



**Invest in ME (Research)**

**BRMEC / IIMEC9**

**2014**

**4<sup>th</sup> Biomedical Research into ME Colloquium**  
**9<sup>th</sup> International ME Conference**

***Synergising Research into Myalgic Encephalomyelitis***

**LONDON, UK**



## FOREWORD

The Invest in ME Biomedical Research for ME Colloquium Meeting (BRMEC4) was held on 29<sup>th</sup> May 2014 in London and was the charity's fourth research meeting. The charity organises and hosts the Colloquium prior to its annual international biomedical research conference every year – which, this year, was the charity's ninth conference. The objectives are:

1. To present the status of the latest initiatives occurring in biomedical research into ME
2. Review experiences and expertise from other research areas in order to assist ME research
3. To generate new ideas regarding research into ME and assess research strategies for ME research
4. To discuss and explore the possibilities for collaboration and for funding for biomedical research into ME

Promising developments have been initiated in recent years which have created important possibilities for changing the way that Myalgic Encephalomyelitis (ME, known also as ME/CFS or Chronic Fatigue Syndrome (CFS)) is researched and the way that patients are treated. High-quality research by an impressive group of researchers and physicians, with an emphasis on international collaboration – these are the aims of Invest in ME and it is our intention to continue to facilitate this and encourage new scientific research endeavours to understand the pathogenesis of ME.

The Co-Chairs of the Colloquium were Dr Ian Gibson, former Dean of Biology at UEA, and Jonathan Edwards, Emeritus Professor of Connective Tissue Medicine, University College London.

Professor Edwards has discussed with participants at the Colloquium and Conference and has produced this conference report which we hope will prove to be useful for healthcare staff when researching or treating or discussing myalgic encephalomyelitis.

Should one require further information please contact the charity at the address or contact points mentioned at the end of this document.

Kathleen McCall  
Chairman Invest in ME

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## Conference Report:

### 4<sup>th</sup> IiME Biomedical Research into ME Colloquium and IIMEC9 9<sup>th</sup> IiME International ME Conference

Jonathan Edwards

The fourth IiME BRMEC (research workshop) was held on 29th May 2014 at St Katharine Docks, London and the ninth IiME Conference (open forum) on 30th May at Westminster. Forty-seven biomedical scientists, from 6 European countries, Australia, New Zealand and the USA, contributed. The aims of the meeting were to bring together researchers in the field of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome to review the current state of knowledge, to present and discuss the latest initiatives, and to foster collaboration. Topics covered ranged through the role of infective pathogens and the microbiome, involvement of inflammatory mediators, evidence for autoimmunity and response to immunotherapy in ME/CFS and other neurological disease, other evidence for dysregulation of the immune response, evidence for disturbed brain, vascular and muscle physiology, immunotherapy and approaches to systematic clinical and biological data collection. Abstracts of the presentations (for both meetings) are appended.

The dominant impression from the meeting was a consensus that although much research into ME/CFS remains exploratory there are strong leads pointing in specific directions that deserve focus of further study. The following points were highlighted as of particular relevance to future strategy.

1. A pressing need to identify clinical and biological subgroups in ME/CFS.
2. The value of further exploration of the possibility that a subgroup of ME/CFS is autoimmune, drawing on progress in other neurological and inflammatory disorders.
3. Clarification of the effector mechanisms of fatigue including central nervous, vasoactive and metabolic pathways and mediators such as cytokine or antibody.
4. Continued debate on the role of micro-organisms, with a focus on modulation of the immune response by viruses and microbiota in particular.
5. The potential importance of mitochondrial dysfunction in linking pathogenesis to symptoms.
6. A need for better communication within the research community to make optimum use of data resources.
7. The potential value of genome analysis to identify genetic risk factors for ME/CFS.

#### Subgroups in ME/CFS

A key difficulty in ME/CFS research has been the identification of consistent biomarkers for use in diagnosis, treatment and monitoring. One plausible explanation for this is that appropriate detection systems have not yet been developed. As **Angela Vincent** pointed out, in a number of rare neurological diseases, diagnostic and prognostic biomarkers

in the form of autoantibodies have only recently been identified through deliberate development of new assay systems. Nevertheless, the problem may also be due in part to the heterogeneity of the ME/CFS population. If a given marker is only relevant to 10% of cases then the standard mode of data presentation, aimed at statistical comparison of unselected populations, may obscure important findings. **Mady Hornig** presented strong evidence for such an effect in the analysis of levels of cytokines such as gamma interferon and interleukin 17a. Levels in an unselected ME/CFS population showed no clear pattern but when cases of less than 3 years duration were compared with those of longer duration a difference emerged.

