

Bridging the blood-brain barrier



Drs Gordon Broderick and Travis Craddock discuss how, through a holistic, systems biological approach, their collaborative work is benefiting the field of neuro-immune medicine



Could you begin by explaining your research objectives?

GB: In a nutshell, our objective is to understand the operating principles, or the basic molecular language, through which the endocrine, immune and nervous systems interact, so that we can intervene therapeutically in a range of immune and neuro-immune disorders.

What interests you about Chronic Fatigue Syndrome (CFS) and Gulf War Illness (GWI)?

GB: These are the poster children for poorly understood and stigmatised illnesses. As yet, there is no discernible lesion or single biomarker, though candidates are beginning to emerge. Instead, they present a complex constellation of symptoms that span across multiple regulatory systems in the body. This is an inescapable feature of many, if not most, illnesses and we believe that the approaches we develop, to advance the diagnosis and possible treatment of CFS and GWI, will have broad-reaching implications.

With separate backgrounds in biochemistry, and engineering and biophysics, respectively, can you explain what led you both to collaborate in systems biology?

GB: A fascination with the complexity of the living machine, but also the possibility

of helping improve lives. The latter is why my group has chosen to embed our research in systems biology within the clinical space. You might say our lab bench brings the supercomputer to the bedside. I think that Travis and I were brought together by intersecting curiosities, each of us standing on opposing sides of the fence; the fence being, in this case, the blood-brain barrier. Travis had been focusing on neuronal processes in the brain and I had been focusing on the emergent organisation in the peripheral immune system.

TC: Biology has always fascinated physicists, whether they like to admit it or not. Unlike machines, living systems are in constant flux, open to their environment and adaptable. Physics has a strong handle on how particles interact, but the interesting question is how these so-called inanimate atoms and molecules interact to create living cells, creatures and societies. When I met Gordon, he introduced me to the wide world of systems biology as it applies to immunity. Knitting our passions together has opened the door to exciting discoveries in neuro-immune illness.

Beginning more than 50 years ago, how do you think systems biology has evolved; and how will develop in the future?

GB: I think the field is evolving with the ever-increasing availability of high-throughput measurement technologies. For example, low-cost gene product sequencing has made a previously unimaginable detail and breadth of coverage affordable, revealing new mechanisms and supporting more sophisticated, higher fidelity computational models. Of course, this is closely linked to the parallel development of more powerful computing platforms such as Pegasus 2 at the University of Miami Centre for Computational Science. The convergence of

these technologies and skill sets makes this an exciting time for biology and medicine.

In your opinion, what are the biggest challenges facing systems biology today?

TC: In today's technological age, clinical and biological information are gathered at a tremendous rate. The challenge is to retain, organise and analyse this information to find meaningful, consistent patterns. Consider this; for 100 genes treated as either 'on/active' or 'off/inactive', it would take a minimum of 1 trillion petabytes of information to describe all of the different behaviours afforded to this rudimentary genome. This is an astronomical amount of memory. Now consider that the human genome contains roughly 35,000 genes, and the problem rapidly becomes unwieldy. The size and breadth of this problem requires state-of-the-art computing resources, as well as ingenious ways of synthesising the data into a coherent picture describing bodily function.

Professor Broderick, you have been awarded the Discovery Learning Preceptor Excellence Award from the Faculty of Medicine, University of Alberta for three consecutive years. How important is it to you to foster the development of the next generation of systems biologists?

GB: I think it is especially important to impart this integrative and systems-based thinking to future clinicians. Medical training and the delivery of care are still partitioned into separate specialities based on physiology and anatomy. I'm hoping that as these students move forward into residency and fellowship training where they will focus even more intensely on a given system – urinary, reproductive, cardiovascular, etc. – that they will do so in a way that is mindful of the greater context in which each of these systems operate.

Institute for Neuro-Immune Medicine

Debilitating multi-symptom disorders are universally underserved in healthcare, but a new educational research and treatment facility at Nova Southeastern University is making them its priority

BASED AT NOVA Southeastern University (NSU)'s College of Osteopathic Medicine, Florida, the Institute for Neuro-Immune Medicine (INIM) is the first of its kind to fully integrate multidisciplinary research with the treatment of complex neuroinflammatory and neurodegenerative disorders such as chronic fatigue syndrome (CFS) – or myalgic encephalomyelitis (ME) – and Gulf War illness (GWI) in the US. Opened in 2013, the Institute provides state-of-the-art facilities for conducting bench-to-bedside research into these illnesses, and has the capacity to treat approximately 1,300 individuals. It is directed by Dr Nancy Klimas, Chair of Clinical Immunology at NSU's College of Osteopathic Medicine, renowned worldwide for her dedication to improving the knowledge and treatment of neuroimmune disorders.

