Carl-Åke Däcker 2022-11-15

Kortfattad beskrivning av verksamheten inom Open Medicine Foundation

1. Historik

Nedan följer en kort, kronologisk historiebeskrivning av Open Medicine Foundations grundande och utveckling.

2012:

- Linda Tannenbaum grundar Open Medicine Foundation (OMF) och blir stiftelsens president. Hennes ambition var att skapa bättre förutsättningar för sin dotter som vid 16-års ålder insjuknade i ME/CFS 2006. Hon fick höra att det inte fanns någon diagnostisk test eller behandling av sjukdomen som skulle kunna förbättra tillståndet för sin sängbundna dotter. Efter att ha undersökt saken noga kom hon till slutsatsen att det i stort sett var en total avsaknad på öppen, globalt samarbetsinriktad forskning inom området samt forskningsmedel. För att råda bot på detta grundade hon OMF med målsättningen att samla in forskningsmedel samt skapa en bred, storskalig forskningsverksamhet för diagnostisering, behandling och slutligen botemedel för ME/CFS och andra kroniska komplexa sjukdomar.
- Hon registrerar in OMF i Kalifornien som en icke vinstdrivande stiftelse med målsättningen att öka forskningsaktiviteten beträffande kroniska komplexa sjukdomar.
- Linda hjälper till att organisera MERIT (Myalgic Encephalomyelitis Research, Immunology and Treatment). Ett möte som hålls i New York med 20 forskare och kliniska experter där hälften kommer från USA och rsten från andra länder.

2013:

- OMF lyckas samla in fonderade medel på drygt 1,6 millioner dollar sedan stiftelsen grundades i augusti 2012.
- Linda och ett team av volontärer bygger upp en internationell databas och börjar kontakta och kommunicera med forskare och organisationer över hela världen angående ME/CFS, fibromyalgi, kronisk borrelia och autism.
- OMF:s volontärer bygger upp sociala media för OMF.
- Linda tar kontakt med tänkbara donatorer och skapar en databas för att samla in medel för grundforskning.
- OMF finansierar inledande forskningsprojekt.
- Linda sprider information om ME/CFS och är talare vid en middag i samband med ”Invest in ME Conference” som hålls i London.
- Hon etablerar ett globalt perspektiv och besöker forskare och patienter i Sverige för att inleda ett internationellt samarbete.

2014:

- Linda och Ronald Davis vid Stanford University kommer överens om att bilda ett vetenskapligt råd för OMF. Linda informerar Ron att om han kan engagera forskare för forskning inom området så ska hon ordna med finansieringen.

- Ronald Davis upprättar OMF:s vetenskapliga råd och dess första möte hålls i oktober hemma hos Linda i Los Angeles.
- Det första välgörenhetseventet för OMF organiseras.
- OMF samlar in medel till det första stora forskningsprojektet som rekommenderats av vetenskapsrådet: ”The Severely Ill Patient Big Data Study (SIPS) — to examine the most severely ill patients for the strongest signals in search for a biomarker”.

2015:

- Etablerar “The End ME/CFS project”. OMF fortsätter att samla in forskningsmedel och öka takten inom forskningsområdet.
- Ökar insamlingsaktiviteterna genom att engagera ett konsultföretag specialiserat på donationer till välgörande verksamheter.

2016:

- OMF har samlat in över 6.15 millioner dollar sedan starten i augusti 2012.
- Finansierar Dr. Naviaux’s ”Validate Metabolics Study”.
- Ökar antalet medlemmar i det vetenskapliga rådet.
- Ger internationell spridning av sin verksamhet genom deltagande i IACFS/ME-konferensen i Fort Lauderdale, Florida.
- Vinner 2016 ”Top-Rated Award, Great Nonprofits award” för positiva utlåtande från sina donatorer.

2017:

- OMF etablerar och finansierar “the ME/CFS Collaborative Research Center” vid Stanford University under ledning av Ron Davis.
- OMF finansierar och är behjälpliga att starta ”OMF ME/CFS Data Center” för att börja analysera data från allvarligt sjuka patienter med data som görs internationellt tillgängliga på OMF:s hemsida.
- OMF finansierar Dr. Jonas Bergquist’s forskargrupp vid Uppsala universitet, för att studera ME/CFS antikroppar i blod och ryggmärgsvätska.
- OMF översätter och kommunicerar sin verksamhet till ett flertal språk för människor i över 100 länder.
- Linda avslutar “the ME/CFS World Wide Tour” som onnefattade 21 presentationer i sex länder och sju städer i USA.
- OMF sponsrar ”The Symposium on the Molecular Basis of ME/CFS” vid Stanford University med 30 forskare och 2700 deltagare via videolänk och 300 på plats.

2018:

- Utökar verksamheten vid ME/CFS Collaborative Research Center, Stanford University genom ökad finansiering av dess ME/CFS forskning.
- OMF lanserar “ME/CFS Clinical Collaborative research Center” vid Harward University.
- Finansierar “Red Blood Cell Deformation” studien som öppen källa.
- Finansierar fler forskare inom området både på Stanford och Harwards Universities.
- OMF Canada ansöker om status som välgörenhetsorganisation.

2019:

- OMF lyckas samla in 24 miljoner dollar sedan starten 2012.

- OMF sponsrar “Third Annual Community Symposium & Working Group Meeting” vid Stanford University. Ämnet för konferensen är “the Molecular Basis of Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME / CFS).
- OMF expanderar sina “Collaborative Research Center” till Uppsala universitet under ledning av Jonas Bergquist, MD, PhD.
- OMF finansierar publicering, i Diagnostics, av artikeln ”On metabolic trap hypothesis” skriven av Dr. Robert Phair.
- Dr. Ron Davis håller föredrag vid “the Biomedical Research into ME Colloquium and the Invest in ME Research International ME Conference i London,

2020:

- OMF adderar ett fjärde “ME/CFS Collaborative Research Center” vid CHU Sainte-Justine/Université de Montréal i Québec, Canada under ledning av Alain Moreau PhD.
- OMF finansierar; “Covid-19 and ME/CFS”, “Study on Covid-19”, “New Brain fog study” och “Nitrogen hypothesis study”.
- OMF:s forskare får forskningsbidrag för ME/CFS forskning från NHMR i Australien.
- OMF lanserar OMF Australien.