Evidence for subgroups was noted in a number of contexts. **James Baraniuk** reported two different patterns of response to cognitive tasks on neuroimaging in a group of Gulf War veterans with fatigue-related illness, correlating with clinical patterns designated START and STOPP. **Julia Newton** reported different patterns of abnormality of muscle physiology, one potentially responsive to training and the other not. **Carmen Scheibenbogen** discussed the potential role of age of exposure to Epstein Barr virus, with possible implications for a role for late EBV infection in a subgroup of ME/CFS cases. Evidence for two subgroups on the basis of susceptibility to common infections was also discussed.

Patient classification and subgrouping may be of crucial importance not only to study of pathogenesis but also treatment, as emphasized by **Julian Blanco**. **Øystein Fluge** reported continued experience with beneficial responses to rituximab in about half of patients with ME/CFS. However, as yet no marker has been identified that seems likely to predict this response. A search for such a marker within B cell phenotypes forms the basis of a study just commencing, discussed by **Jo Cambridge**.

### Is a subgroup of ME/CFS autoimmune?

Even Øystein Fluge and **Olav Mella** remain cautious following their study of rituximab in ME/CFS, but there is clearly a groundswell of interest in the possibility that some ME/CFS has an autoimmune basis. **Jonas Blomberg** raised the interesting possibility that mitochondria might be the target for autoimmunity in ME/CFS, as is known to be the case in primary biliary cirrhosis, in which fatigue is also often a major problem. Throughout the two days there was discussion of the complexity of the causal mechanisms that may lead to autoimmunity or immune dysregulation on a wider basis. Dr Hornig discussed animal studies of post-infective neurological disease. Dr Scheibenbogen discussed the potential role of immunomodulation by EBV. **Maureen Hanson** and **Simon Carding** described progress with study of the microbiome in ME/CFS and its potential role in immunomodulation. **Sonya Marshall-Gradisnik** described changes in immune cell, and in particular natural killer cell, function in ME/CFS patients suggestive of abnormal immune activation. Dr Vincent and **Jonathan Edwards** described experience in other autoimmune diseases that might provide clues to interpretation of findings in ME/CFS.

### Effector mechanisms in symptomatology

Another question of central importance to an understanding of pathogenesis in ME/CFS, as emphasized by **Amolak Bansal**, is the nature of the effector pathway or

pathways that lead to fatigue. Dr Newton provided evidence to support a vasomotor mechanism associated with disordered blood flow regulation. Dr Fluge also mentioned early work on possible vasomotor pathways. Dr Baraniuk focused on central nervous pathways. **Jonas Bergquist** described altered patterns in CSF proteins in ME/CFS. Circulating cytokines and related immune mediators were discussed by Dr Hornig, Dr Hanson and Dr Marshall-Gradisnik and possible direct effects of antibodies by Dr Vincent and Dr Blomberg. Metabolic changes in muscle and other tissues were also raised by Dr Newton, Dr Hanson and Dr Blomberg.

This range of possible effector pathways may seem too wide to make sense of. However, evidence from other diseases suggests that effector pathways are often complex, not only with several pathways acting in series or in synergy but also with links through feedback mechanisms. Moreover, pathways may be different for different subgroups at an upstream level, such as an immune response, but with common pathways at a downstream level as in the central perception of fatigue. (An analogy is provided by inflammatory rheumatic disease where final pain pathways can be blocked in most subgroups by prostaglandin blockade but immunomodulators such as cytokine inhibitors and rituximab are highly effective in some subgroups but ineffective in others.)

### **Role of micro-organisms**

This year's meeting followed last in emphasizing the lack of evidence for persistent viral infection in ME/CFS despite detailed search. The presence of higher levels of gamma interferon in cases of less than 3 years duration, as described by Dr Hornig, and the altered responses to EBV described by Dr Scheibenbogen still suggest that, as clinically seems likely, viruses may be involved early on in disease, but evidence for persistent replication is lacking. As indicated above, interest has also moved to gut microbiota with at least three studies now being under way in the research groups represented at the meeting.