COMMUNAL CONDITIONS

The Institute's focus on integrated programmes and collaboration between the disciplines and external research facilities is reflected in its physical layout. In strong opposition to a 'silo mentality', its clinical, research and educational objectives are tied together in one location to avoid any disconnect between them. Fostering an atmosphere of cross-pollination between skill sets and bodies of knowledge, this communal approach means that the end goal of patient wellbeing remains clearly in focus.

Based on a think-tank model, INIM reaches out to outstanding scientists and clinicians of neuroimmune disorders and related fields via onsite and online meetings in order to capitalise on community-wide know-how. Connecting with the expertise of these diverse individuals opens up doors to new transformative technologies, integrating the latest genomic, proteomic and computational techniques, and helping develop fresh ways of thinking about ME/CFS and GWI, as well as a host of other complex chronic illnesses.

INIM's philosophy of integration does not only extend to the networking of professionals and students, however. By facilitating cooperation between its clinics and research programmes, patients are able to benefit from ongoing studies at the Institute, with the option to share their clinical information and take part in clinical trials.

RESEARCH AT INIM

As evidenced by the work of Dr Gordon Broderick's Clinical Systems Biology Group, the Institute's clinical research programmes are currently labouring toward the discovery of biomarkers and clinical intervention strategies. Funded projects include studies of clinical subgroups of ME/CFS, pathogen discovery and large-scale computer aided design of treatment courses using new and existing pharmacological agents. Of particular interest to INIM investigators is the evaluation a number of agents directed specifically at improving natural killer (NK) immune cell function. These include, but are not limited to, an experimental immunomodulatory drug that is still undergoing trials in accordance with the US Food and Drug Administration (FDA). Through its own development efforts and collaborations with other groups, INIM will continue to be a key player in making the world's first ever medication for treating ME/CFS a reality.

In support of drug target and biomarker discovery, basic research into the fundamental mechanisms of illness focusing on gene expression and regulation in ME/CFS and GWI, are taking place. Important steps are also being taken to develop and validate high fidelity animal models mimicking the course of GWI in humans, a vital component of laboratory research. Concerned with providing the best tools for the job, INIM's lab facilities now host the latest in NanoString gene profiling technology, initially developed at

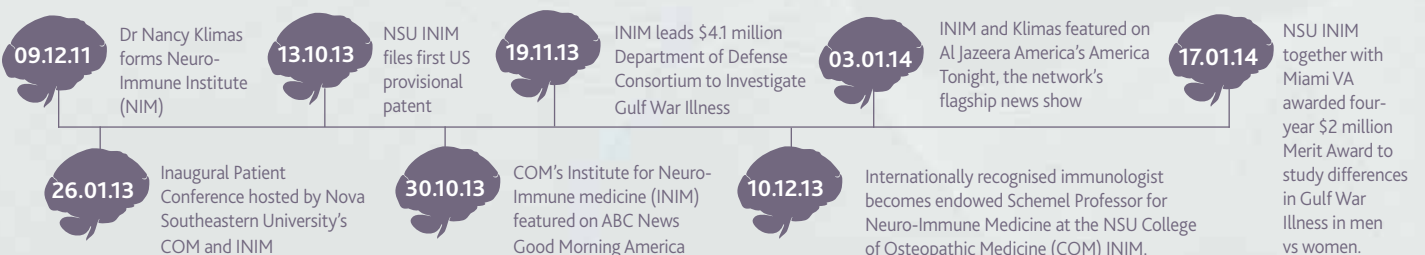
Seattle's Institute for Systems Biology. Using Lambda Rail, South Florida's ultra-high speed data highway, INIM is also combining its own supercomputing resources with those of the University of Miami's Center for Computational Sciences, a top-500 platform worldwide. This will provide researchers and students with access to the best available technologies in molecular, cellular and computational medicine for conducting translational research.

Using novel computational models, research at INIM is brought to life by its onsite ability to assemble seemingly disparate streams of data into cohesive models of illness pathogenesis and use these to simulate and refine the efficacy of possible interventions. Using these methods, INIM is engaged in a multi-site clinical assessment of ME/CFS and GWI, charting the natural history of these and related chronic illnesses, epidemiological studies assessing their impact on public health and the development of a data archive for enabling the discovery of illness triggers and pathogenic mechanisms.