2021:

- 4.5 millioner dollar samlades in under 2020.
- 7 forskningsartiklar finansierade av OMF publicerades under året.
- OMF adderar formellt ett sjätte ME/CFS Collaborative Research Center för att förbättra den datatekniska analysen av forskningsdata med Wenzhong Xiao Phd som ledare med ambitionen att vara en resurs för de övriga fem forskningscentra vad gäller dataanalys och kvalificerad utvärdering.
- OMF finansierar ett behandlingsinriktat projekt som drivs vid Harward University med målsättningen att lindra hjärndimma.

2022:

- OMF hedras med det förstklassiga priset 2022 från ”Great Nonprofits”. Det är sjunde året i rad som OMF tilldelas denna utmärkelse.
- Ett decennium av hopp, OMF firar 10-års jubileum 2022!
- OMF lanserar sitt sjunde forskningscenter “The OMF Supported Medical Education Resource Center (MERC) vid Bateman Horne Center. I partnerskap med Bateman Horne Center, har MERC ambitionen att öka andelen kunniga vårdgivare med kompetens att behandla ME/CFS, lång-covid och relaterade multisystemt kroniska komplexa sjukdomar.

2. Publikationer från forskning som sponsrats av OMF

De första åren av OMF:s verksamhet var ägnad åt att samla in forskningsmedel och knyta till sig forskningsutövare för att bedriva forskning inom området. När forskningen väl kommit i gång tog det ett antal år innan det ledde till vetenskapliga publikationer men från 2019 kommer det fram artiklar i en god takt vilket visar att verksamheten bedrivs med hög aktivitet och många olika angreppsvinklar.

2016:

Metabolic features of chronic fatigue syndrome by Robert Naviaux, MD, PhD, Stanford Collaboration.

2019:

The IDO Metabolic Trap Hypothesis for the Etiology of ME/CFS by Robert D. Phair, PhD and Ron Davis, PhD, Stanford Collaboration.

A Nanoelectronics-blood-based diagnostic biomarker for ME / CFS by Rahim Esfandyarpour, PhD and Ronald W. Davis, PhD, Stanford Collaboration.

Red Blood Cell Deformability is diminished in patients with Chronic Fatigue Syndrome, by Anand Ramasubramanian, PhD and Ronald Davis, PhD, Stanford Collaboration.

2020:

Profile of circulating microRNAs in myalgic encephalomyelitis and their relation to symptom severity, and disease pathophysiology by Alain Moreau, PhD, Montreal Collaboration.

Autoantibodies to beta-adrenergic and muscarinic cholinergic receptors in Myalgic Encephalomyelitis (ME) patients by Jonas Bergquist, Uppsala Collaboration.

Acute necrotizing encephalopathy with SARS-CoV-2 RNA confirmed in cerebrospinal fluid by Jonas Bergquist, Uppsala Collaboration.

2021:

Lessons From Heat Stroke for Understanding Myalgic Encephalomyelitis/Chronic Fatigue Syndrome by Dominic Stanculescu, Nuno Sepúlveda, Chin Leong Lim and Jonas Bergquist.

A Comprehensive Examination of Severely Ill ME/CFS Patients," by Ronald W. Davis, PhD and Wenzhong Xiao, PhD, Stanford Collaboration.

Theory: Treatments for Prolonged ICU Patients May Provide New Therapeutic Avenues for ME/CFS, by Jonas Bergquist, MD, PhD, Uppsala Collaboration.

Phase 1 study to access safety, tolerability, pharmacokinetics09, and pharmacodynamics of kynurenine in healthy volunteers, by Jonas Bergquist, Uppsala Collaboration.

Insights from Invasive Cardiopulmonary Exercise Testing by David Systrom, MD, Harvard Collaboration.

Mechanisms That Prevent Recovery in Prolonged ICU Patients Also Underlie ME/CFS by Jonas Bergquist, MD, PhD, Uppsala Collaboration.

Microfluidic Point-of-Care Testing: Commercial Landscape and Future Directions by Ronald W. Davis, PhD and Amit K. Saha, Stanford Collaboration.

2022:

When a 17-Year-Old Girl Is Diagnosed with Myalgic Encephalomyelitis: A Case Study from the Swedish Health Care System—A Parent Perspective by Eva Bojner Horwitz, Jonas Axelsson, Olli Polo, Leif Widebert, Töres Theorell, Anabelle Paulino, David Ullman, Jonas Bergquist.

Predictors of post-COVID-19 and the impact of persistent symptoms in nonhospitalized patients 12 months after COVID-19, with a focus on work ability by Marta A. Kisiel, Helena Janols, Tobias Nordqvist, Jonas Bergquist, Simone Hagfeldt, Andrei Malinovschi and Magnus Svartengren.

Phenotypic Characteristics of Peripheral Immune Cells of Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome via Transmission Electron Microscopy: A Pilot Study by Fereshteh Jahanbani, Rajan D. Maynard, Justin Cyril Sing, Shaghayegh Jahanbani, John J. Perrino, Damek V. Spacek, Ronald W. Davis, Michael P. Snyder.