### **Mitochondrial targeting**

Dr Blomberg made the interesting observation that the mitochondrion has a number of peculiar and interesting features to its biology that might be relevant to ME/CFS. Mitochondria are believed to be derived from 'co-opted' bacteria early in eukaryotic evolution. They have their own genetic material and a number of their proteins show marked conservation over a long period of evolutionary time. Known primary mitochondrial diseases are rare but they tend to involve muscle. One mitochondrial protein is targeted by antibodies in PBC and there are many other potential targets. Dr Blomberg reported interesting findings on antibodies to Heat Shock Protein 60 in the context of ME/CFS.

### **Collaboration and Communication**

A number of delegates at the BRMEC emphasized the importance for ME/CFS research not only of specific avenues of biological study but also of building an operational infrastructure that would allow effective data gathering and pooling of resources. In his external review of ME Research Strategy, Dr Blanco highlighted the need for infrastructure that could take advantage of new technologies and analysis tools. **Andreas Kogelnik**

described the setting up of such infrastructural facilities at the Open Medicine Institute and the instigation of a number of new programmes with particular emphasis on molecular screening techniques. **Luis Nacul** and **Eliana Lacerda** described the setting up of an ME/CFS Biobank at the London School of Hygiene and Tropical Medicine with systematic collection of both clinical data and blood samples. **Ian Gibson** raised in discussion the importance not only of the setting up of these facilities but the value for the sort of communication fostered by the BRMEC that ensured that everyone working in the field was aware of the resources so that they could be used optimally.

### **Genetic studies**

Dr Kogelnik presented findings on a possible association between ME/CFS and variations in a tetrahydrofolate reductase gene. This raised discussion of the need to consider further exploration of genetic predisposition to ME/CFS, perhaps including MHC genes in particular (associated with a number of autoimmune conditions). Genome searches require the sort of infrastructure for data collection described above so there is a prospect of their being more practical in coming years.

### **Conclusion**

A particularly encouraging feature of the two days of meetings was the evidence for ever-increasing interest in ME/CFS from scientists in other fields. The extent and urgency of the challenge presented by ME/CFS is increasingly being recognized. Moreover, not only is there a consensus that there is a real, disabling condition worthy of the designation of Myalgic Encephalomyelitis, that requires investigation, but also that there are almost certainly several such conditions, each equally important, that we need to distinguish, so that they may be managed on a 'personalised medicine' basis.

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## IAN GIBSON PHD

Institution: Former Dean School of Biological Sciences  
University of East Anglia Norwich UK  
Title: Dr

Dr Ian Gibson, former Labour MP for Norwich North, worked at University of East Anglia for 32 years, became Dean of the school of biological sciences in 1991 and was head of a cancer research team and set up the Francesca Gunn Leukaemia Laboratory at UEA.

In 2011 Dr Gibson received an honorary doctorate of civil law from UEA.

## PROFESSOR JONATHAN EDWARDS MD

Institution: University College London, UK  
Title: Professor  
Position Held: Emeritus Professor of Connective Tissue Medicine University College London (UCL)

Professor Jonathan Edwards, of UCL's Department of Medicine, announced a highly original new treatment for rheumatoid arthritis in October 2000.

His team has conducted trials of a new combination of drugs on patients who have suffered from rheumatoid arthritis for as long as 20 years; all but two of the 22 patients have so far shown marked improvements in their symptoms of the disease.

More information - <http://www.ucl.ac.uk/medicine/research>

## IIMEC9 Abstract Professor Jonathan Edwards:

### Key Note Speech

People with ME may rightly feel that their illness has been neglected by science. However, this 'neglect' may in part simply reflect just how difficult a scientific problem ME poses.

To get a foothold, science needs both reproducible objective findings and well enough structured hypotheses to choose the right questions to ask in further experiments.

For ME these have been hard to pin down.

The recent finding of a response to rituximab in ME patients indicates that at least a proportion of cases may have an autoimmune basis. This suggests that lessons learned in the study of conditions such as rheumatoid arthritis, which led to the initial use of rituximab for autoimmunity, may provide clues for research into ME.

The story of how rituximab came to be used in RA, and the pitfalls encountered both in terms of finding objective disease markers and in formulating a hypothesis for disease mechanism, will be discussed.

