the occasion.' This has never been more applicable to the here and now in the field of ME/CFS research. That is precisely why we, through our research programming, are shifting the paradigm and altering the status quo." ■