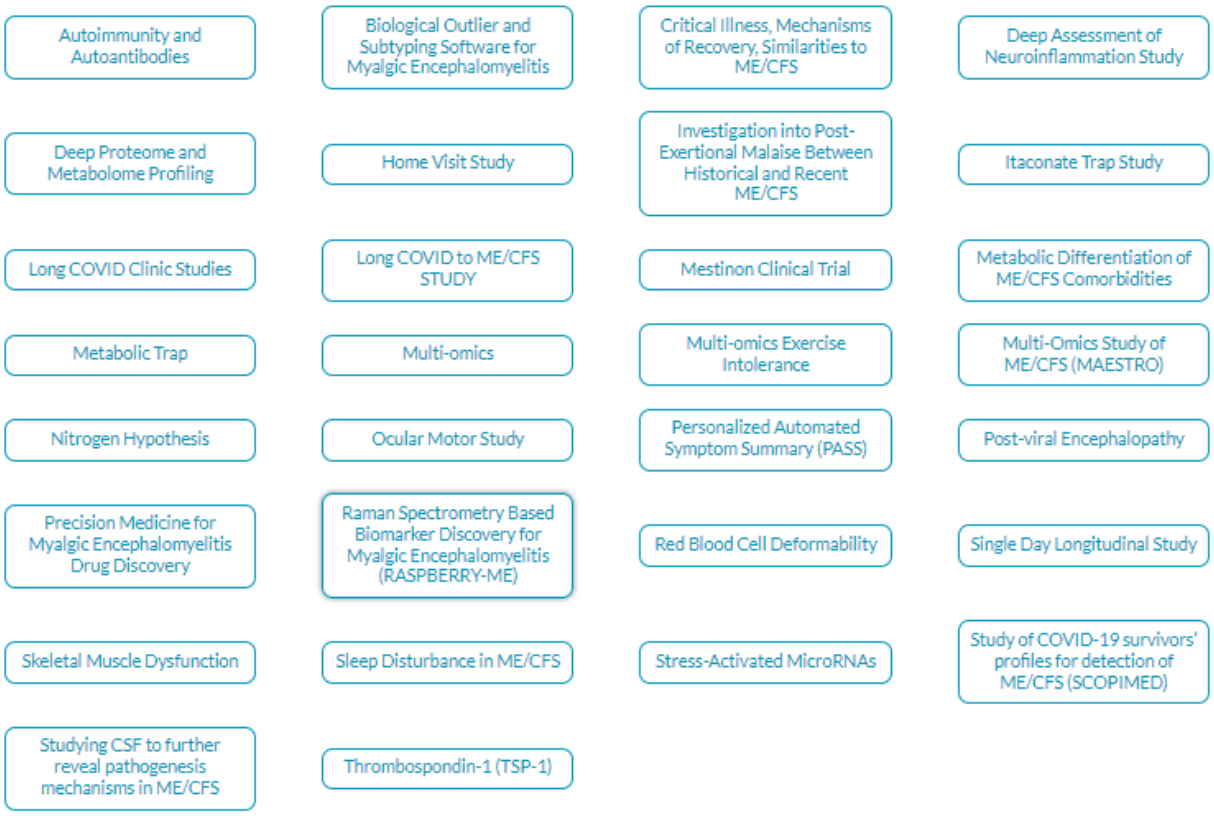
Neurovascular Dysregulation and Acute Exercise Intolerance in ME/CFS: A Randomized, Placebo-Controlled Trial of Pyridostigmine by Phillip Joseph, MD, Rosa Pari, MD, Sarah Miller, BS, Arabella Warren, BS, Mary Catherine Stovall, BS, Johanna Squires, MSc, Chia-Jung Chang, PhD, Wenzhong, Xiao, PhD, Aaron B. Waxman, MD, PhD, David M. Systrom, MD.

The underlying sex differences in neuroendocrine adaptations relevant to Myalgic Encephalomyelitis Chronic Fatigue Syndrome by Natalie Thomas, Caroline Gurvich, Katherine Huang, Paul R Gooley, Christopher W Armstrong.

Drawing on Findings From Critical Illness to Explain Myalgic Encephalomyelitis / Chronic Fatigue Syndrome by Jonas Bergquist and Dominic Stanculescu.

3. Aktuell forskningsverksamhet

Under överinseende av OMF:s styrelse och vetenskapliga råd drivs inte mindre än 30 forskningsprojekt med OMF:s strategiska målsättning att förbättra diagnos och behandling av ME/CFS, efterbehandling av borrelia samt relaterade kroniska komplexa sjukdomar.



1. Autoimmunity and Autoantibodies

Study aim: Investigate potential differences in adrenergic and muscarinic receptor autoantibody levels in plasma and cerebrospinal fluid (CSF) samples between ME/CFS patients and healthy controls, examine why these autoantibodies start to show up in the disease process and how we might positively impact this process with various drug targets and immune regulatory treatments. Being able to explain these underlying mechanisms may provide the validation needed for specific ongoing treatments.

Study hypothesis and description: The development of autoimmune antibodies is a consistent finding across HSE, ME/CFS, Long COVID and provide a window into the neurocognitive disturbances, peripheral symptoms, POTS, pain, and other targets of these autoantibodies. Previously, autoantibodies have been observed to have increased binding to adrenergic and muscarinic receptors in ME/CFS patients. It is hypothesized that these autoantibodies may be part of the pathogenesis of ME/CFS and patient symptom.

Research team: Uppsala.

2. Deep Proteome and Metabolome Profiling

Study aim: Collaborate with OMF CRCs in Uppsala and Melbourne to establish a global perspective. Decode the molecular mechanisms underlying ME/CFS and contributing to specific symptoms with a particular emphasis of post-exertional malaise (PEM) through:

- Deep phenotyping of ME patients.
- Global proteomic plasma profiling of ME patients.
- Global metabolomics plasma profiling of ME patients.