Key steps in that process were the recognition that in autoimmune disease external trigger factors may be less important than spontaneous errors within the immune regulatory mechanism itself and that B cell tolerance of self may fail independently of T cell tolerance. It also became clear that there are many ways in which autoantibodies can cause disease and that one should not expect to find a 100% match between traditional antibody findings and disease.

Moreover, the use of rituximab has itself proved to be a powerful tool in studying details of disease mechanism and perhaps the same may prove true for ME.

## PROFESSOR ANGELA VINCENT

### Angela Vincent PhD

Institution: University of Oxford, UK

Title: Professor

Position Held: Emeritus Professor of Neuroimmunology  
Emeritus Professor of Neuroimmunology, University of Oxford

Professor Vincent is Emeritus Professor of Neuroimmunology at the University of Oxford, and an Emeritus Fellow of Somerville College. She holds an Honorary Consultant position in Immunology and runs the Clinical Neuroimmunology service which is an international referral centre for the measurement of antibodies in neurological diseases.

Together with colleagues she collaborates with neurologists worldwide.

She was formerly Head of Department of Clinical Neurology (2005-2008), and is a Past President of the International Society of Neuroimmunology, and an Associate Editor of Brain.

She was a co-applicant and group leader of OXION, the Wellcome Trust-funded Integrative Physiology Initiative "Ion channels and Diseases of Electrically Excitable Cells".

She is a member of Faculty of 1000 (Neuroscience, Neurobiology of Disease and Regeneration).

Her major interest is in the role of autoimmunity in neurological diseases, including multiple sclerosis and auto-antibody mediated ion channel and receptor disorders.

Recent advances have included (a) the discovery that maternal antibodies to different fetal proteins can cause rare neuromuscular disorders, and may be involved in some forms of autism or other neurodevelopmental disorders; (b) the definition and characterisation of a new form of myasthenia gravis associated with antibodies to a receptor tyrosine kinase, MuSK, that performs an important maintenance role at the neuromuscular junction; and (c) the recognition that some central nervous system disorders, involving memory loss, seizures, movement disorders, can be caused by antibodies to potassium ion channels and to various receptor proteins.

In these, and several other conditions, new ways are being devised to measure the pathogenic antibodies for better clinical diagnosis, and establishing model in vitro and in vivo systems for investigation of the pathophysiology of the diseases. Her group also works, in collaboration with Profs David Beeson and Nick Willcox, on the genetics of myasthenia and the factors that determine autoimmune responses to the main target, the acetylcholine receptor. More information - <http://www.cneuro.ox.ac.uk/team/principal-investigators/angela-vincent>

## **IIMEC9 ABSTRACT PROFESSOR ANGELA VINCENT:**

### **AUTOANTIBODIES IN DIFFERENT FORMS OF NEUROLOGICAL DISEASE: RELEVANCE FOR ME?**

Autoantibodies to a variety of receptors and ion channels on cells of the nervous system can be identified in children and adults with newly acquired neurological diseases. Most of the patients have classical features of myasthenia gravis or central nervous system diseases including loss of memory, seizures, confusion or bizarre movements. The diseases improve with immunotherapies that reduce the levels of the "pathogenic" antibodies. The field is still developing and some antibodies are now being detected in patients with other conditions including first episode psychosis, unexplained epilepsy, sleep disorders or pain.

But the relevance of the antibodies in these disorders is not yet established and some findings may be entirely incidental.

## **PROFESSOR JONAS BLOMBERG**

### **Jonas Blomberg MD PhD**

Institution: Department of Medical Sciences, Uppsala University, Sweden  
Title: Professor  
Position Held: Research Group Leader  
Emeritus Professor of Clinical Virology, Department of Medical Sciences, Uppsala University, Sweden

Professor Jonas Blomberg is an MD and PhD, graduating at the University of Gothenburg.

Has worked with Lipids at the department of Medical Biochemistry 1965-1972 as a Clinical Virologist in Gothenburg 1972-1979 and as a postDoc at John Stephenson's Lab at NCI Frederick on retroviruses 1979-1981. He then worked as a Clinical Virologist in Lund, Sweden 1981-1995 and then as a professor of Clinical Virology in Uppsala 1996- to the present.

His main fields of interest are: Retrovirology, Bioinformatics, Clinical Virology and broadly targeted and multiplex methods for detection of microbial nucleic acid.