EXPANDING HORIZONS

Already bringing together some of the most qualified experts in the field, INIM's commitment to groundbreaking research for the benefit of its patients means it will continue to foster relationships between members of its core research team and institutions further afield. Plans for the near future to develop funded training programmes for the younger faculty and trainees are underway, as well as an extension of its membership to established international researchers and clinicians as fellows of the Institute. Leveraging government funding with major philanthropic contributions, the relationships that INIM establishes enable the Institute to keep growing and remain a model for integrated cross-disciplinary research into neuroimmune disorders in the US.

Timeline: INIM: Big news



Integrated systems

Researchers at **Institute for Neuro-Immune Medicine** at Nova Southeastern University's College of Osteopathic Medicine, USA, are combining seemingly disparate scientific fields to gain new insights into the immune functions of the brain and its relation to the broader immune response

ACCORDING TO THE Chronic Fatigue and Immune Dysfunction Syndrome Association of America (CFIDS), at least 1 million individuals in the US currently suffer from what is commonly known as chronic fatigue syndrome (CFS) – or myalgic encephalomyelitis (ME). With no conclusive tests available to physicians, this debilitating illness is thought to go improperly diagnosed in approximately 80 per cent of patients. Clinically similar to CFS, Gulf War illness (GWI) has been reported in around 25 per cent of American veterans returned from the first Gulf War. Equal in their severity to chronic conditions such as late-stage AIDS and congestive heart disease, these illnesses have received comparatively little attention, which has led to a lack of public awareness and stigmatisation.

Traditionally, the reaction to these illnesses has been a misguided attempt to compartmentalise and label them as either sleep, cognitive, endocrine or immune disorders. Now recognised as tightly integrated and highly interactive systems, a holistic approach is being taken to study the interconnectedness of the endocrine, nervous and immune system, in efforts to elucidate how immune function in the brain converses with the body's broader immune response. With new establishments like the Institute for Neuro-Immune Medicine

(INIM) at Nova Southeastern University (NSU)'s College of Osteopathic Medicine in Florida dedicating its activities to neurodegenerative illnesses, the shroud over ME/CFS and GWI is beginning to lift.

DOUBLE DISCIPLINE

Looking at these systems in unison, Drs Gordon Broderick and Travis Craddock have combined their backgrounds in engineering, biochemistry, physics and computer science to deploy the mathematics of telecommunication networks in order to gain a deeper understanding of the conversations going on between them. Originally based at the University of Alberta, Canada, the collaboration between Broderick and Craddock has seen them move as Professor and Assistant Professor, respectively, to NSU's Centre for Psychological Studies, and continue their work directing the Clinical Systems Biology Group at INIM.

In order to make maximal use of inherently limited observational data, these researchers have focused much of their efforts on identifying avenues for integrating these data in a framework built on first principles and prior medical knowledge. Addressing the hurdles involved in capturing and using such information has proven challenging, but Broderick's group has successfully developed and implemented models based on decision logic. Understanding how these systems communicate would make it possible to intercede with designed therapeutic messages directed specifically at the differences between healthy individuals and those with ME/CFS or GWI. This approach could enable the development of diagnostic tests, targeted therapies and,



Counterintuitive though it may be, a convergence of engineering and physics with the life sciences is delivering exciting new insight into the field of neuro-immune medicine

perhaps, a strategy for managing the broader scope of neuroimmune disorders so patients can function at their full capacity.

CHARTING RECOVERY

The clinical similarities between ME/CFS and GWI have given rise to the idea that they are variants of one illness, but Broderick and Craddock's studies have demonstrated otherwise. While they may share some immune responses and low-level inflammatory response in the brain, ME/CFS appears to behave more as a latent viral infection might. GWI, on the other hand, appears to present more as a classical autoimmune cascade.

One of the better-recognised triggering events of ME/CFS is infectious mononucleosis (IM), a viral disease caused by the Epstein-Barr virus (EBV). In some cases, patients continue to suffer from ME/CFS for an inordinate period of



Layered network of intracellular communication. Saurabh Vashishtha – PhD student



Dr Gordon Broderick with research fellows Drs Landon Berger and Andrea Kreitz. Photo courtesy of *Edmonton Journal* / Rick MacWilliam



Dr Travis Craddock with Chief Programmer Mark Rice (left) and Lead Programmer Ryan del Rosario (right).

time afterward. Where most studies focus on a snapshot in time of an illness, Broderick joined researchers at the University of Illinois and Northwestern University to track changes in the immune and endocrine responses of over 300 adolescents for 24 months after contracting IM and developing chronic fatigue. They found that after two years, 5 per cent of the cohort still had the illness and three distinct progressions emerged. The difference in recovery profiles has raised an interesting question – whether biomarkers can be identified that might predict in its very early phases how the illness will progress in a specific patient. Looking at different expression levels between cytokines at 24 months from the more integrated perspective of immune context, they identified two cytokines that would have otherwise been passed over. The identification of interleukin-6 (IL-6) and interferon-gamma (IFN- γ), whose expression levels remained the same between patients and controls at 24 months, significantly enhanced the diagnostic potential of IL-8 and IL-23 to discriminate between the recovered controls and patients who remained ill. A closer look using genomic profiling highlighted significant mechanistic pathways for recognising ME/CFS. Significantly down-regulated in the more severe cases and less so in patients who might be getting better, the phenylalanine pathway provides a signpost for distinguishing among post-infectious ME/CFS sufferers the level of care that needs to be delivered and when.