Study hypothesis and description: By leveraging our expertise across Open Medicine Foundation ecosystem and through a unique partnership between three OMF Collaborative ME/CFS Research Centers (Melbourne, Montreal, and Uppsala), our research team will examine the connections between molecules circulating in the blood and ME.

This project will provide a more comprehensive understanding as to why some ME patients exhibit different symptoms and how post-exertional malaise exacerbated many symptoms. Identifying specific biomarkers will aid in the development of risk prediction of complications associated with ME, early prevention and better treatments to alleviate the most severe symptoms, which can lead eventually to new therapeutic approaches to cure ME.

No single-omics approach can completely elucidate the multitude of alterations taking place in ME. The DOMINO-ME project will couple a deep phenotyping characterization of ME patients to unbiased discovery strategies by combining global proteomic and metabolomics plasma samples profiling to uncover ME pathogenesis.

Research team: Melbourne/ Montreal/Uppsala.

3. Long Covid Clinic Studies

Study aim: The newly established clinic in Uppsala will continue the work of the OMF-Funded Multicenter Collaborative Study on COVID to ME/CFS progression.

Study hypothesis and description: The clinic provides an opportunity to continue studying the disease process as it develops, and hopefully better understand ME/CFS. A subset of the previously critically ill patients will be monitored for disease progression over time alongside non-critically ill Long Covid patients who will also visit the clinic for continuing symptoms.

As with the previous study investigators will use genomics, proteomics, metabolomics, and immunology to recover as many immune cells as possible, and to characterize their evolution to ME/CFS. Furthermore, we are studying the plasma and cerebrospinal fluid (CSF) to identify proteins and large molecules (e.g., antibodies) as well as small molecules that appear or disappear in association with the development of ME/CFS.

Research team: Uppsala

4. Metabolic Trap Study

Study aim: Beginning in 2018, the aim of this study was to test the hypothesis developed by Dr Phair that a crucial component of metabolism in ME/CFS patients appears to be “trapped” in an unhealthy state.

Study hypothesis and description: The metabolic trap theory emerged from the genetic and metabolomics data from the Severely ill Patients Study (SIPS). Using previously published work, Dr Phair has developed a computational program that can model the flow of metabolism throughout the body and its cells. Using this technology, Dr Phair can determine any points that may disrupt the flow using genomic and metabolic information and this has led to the hypothesis of a metabolic trap that occurs in ME/CFS patients at the point in metabolism where tryptophan is converted to serotonin and kynurenine.

Research team: Melbourne

5. **Nitrogen Hypothesis**

Study aim: This project aims to test the nitrogen hypothesis, which is that damaging, nitrogen-containing by-products of energy metabolism accumulate more readily in the cells of ME/CFS patients.

Study hypothesis and description: ME/CFS is diagnosed by its symptoms, which include post-exertional malaise, fatigue, and brain fog. It is unclear how these symptoms arise, and there are likely multiple routes to arrive at this chronic pathological state. However, there is a fundamental defect in energy metabolism in ME/CFS, which may be a common underlying cause of its symptoms.

We have hypothesized that reactive nitrogen by-products are accumulating in the cells of ME/CFS patients as a result of using amino acids for energy production in the mitochondria. To test this hypothesis, we will culture blood-based immune cells and feed them with labelled sugar, fats and amino acids. As the cells use the labelled sugar, fat and amino acids for energy production we will be able to monitor how their metabolism differs from healthy controls.

Research team: Melbourne.

6. **Precision Medicine for Malgic Encephalomyelitis. Drug discovery and clinical trials (REMEDIAL)**

Study aim: The REMEDIAL project continues the work commenced with MAESTRO and will lead to a better understanding of the molecular mechanisms underlying ME/CFS pathophysiology, the persistence and variability of the symptoms, and will contribute to the identification of targets and therapeutic agents for intervention.

Study hypothesis and description: Our study will couple a deep phenotyping characterization of ME/CFS patients to the development of cellular and animal models for repurposing current drugs to accelerate the proof-of-concept of different therapeutic interventions for ME/CFS. Indeed, precision medicine is essential to address the clinical complexity of ME/CFS and to identify the best therapeutic options to cure ME/CFS.

Research team: Montreal.

7. **Skeletal Muscle Dysfunction Research**

Study aim: This project aims to explore the biological changes that occur in the muscles during Post-exertional Malaise (PEM).

Study hypothesis and description: Post Exertional Malaise (PEM) is the key feature of ME/CFS, given the extensive characterization of muscle exertion and recovery in healthy people, the evaluation may indicate how the disease perpetuates.

The hypothesis is that the inflammation-related recovery mechanisms become dysfunctional in the ME/CFS disease, and this dysregulation causes a delayed recovery of muscle after exertional stress.

Research team: Harward.

8. Studying CSF to further reveal pathogenesis mechanisms in ME/CFS

Study aim: The goal of this research is to reveal more information about the role of immunology and neuroinflammation in ME/CFS, and the underlying mechanisms of related pathogenesis that takes place.

Study hypothesis and description:

- Underlying pathological mechanisms of ME/CFS are to a large extent unknown, but the presence of autoantibodies, cytokine pattern deviations and the presentation of cognitive and autonomic nervous system related symptoms indicate the role of immunology and neuroinflammation in the pathogenesis of the disease.
- Studying cerebrospinal fluid (CSF) could specifically provide information of the pathological processes occurring in the central nervous system.

Research team: Uppsala/Melbourne

9. Biological Outlier and Subtyping Software for Myalgic Encephalomyelitis

Study aim: This project will develop a software tool to rapidly look for metabolism anomalies in an individual which might be explained by their genes. It will also look for potentially damaging genes in individuals and it will attempt to group ME/CFS patients based on their genetic and metabolic profiles.