He also is interested in evolution and Infection biology.

Professor Blomberg is on the editorial board of Journal of Virology  
<http://jvi.asm.org/site/misc/edboard.xhtml>

## **IIMEC9 Abstract: Professor Jonas Blomberg:**

### **Infection-induced autoimmunity in ME**

ME is commonly initiated by an infection. Infections commonly give rise to antibodies which are present for a long time, even when the infection is no longer active. We therefore searched for antibodies to a number of microbes which have been connected with ME. Because several microbes have been connected with ME, we prioritized looking for antibodies

to microbial structures which are common to many microbes, in the hope of finding a common pattern in the immune response to them. After having tested almost 1000 microbial antigens against blood samples from ME patients diagnosed at the Gottfries clinic with the Canadian criteria, and the same number of blood donors, we found a few who reacted preferentially against ME. They were either from heat shock protein 60 (HSP60) or from capsid proteins of some small viruses. HSP60 is a highly conserved protein which is common to both microbes and man. HSP60 antibodies occur in several autoimmune diseases. It is an autoantigen. Presumably, the immune system cannot distinguish microbial HSP60 from the patient's own HSP60. We found that a subset (25-30%) of ME patients have elevated IgM antibodies against a specific portion of HSP60. These antibodies can react with both human and microbial HSP60. They are autoantibodies. HSP60 is a mitochondrial protein. Mitochondria are essentially bacteria which entered our cells over a billion years ago. Mitochondria are responsible for an important part of human energy metabolism. An important component of ME is post-exertional malaise (PEM). There are signs that PEM is due to an abnormally slow replenishment of energy from mitochondria. Our working hypothesis is that antibodies reactive with mitochondrial antigens somehow interfere with mitochondrial function in ME. It is far from clear how our findings of anti-HSP60 antibodies in ME should be interpreted.

We are currently working on the antibodies to capsid proteins of small viruses. The capsid is the cloak that viruses use to protect themselves. Although HSP60 and viral capsid proteins are different from each other, we hypothesize that they have common structural features that could explain why we often see antibodies to both in ME patients. If this is correct, the immune response to a virus could paradoxically give rise to immunity to human and microbial HSP60.

Evidence for autoimmunity in ME is accumulating. Postural hypotension, thyroid disorder and fibromyalgia, all of which are frequent in ME patients, involve a more or less clear autoimmunity. Autoimmunity seems to be a fruitful line for the large remaining amount of research.

Hopefully, our work will lead to a better understanding of the genesis of ME, and to biomarkers useful for laboratory diagnosis of ME.

## PROFESSOR MADY HORNIG

### Mady Hornig MD

Institution: Center for Infection and Immunity (CII), Mailman School of Public Health, Columbia University, New York, USA  
Title: Associate Professor  
Position Held: Director Translational Research / Assoc.Professor Epidemiology  
Associate Professor Mady Hornig, Center for Infection and Immunity (CII), Columbia University Mailman School of Public Health, New York, USA

Mady Hornig, MA, MD is a physician-scientist in the Center for Infection and Immunity (CII) at the Columbia University Mailman School of Public Health where she serves as Director of Translational Research and is an associate professor of epidemiology.

Her research focuses on the role of microbial, immune, and toxic stimuli in the development of neuropsychiatric conditions, including autism, PANDAS (Pediatric Autoimmune Neuropsychiatric Disorders Associated with Streptococcal infection), mood disorders and myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS).

She is widely known both for establishing animal models that identify how genes and maturational factors interact with environmental agents to lead to brain disorders and for her work clarifying the role of viruses, intestinal microflora and xenobiotics in autism and other neuropsychiatric illnesses that may be mediated by immune mechanisms.

Under her direction, proteomic analyses of umbilical cord samples are identifying potential birth biomarkers for autism in a prospective study in Norway, the Autism Birth Cohort (ABC).

She established that there was no association between intestinal measles virus transcripts and autism, and, with Brent Williams and W. Ian Lipkin at CII, has found altered expression of genes relating to carbohydrate metabolism and inflammatory pathways and differences in the bacteria harboured in the intestines of children with autism.

She also leads projects examining the influence of immune molecules on brain development and function and their role in the genesis of schizophrenia, major depression, and cardiovascular disease comorbidity in adults, and directs the Chronic Fatigue initiative Pathogen Discovery and Pathogenesis Project at CII.