ALTERED AXES

Presenting a completely different cohort to the ME/CFS study, Gulf War veterans suffering GWI are predominantly male and much older. Building on work by senior INIM investigators, Drs Nancy Klimas and Mary Ann Fletcher, subjecting healthy individuals and patients to an exercise regime, Broderick aimed to differentiate between the two illness groups by studying blood samples



Influential regulatory hub holds court over satellite pathways. Saurabh Vashishtha – PhD student

taken at peak activity and after a period of rest. Looking primarily at the immune signalling and detoxification pathways, they were eventually able to achieve 90 per cent accuracy in distinguishing between the groups. As with the post-infectious ME/CFS patients, phenylalanine suppression was found to be the characteristic factor.

Both groups, though suffering from illnesses with very different causes and intracellular behavioural characteristics, are linked by chronic dysfunction of the hypothalamic-pituitary-adrenal (HPA) axis. To restore the HPA axis to its natural homeostatic rest point, conventional treatments have focused unsuccessfully on replacement therapies to address the altered levels of sex and stress hormones observed in patients. The failure of these time-invariable and single agent treatments suggests that the body's response to this dysfunction is to implement a new stable regulatory programme that promotes natural resistance to replacement therapies. In early proof-of-concept work, Broderick and Craddock proposed a treatment strategy that reduces the bioavailability of cortisol, a hormone that modulates immune functions, instead of increasing it. "We can apply dynamic control theory to design time-dependent treatment courses that exploit the body's own regulatory drive," Broderick explains. Delivered according to an optimal treatment schedule, the HPA axis overcompensates for the sudden reduction in cortisol, causing it to reset itself to the correct regulatory regime and back to its natural homeostatic rest point. Continued development of these models is reinforcing the notion that such reprogramming may require a two-pronged attack, namely the coordinated use of both immune and endocrine modulators.



Intricate fabric of regulatory islands in Gulf War Illness.

Saurabh Vashishtha – PhD student

TOWARDS TREATMENT

As physicians currently lack the tools for effective recognition of these debilitating conditions, the development of diagnostic tests could significantly change millions of lives, allowing ME/CFS and GWI cases to be legitimised, and public awareness of them increased. A relatively new field of medicine, Broderick and Craddock's integrative approach has looked beyond the conventional notions of these illnesses to view the body's broader immune system as a whole. In doing so, they have identified signposts of these conditions and treatment strategies. Although biomarkers have been identified in moderate sized groups it has proven difficult to validate these in larger, external cohorts, possibly due to variations in durations of illness and sex. They provide a promising start, however, and the first phase of clinical trials is being sought out. Counterintuitive though it may be, a convergence of engineering and physics with the life sciences is delivering exciting new insight into the field of neuro-immune medicine.

INTELLIGENCE

INSTITUTE FOR NEURO-IMMUNE MEDICINE

OBJECTIVES

To maintain a patient-orientated clinical research environment that is committed to providing customised treatment plans with thorough follow-up and patient review. As a result, patients receive comprehensive care that is personally tailored for their best result.

FUNDING

National Institutes of Health (NIH) • US Department of Defense (DoD) • US Veterans Affairs (VA)

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GORDON BRODERICK is Professor of Psychology and Pharmacy at Nova Southeastern University (NSU). He also holds adjunct faculty positions in Medicine at the University of Alberta (UoA) and the University of Miami. A biochemical and systems engineer by training, his current research efforts are focused on understanding immune dysfunction and autoimmunity from an integrated systems perspective.

TRAVIS CRADDOCK is Assistant Professor of Psychology and Computer Science funded by the Congressionally Directed Medical Research Program (DoD) to apply systems biology methods towards the purpose of identifying novel treatments for Gulf War Illness. He joined NSU faculty following postdoctoral studies in systems biology under the supervision of Broderick at his lab at UoA. Recipient of a BSc in Physics from the University of Guelph, Craddock had previously completed MSc and PhD studies in the field of neurobiophysics at UoA under Dr Jack Tuszynski.