Study hypothesis and description: The analytical tool will be developed using pre-existing UK Biobank gene and metabolism data from over 1000 self- reported ME/CFS patients. Findings from this data will then be validated on gene and metabolism data we produce ourselves from blood received from 300 ME/CFS patients recruited by the Australian ME/CFS Biobank.

This tool will be important in understanding the complexity of the individual with ME/CFS and may provide clues to potential missed diagnoses.

Research team: Melbourne.

10. Home Visit Study

Study aim: This study provides a unique opportunity to bring the lab directly into patient's homes and provide immediate analysis of samples over an extended period of time. This longitudinal approach, without the invasive and/or PEM-induced measures, will be vitally important in other patient cohorts and will decrease the study impact on patients from using more invasive and impactful measures (use of 1 peripheral vein catheter for all blood samples, limits the impact on patients).

Study hypothesis and description: Combined with clinical data and survey data, this massive data set should provide a significant picture to understand post-viral diseases.

- Energy metabolism markers during mild mental and physical exertion analyzed on-site inpatient homes with immediate analysis of samples.
- Samples collected every 5-15 minutes over 6-7 hours, monitoring in real time baseline compared to longitudinal data.
- Complement this with full metabolomics screening to compare and contrast the findings in metabolic/mitochondrial disturbances over time.
- Targeting 25 PWME (ell/SIPS) + 25 Controls + 25 Contrast (elite athletes)

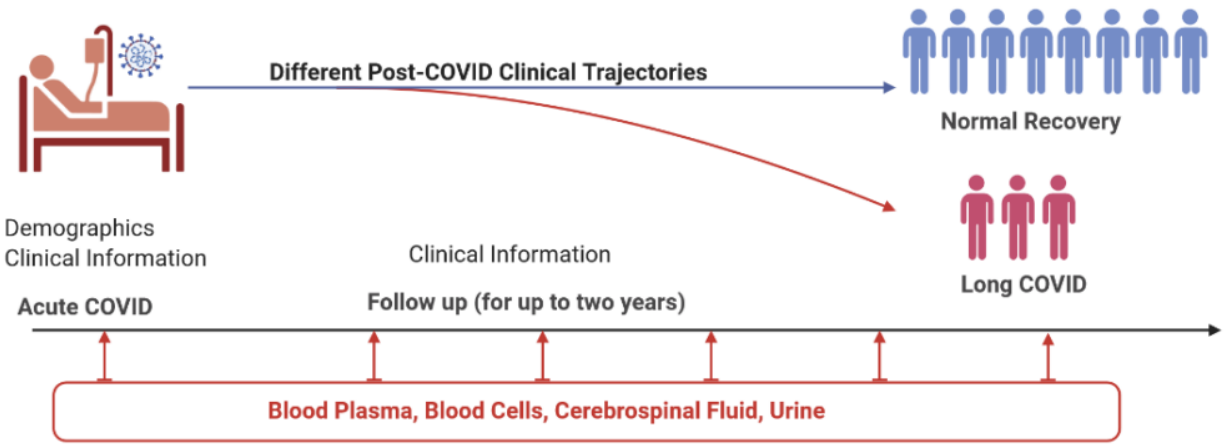
Research team: Uppsala

11. Long Covid to ME/CFS Study

Study aim: OMF secured a $1 million grant to launch the first year of an international, multi-year study across the six OMF supported Collaborative Research Centers (CRC). The aim of this study is to examine Long COVID transitioning to ME/CFS.

Study hypothesis and description: OMF has brought together its global collaborative network, across 6 research centers to carry out this global effort in several stages, using a $1,000,000 grant made specifically for this effort. We are actively working to raise additional funding to continue this critical study.

Researchers are testing and analyzing data from individuals from the point of early COVID-19 illness through their recovery or prolonged illness state. This study has an opportunity to reveal what causes one to fully recover versus those at high risk of developing ME/CFS.



Time-Series Multi-Omics Analyses: Viral Sequencing, Cytokines, Hormones, Metabolomics, Proteomics, and Transcriptomics

This data will be compared to the OMF-Funded Post-Viral Complications in Herpes Simplex Encephalopathy (HSE) study data to provide another post-viral contrast. This study design offers the chance to elucidate precise pathological mechanisms of ME/CFS and other post-viral illnesses, uncomplicated by factors associated with the chronicity of the illness, the potential identification of diagnostic biomarkers and potential targets for the development of treatments for the future.

Research team: All

12. Multi-omics

Study aim: Beginning in 2016, the aim of this study was to extend the Severely ill Patient Study (SIPS) and conduct a comprehensive “Big Data” analysis on ME/CFS patients and their families.

Study hypothesis and description: The rationale of this study is that by using the unaffected family members as a control, the differences observed in the ME/CFS patients will be more specific to the disease and less related to differences in genetics, environment, and diet.

Research team: Stanford.

13. Ocular Motor Study

Study aim: The aim of this project is to fully characterize eye movement changes in ME/CFS on two consecutive days, identifying an ocular motor signature that is unique to the disorder.

Study hypothesis and description: Ocular motor (eye movement) assessment can be used in the diagnosis of various neurological diseases. Eye movement requires signaling across a vast, well-defined neural network that incorporates over 50% of the brain. Damage at any point across this extensive network manifests as abnormalities in eye movement. In a given disease/disorder, this manifests in a unique eye movement signature that can be measured using high powered eye-tracking technologies, allowing the quantification of even the subtlest of changes. This is especially relevant for those with ME/CFS as symptoms can often be subtle and prone to fluctuation (i.e., tending to worsen following exertion).

A defined ocular motor signature for ME/CFS would provide the first, objective, quantifiable marker for this disease that can be used to provide diagnostic certainty, provide a sensitive measure of progression or future treatment effect, and to inform the pathophysiological underpinnings of the disease.