In 2004, Dr. Hornig presented to the Institute of Medicine Immunization Safety Review Committee and testified twice before congressional subcommittees regarding the role of infections and toxins in autism pathogenesis.

Her work in ME/CFS is establishing immune profiles and helping to identify pathogens that may be linked to disease.

Her work on the MIND (Microbiology and Immunology of Neuropsychiatric Disorders) Project, one of the largest studies of immune factors in mood disorders and schizophrenia, examines the role of viruses and immune responses in the pathogenesis of these disorders.

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### **IIMEC9 Abstract: Professor Mady Hornig Pathogen Discovery in ME/CFS**

Infection and dysregulated immune signaling have been implicated as triggers or exacerbatory factors in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS); however, focused research in large, well-characterized patient populations has been lacking. A program dedicated to the investigation of infectious and immune factors in ME/CFS, the Chronic Fatigue Initiative (CFI), has been working to address this research gap. As part of the CFI mission, the Center for Infection and Immunity (CII) at Columbia University Mailman School of Public Health has analyzed blood samples from 200 cases and 200 controls using molecular, metabolomic and proteomic methods. Findings from studies aimed at discovering pathogens, defining immune signatures and determining how host and microbial metabolism may relate to ME/CFS in the CFI cohort will be presented. Data support the existence of specific phenotypic subsets with different clinical characteristics, including duration of illness, degree of cognitive impairment and presence of comorbid features such as allergies and fibromyalgia. The rationale for pursuit of additional studies that will examine the gut and oropharyngeal microbiome in conjunction with metabolomic and immune profiling, and that will provide an understanding of how these microbial, biochemical and immune markers change over the course of illness will be reviewed.

## PROFESSOR CARMEN SCHEIBENBOGEN

### Carmen Scheibenbogen MD

Institution: Institute of Medical Immunology, Berlin Charité, Germany  
Title: Professor  
Position Held: Deputy Director of the Institute of Medical Immunology  
Professor for Immunology and Deputy Chair, Institute of Medical Immunology, Berlin Charité, Germany

Group leader of a Tumour Immunology Laboratory and Attending Physician at the Dept. of Haematology, Oncology und Transfusionsmedizin, CBF, Charité,,2/1997 Venia legendi for Internal Medicine "Habilitation", 1990 - 1998 Residency at the Med. Klinik und Poliklinik V, Hämatologie, Onkologie und Rheumatologie, Universität Heidelberg, 1988 - 1990 Postdoctoral fellowship at the Med. Klinik, Dept. of Hämatologie und, Onkologie, Universität Freiburg, 1982 - 88 Medical school at the Universities of Bonn, Marburg and Denver

### IIMEC9 Abstract: Professor Carmen Scheibenbogen

#### Role of EBV and ME/CFS

Carmen Scheibenbogen, Madlen Löbel, Sandra Bauer, Agnes Mooslechner, Leif Hanitsch, Patricia Grabowski, Kirsten Wittke, Ulf Reimer, Maren Eckey, Klemens Ruprecht, Hans-Dieter Volk Institute for Medical Immunology and Neurology, Charité, and JPT Peptide Technologies, Berlin

Late first Epstein-Barr virus (EBV) infection is a frequent trigger of Chronic Fatigue Syndrome (CFS). About 20% of patients have serological or PCR evidence of EBV reactivation. A deficient EBV-specific immune response became evident in more than half of our patients when specific B cell and T cell memory responses were analysed (Löbel M. *et al.*, *Plos One*, January 2014). By analysing the spectrum of EBV-specific antibodies against various proteins we observed a pattern of EBV-specific antibody responses, which could distinguish CFS from healthy controls and patients with multiple sclerosis (Ruprecht K. *et al.*, *J. Neuroimmunology*, April 2014). When comparing EBV load in blood immune cells, we found more frequently low but detectable levels of EBER-DNA in CFS patients compared to healthy controls. However, no evidence of lytic EBV reactivation was observed indicating that no severe defect in T- and NK cell control of EBV exists. In line with this observation we found normal NKG2D expression on NK cells, which is important for killing of EBV-infected B cells.

There is accumulating evidence that B cells are dysregulated in CFS.

Many patients have alterations of immunoglobulin levels and those with diminished levels often suffer from recurrent respiratory tract infections. Both B cell depletion and high dose immunoglobulin therapy is effective in a subset of patients. Our current research focuses on the detailed characterisation of B cells and the EBV-induced regulation of B cell genes in CFS. Taken together, our findings give evidence for a deficient or dysregulated EBV-specific immune response in many CFS patients. Our data may point to an impaired ability to control early steps of EBV reactivation.

## PROFESSOR SIMON CARDING

### Simon Carding PhD

Institution: University of East Anglia, UK  
Title: Professor  
Position Held: Professor of Mucosal Immunology  
Professor of Mucosal Immunology at University of East Anglia and Institute of Food Research.

Following his PhD at London he held postdoctoral positions at New York University School of Medicine, New York and at Yale University School of Medicine, New Haven, USA. He then moved to the University of Pennsylvania, Philadelphia, USA as Assistant and later Associate Professor. He joined University of Leeds as Professor of Molecular Immunology in the Institute of Molecular and Cellular Biology in 1999. His scientific interests are in understanding how the immune response in the gut functions and in particular, is able to distinguish between the commensal microbes that reside in the gut and environmental microbes that cause disease, and in the mechanisms by which the body's immune system no longer ignores or tolerates commensal gut bacteria and how this leads to immune system activation and inflammatory bowel disease.

### IIMEC9 ABSTRACT: PROFESSOR SIMON CARDING

#### **A ROLE FOR A LEAKY GUT AND THE INTESTINAL MICROBIOTA IN THE PATHOPHYSIOLOGY OF MYALGIA ENCEPHALOMYELITIS/ CHRONIC FATIGUE SYNDROME?**

Simon R Carding<sup>1,2</sup>, Tom Wileman<sup>1</sup>, Daniel Vipond<sup>1,2</sup>, Bharat Harbham<sup>1</sup>, Eleanor Cottam<sup>3</sup> and Amolak Bansal<sup>4</sup>

<sup>1</sup>Norwich Medical School, University of East Anglia, <sup>2</sup>Gut Health and Food Safety Research Programme, Institute of Food Research, Norwich Research Park, Norwich, <sup>3</sup>The Pirbright Institute, Woking, <sup>4</sup>Dept. Immunology, St. Helier NHS Trust, Carshalton.

Recent studies point to a link between autoimmunity and myalgic encephalomyelitis (ME) raising the possibility that the neuro-inflammation seen during ME may be triggered by systemic infections. The gastrointestinal tract contains a vast population of resident microbes (the microbiota) consisting primarily of bacteria and fungi, yeasts and viruses.

The microbiota influences intestinal barrier function and host defences against microbial challenge with microbial dysbiosis leading to both local and systemic chronic inflammation. The microbiota may also influence cognitive function and behaviour. It is known that gut infections can cause anxiety, depression and cognitive dysfunction; and microbe-free, germfree mice that have no intestinal microbiota display alterations in stress-responsivity, central neurochemistry and behaviour indicative of a reduction in anxiety.

Many ME patients have gastrointestinal disturbance, are more likely to develop irritable bowel syndrome, and may have increased intestinal permeability (a "leaky" gut").

Together these observations suggest that changes in intestinal barrier integrity, which may be driven by or are a consequence of intestinal dysbiosis, as a result, for example, of a gut infection could contribute to ME by driving systemic inflammation and/or influencing the microbiota-gut-brain axis. With support from Invest in ME we have initiated a project to

address the hypothesis that alterations in intestinal barrier integrity and the resulting influx of luminal antigens triggers and perpetuates a state of chronic inflammation both locally and systemically that contributes to the pathophysiology of CFS/ME.

The aim of this three-year, multi-centre collaborative project therefore is to determine if alterations in the intestinal barrier integrity and microbiota composition and function exist in CFS patients.

## **PROFESSOR SONYA MARSHALL-GRADISNIK**

### **Sonya Marshall-Gradisnik PhD**

Institution: Griffith University, Australia  
Title: Professor  
Position Held: Professor National Centre for Neuroimmunology and Emerging Diseases  
School of Medical Sciences, Griffith University, Australia

Professor Marshall-Gradisnik is one of Australia's foremost researchers in the area of neuroimmunology and has been instrumental in establishing the Public Health and Neuroimmunology Unit (PHANU) at Bond University, and now at Griffith University.