The aim of this project, therefore, is to fully characterize eye movement changes in ME/CFS on two consecutive days, identifying an ocular motor signature that is unique to the disorder.

Research team: Melbourne

14. Raman Spectrometetry Based Biomarker Discovery for ME

Study aim: The overarching goal of RASPBERRY-ME project is the characterization of the biomolecular signature of Myalgic Encephalomyelitis using Label-free Raman Spectroscopy (RS) and machine learning model.

Study hypothesis and description: Raman spectroscopy is a non-destructive, rapid, and low-cost technique allows the study of the molecular composition of biological fluids like blood, or inside a cell when combined with confocal microscopy. This innovative approach could lead to the development of diagnostic tools to better stratify ME patients and find the underlying causes of different symptoms like post-exertional malaise as well as clinical tools to validate the therapeutic potential of pharmacological treatments to treat, stop or mitigate ME through precision medicine.

We hypothesize that our approach will allow the identification of a biomolecular signature of ME both at baseline and in response to the application of a post-exertional stress challenge. We

expect to stratify patients by differentiating severe cases from mild forms of ME. Results from this study will be further combined to ongoing proteomic and metabolomic profiling approaches to better understand the pathophysiology of ME.

Research team: Montreal

15. Sleep disturbance in ME/CFS

Study aim: We intend to examine multiple sleep studies that have been conducted in the past two years and performed at the MGH Neurology Sleep Medicine Laboratory in well characterized patients with ME/CFS.

Study hypothesis and description: In previous sleep studies using traditional methods and techniques, no specific sleep abnormalities have been seen with a single exception highly investigative methods. This proposal intends to examine multiple sleep studies that have been conducted in the past two years and performed at the MGH Neurology Sleep Medicine Laboratory in well characterized patients with ME/CFS.

Furthermore, in previously collected brain fluid samples, we will develop techniques to measure orexin, which is an important protein that control sleep boundary states. Lastly, in a pilot study, we will examine a small ME/CFS patient cohort with our sleep colleagues at the Beth Israel Deaconess Medical Center Clinical Research Center using the most advanced technologies available to better identify and understand any possible, if not likely, abnormalities in high frequency signals in the deep brain function.

Prior reports using older methods that are highly influenced by more superficial EEG signals from the brain cortex have failed to identify any identifiable similarities to sleep disorders. However, excessive sleep fragmentation is seen. Deeper brain function, particularly as identified looking at higher frequency events, are possible, if not likely, to be identified as dysfunctional in some way in these patients. From the perspective of symptoms and signs as well as a suggestive prior study evaluating spectral coherence data, the possibility is worthy to explore.

16. Study of Thrombospondin-1 (TSP1) in ME / CFS pathogenesis (STOP-ME)

Study aim: Little is known about the mechanisms causing brain fog, orthostatic intolerance as well as postural orthostatic tachycardia (POTS) in ME/CFS. In that context, we used our previous method with a specific stress-test to identify possible biomarkers that could be involved in the onset and/or progression of the symptoms associated with specific vascular instabilities identified above.

Study hypothesis and description: We propose that elevation of circulating thrombospondin-1 (TSP-1), a multifunction protein, in the blood could reduce brain-blood flow in some persons suffering from ME / CFS leading to a brain fog and post-exertional malaise (PEM). Conversely, a rapid decrease in TSP-1 blood levels in some ME / CFS patients could induce a hypotension resulting in orthostatic intolerance or even POTS.

Research team: ?

17. Critical Illness, Mechanisms of Recovery, Similarities to ME/CFS

Study aim: We propose an initial explanation for how ME/CFS could originate and perpetuate by drawing on findings from critical illness and heat stroke research.

Study hypothesis and description:

- Specifically, we combine emerging findings regarding (a) hypoperfusion and endotheliopathy, and (b) intestinal injury in these illnesses with our previously published hypothesis about the role of (c) pituitary suppression, and (d) low thyroid hormone function associated with redox imbalance in ME/CFS.
- We also describe interlinkages between these pathophysiological mechanisms as well as "vicious cycles" involving cytokines and inflammation that may contribute to explain the chronic nature of these illnesses.

Research team: Uppsala

18. Investigation into Post-Exertional Malaise Between Historical and Recent ME/CFS

Study aim: The study expands on a previously awarded proposal to thoroughly explore the underlying pathophysiology of post exertional malaise (PEM), the hallmark symptom of ME/CFS.

Study hypothesis and description: The hallmark symptom of ME/CFS is the flu-like worsening of symptoms after physical, mental, or emotional exertion known as post exertional malaise (PEM). The underlying mechanism behind this response is currently unknown, and this study aims to contribute useful insights to begin filling this gap. Twenty ME/CFS patients (10 recent and 10 historical) and 10 controls will complete 2-Day serial cardiopulmonary exercise tests (CPET) to not only stimulate physical exertion but also gather pulmonary gas exchange data in these groups. In addition, muscle biopsies after each CPET as well as pre and post blood draws will be performed to provide further mechanistic insights into PEM.

Research team: Harward

19. Mestinon Clinical Trial

Study aim: Open Medicine Foundation is delighted to announce its support of a clinical trial to test the exercise response to Mestinon in people with Myalgic Encephalomyelitis / Chronic Fatigue Syndrome (ME / CFS) with Preload Failure (Clinical Trials Number NCT03674541). This trial is being conducted at the Brigham & Women's Hospital by Dr. David Systrom in association with the Harvard ME / CFS Collaboration at the Harvard Affiliated Hospitals. OMF has provided $150,000 to study people with ME / CFS who demonstrate Preload Failure (PLF) during an invasive cardiopulmonary exercise test (iCPET).

Study hypothesis and description: Dr. Systrom has consistently found that people with ME/CFS suffering from fatigue have PLF. In this instance, PLF is thought to come from an imbalance in the autonomic nervous system and results in reduced filling of the heart during exertion.

Prior studies have shown symptomatic improvement in patients with PLF after treatment with Mestinon. Dr. Systrom intends to evaluate the short-term effects of Mestinon on the autonomic nervous system and neurovascular control in people with ME/CFS with PLF. Studying these features will improve our understanding of ME/CFS and this trial may lead to new therapeutic options for people with ME/CFS.

Research team: Harward in collaboration with Brigham&Womens's hospital.

20. Multi-omics Exercise Intolerance

Study aim: This project aims to understand the origin of postural orthostatic tachycardia syndrome (POTS).

Study hypothesis and description: POTS is one of the more common symptoms of ME/CFS. This syndrome appears to involve the cardiopulmonary and peripheral vascular systems, both are modulated by the autonomic nervous system. It is unclear why these systems become dysfunctional to cause POTS but understanding the biological pathology underlying it will be relevant to helping understand its relationship to ME/CFS.

Cardiopulmonary exercise testing together with direct measurement through invasive arterial catheters (iCPET) has been useful to define the reason for unexplained dyspnea in general populations thought to be heart or lung in origin. Using this same diagnostic tool, ME/CFS patients have been evaluated and found to demonstrate a preload failure (PLF) pattern under maximum exercise. There are two forms of this PLF that has been observed: low flow and high flow. The low flow phenotype appears to be consistent with a failure of the autonomic nervous system to shift blood from the venous to the arterial side of the circulation or another possibility is a reduced total blood volume. On the other hand, the high flow phenotype appears as an arterial to venous shunt in the peripheral circulation or another possibility is a reduced oxygen delivery to peripheral circulatory beds or a reduced utilization by the mitochondria.

Research team: Harward

21. Personalized Automated Symptom Summary (PASS)

Study aim: Given meager research funding and the absence of a consensus on disease mechanism, there has been no definition or single set of criteria that has been validated to make a ME/CFS diagnosis. Therefore, we propose to develop a patient-driven tool named “Personalized Automated Symptom Summary (PASS)” that is intended to aid a clinician more efficiently to define the character and priorities of a patient’s current symptoms of ME/CFS, Post-treatment Lyme Disease (PTLD), or Fibromyalgia (FM).

Study hypothesis and description: Using machine learning and artificial intelligence PASS will enable the patient to create a symptom summary, in less than 30 minutes, that accurately describes their individual current symptoms (including the symptom character and its priorities from their own perspective) in preparation for their upcoming clinician visit. From the patient’s perspective, there are as many as 65 different symptom categories in chronic, complex diseases. This patient summary (and also a clinician summary version) will then be readily available for their clinician to review when the patient arrives for his or her visit. The clinician might choose to confirm facts about those symptoms emphasized in the summary as well as ensure that other relevant symptoms may or may not be present.

Research team: Harward

22. Red Blood Cell Deformability in ME/CFS

Study aim: This work has been accepted for publication in Clinical Hemorheology and Microcirculation and also has been accepted as an abstract for the American Society of Hematology 60th Annual Meeting.

Study hypothesis and description: Several studies have implicated a role of oxidative stress in ME/CFS. Red blood cells (RBCs) are potent scavengers of oxidative stress and their shape changes appreciably in response to oxidative stress; this has been observed in certain inflammatory conditions including obesity and diabetes. The shape of RBCs determine how well these cells can move through blood vessels so it seems pertinent to determine if RBCs in ME/CFS patients are affected. This has led to the development of a microfluidic device that mimics blood flow through microcapillaries.

Research team: Stanford

23. Stress-Activated MicroRNAs in ME/CFS Pathogenesis

Project aim: ME / CFS is a multi-systemic complex chronic disease exhibiting a clinical heterogeneity as main symptoms vary between affected individuals and also overtime. This situation adds to the complexity to decipher its causes and mechanisms as well as to find potential therapeutic targets. Furthermore, severely affected persons with ME / CFS are rarely being investigated. Identifying a specific microRNA signature in ME / CFS will aid in the development of disease risk prediction and improve the clinical stratification of symptomatic patients. Ultimately, discovery of biomarkers may lead to diagnoses that are more accurate, disease prevention measures, and indications on how to treat ME / CFS effectively.

Study hypothesis and description: We designed a clinical intervention, safely producing a post-exertional malaise (PEM), a hallmark symptom of ME/CFS. We hypothesized that a standardized stress-test inducing PEM, will reveal a more specific disease signature associated with ME / CFS symptoms. In that context, we investigated the role of circulating microRNAs, which are small non-coding RNA molecules that can be detected in the blood as well as in other biological fluids.

Research team: ?

24. Deep assessment of Neuroinflammation Study

Study aim: To explore the hypothesis that deranged flow of the cerebrospinal fluid (CSF) due to craniocervical obstructions and/or instability may cause deranged intracranial pressure (ICP), neuroinflammation and cardinal symptoms of ME/CFS.

Study hypothesis and description: The overall aim is to explore the hypothesis that deranged flow of the cerebrospinal fluid (CSF) due to craniocervical obstructions and/or instability may cause deranged intracranial pressure (ICP), neuroinflammation and cardinal symptoms of ME/CFS. If this hypothesis proves true it opens a new research area in ME/CFS and hopes for effective treatment to regulate ICP and relieve symptoms associated with ME/CFS. This study will make use of CNS imaging and analysis of CSF, blood, saliva samples, and will identify proteomic and metabolomic biomarkers of the disease, a highly needed tool in the diagnostic and prognostic process. By the combination of more detailed clinical examination and evaluation and multiOmics biomarker analysis we will be able to provide a more individually adapted care and hopefully cure.

Research team: Uppsala in cooperation with Harward

25. Itaconate Trap Study

Study aim: This project aims to look at metabolic traps in central carbon metabolism that lead to observed altered energy production pathways in ME/CFS.

Study hypothesis and description: One of the key metabolic theses aiming to explain ME/CFS symptoms is the dysregulated nitrogen metabolism theory proposed by Armstrong and colleagues. Three features of this theory make it attractive:

1) it is consistent with the observed shift from carbohydrate to alternative sources of energy (amino acids and fatty acids),

2) it predicts a reduction in oxygen consumption consistent with a hypometabolic state, and

3) it predicts overproduction of ammonia, a known neurotoxin that could explain ME/CFS neurological symptoms. One underdeveloped aspect of the nitrogen metabolism theory of ME/CFS is the mechanistic chain of events connecting the initial infectious or traumatic trigger to a chronically altered state of central carbon and mitochondrial metabolism.

This computational proposal aims to fill that gap by testing mechanisms that have the potential for switch-like or bistable behavior.

Research team: Melbourne

26. Metabolic Differentiation of ME/CFS Comorbidities

Study aim: To investigate the metabolite signatures of ME/CFS patient stool, urine and blood samples and the impact that co-morbidities (IBS and Fibromyalgia) have on these signatures.

Study hypothesis and description: ME/CFS patients often suffer from multiple comorbidities. When observing a cohort of ME/CFS patients we often neglect to consider the impact that co-morbidities are having on the biological signatures produced that might be distinct from ME/CFS alone. In this study we look at ME/CFS patients with and without IBS and Fibromyalgia to determine the impact of these comorbidities.

We expect their impact will highlight the importance of matching for co-morbidities when conducting case-control studies.

Research team: Melbourne

27. Multi-Omics Study of ME/CFS (MAESTRO)

Study aim: The primary goal of this project is to complete our comprehensive analysis of the genome, methylome, miRnome, and their interactions in order to fill the gaps in our understanding of ME/CFS pathophysiology and to identify clinically useful biomarkers.

Study hypothesis and description: Identifying ME/CFS biomarkers will aid in the development of disease risk prediction and improve the clinical stratification of symptomatic patients. Ultimately, the discovery of biomarkers may lead to diagnoses that are more accurate, disease prevention measures, and indications on how to treat ME/CFS effectively.

We also intend to investigate specific targets to determine their clinical utility for the elaboration of novel therapeutic approaches to treat the main symptoms associated with ME/CFS (e.g., PEMS, POTS, sleep disturbances and fatigue). We intend to develop better clinical tools allowing clinicians to diagnose ME/CFS and select the best treatments to address their medical needs.

Research team: Montreal

28. Post-viral Encephalopaty

Study aim: To investigate the correlation between biomarkers for brain injury and long-term neurocognitive outcome, and the interplay with intrathecal inflammation, in patients with herpes simplex encephalitis (HSE).

Study hypothesis and description: The further understanding of the post-viral fatigue phenomenon that many HSE patients present which could give new insights in the initial episode of Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome (ME / CFS) since very many of the patients (70-80%) reports on an initial infection (e.g. mononucleosis) in the onset of the disease.

Our findings could give predictive evidence of long-term neurocognitive outcome in HSE and suggest a causative chain of events where brain tissue damage increases the risk of subsequent prolongation of CSF inflammation and post-viral fatigue. The data could provide guidance for a future intervention study of immunosuppressive therapy administered in the recovery phase of HSE and other viral infections with neurological sequelae.

Research team: Uppsala

29. Single Day Longitudinal study

Study aim: This study seeks to understand the biological mechanisms driving the symptomatology of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) using metabolomic and lipidomic high-throughput analysis and high-frequency blood sampling over a 6.5 to 7.5 hour period conducted at two separate sites (Melbourne and Uppsala).

Study hypothesis and description: A growing body of literature suggests that energy, amino, and lipid metabolism are clearly implicated in the pathophysiology of Myalgic Encephalomyelitis / Chronic Fatigue Syndrome.

Although many studies have shown differences in several metabolites and lipids between ME/CFS and control populations, no single metabolite has been demonstrated to be consistently observed through these studies. This may be due to the high variability amongst ME/CFS patients both clinically and biologically speaking.

One way to overcome this is to conduct repeated measures study designs whereby numerous biological replicates are collected for each patient and control, allowing for each subject to act as their own control. This reduces sources of variation and controls for factors that cause variability between subjects and is an important technique for research into highly variable or heterogenous populations like ME/CFS.

This study proposes to measure metabolites and lipid species using a novel, sophisticated repeated-measures study design. This will help elucidate the biological mechanisms driving ME/CFS symptoms, and works towards finding clinically useful diagnostic blood tests, and new treatment avenues for ME/CFS patients based on the underlying patho-biology.

Research team: Melbourne and Uppsala

30. Study of COVID-19 survivors' profiles for detection of ME/CFS (SCOPIMED)

Study aim: The purpose of this study is to capture a post-COVID-19 infected population willing to participate in phenotyping studies early in the post-COVID-19 illness progression, with an aim of providing targeted effective therapies and preventing the onset and progression of ME/CFS.

Study hypothesis and description: The development of ME/CFS and related conditions like fibromyalgia (FM) among a subset of COVID-19 long-haulers is thought to be the result of a broad molecular-level reorganization occurring at the epigenetic level, which drives the host response following SARS-CoV-2 viral infection.

While ME/CFS researchers understand that many factors likely contribute to the onset of the condition, it is important to identify the risks of ME/CFS sequelae as early as possible. Studying the post-COVID-19 infected population may offer insight that helps ME/CFS patients by expanded understanding of the progression of the condition and identifying targeted treatment strategies. Finally, the study of COVID-19 long-haulers may shed light on ME/CFS and post-infectious fatigue syndrome following infections other than COVID-19.

Research team: Montreal