Much of her work relates specifically to autoimmunity in Chronic Fatigue Syndrome sufferers and she is regularly asked to speak to community groups on behalf of Queensland Health and NSW Health.

Her research in the area of exercise immunology has also contributed to the body of knowledge relating to the effect of doping in sport and she serves as Sports Medicine Australia's national spokesperson in this area.

The vital research conducted by Professor Marshall has attracted more than \$1 million in grant funding and she has produced 21 peer-reviewed papers, five book chapters and one provisional patent. In 2008 Dr Marshall was joint leader of the Bond University team responsible for developing the BioSMART program. The team was awarded a prestigious Australian Teaching and Learning Council Award (formerly known as the Carrick Award) for Outstanding Contribution to Student Learning and for the quality of student learning over a sustained period of time.

Professor Marshall-Gradisnik is also leading The National Centre for Neuroimmunology and Emerging Diseases (NCNED), a research team situated at Griffith University on the Gold Coast. The team focuses on Myalgic Encephalomyelitis.

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### **IIMEC9 ABSTRACT: PROFESSOR SONYA MARSHALL-GRADISNIK:**

#### **INNATE AND ADAPTIVE IMMUNE CELLS IN CHRONIC FATIGUE SYNDROME/MYALGIC ENCEPHALOMYELITIS.**

**Brenu EW<sup>1</sup>, Hardcastle SL, Huth, T, Johnston S, Nguyen, T., Ramos SB, Staines DR, Marshall-Gradisnik SM.**

National Centre for Neuroimmunology and Emerging Diseases, Griffith Health Institute, Griffith University, Parklands, Queensland, Australia.

Queensland Health, Gold Coast Public Health Unit, Robina, Gold Coast, Queensland, Australia.

Immunological abnormalities are consistent in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) patients, namely reduced Natural Killer (NK) cell cytotoxic activity. However, reports on other basic immune cell parameters are inconsistent in CFS/ME, possibly related to the heterogeneity or variation in severity of the illness.

The purpose of this research was to assess innate and adaptive immune cells that have not been previously examined in CFS/ME in cohorts of both moderate and severely affected patient severities.

CFS/ME patients were assessed using the 1994 CDC Case Definition for CFS/ME. Health, mobility and quality of life questionnaires were used to assess all participants and also to further distinguish CFS/ME participants as either moderately or severely affected. Using flow cytometric assays, NK cells, neutrophils, monocytes, T regulatory cells (Tregs), iNKT cells, B cell phenotypes and dendritic cells (DCs) were examined each of these groups.

DC, B, neutrophil and Treg phenotypes were significantly different between the CFS/ME and non-fatigued controls. NK cytotoxic activity was significantly reduced in CFS/ME patients compared to controls and was further reduced in severely affected patients. The severe CFS/ME patients also demonstrated significantly increased DC, B, iNKT and NK phenotypes when compared to both the moderate CFS/ME patients and healthy controls.

These results have confirmed previous reports that NK cell cytotoxic activity is consistently reduced in CFS/ME.

This data has further suggested that further immune cells, including DCs, B, Tregs and iNKT cells have immune perturbations related to cytotoxic activity and phenotypes in CFS/ME and this may be contributing to the overall immune profile demonstrated in this illness and other autoimmune disorder.

## **PROFESSOR JAMES BARANIUK**

### **James Baraniuk MD**

Institution: Georgetown University Medical Centre, USA  
Title: Professor  
Position Held: Professor of Medicine  
Professor of Medicine at Georgetown University Medical Centre

James N. Baraniuk was born in Alberta, Canada, south of Banff. He earned his honours degree in chemistry and microbiology, medical degree, and unique bachelor's degree in medicine (cardiology) at the University of Manitoba, Winnipeg, Canada. Thereafter, he moved to Akron, OH, USA, for his internship and internal medicine residency at St Thomas Hospital.

After another year of internal medicine residency at Duke University Medical Center, Durham, NC, he trained with Dr C.E. Buckley, III, in allergy and clinical immunology.

He moved to the laboratory of Dr Michael Kaliner at the National Institute of Allergy and Infectious Diseases, Bethesda, MD, and there began his long-standing collaboration with Dr Kimihiro Ohkubo.

After 2 years studying neuropeptides, he joined Dr Peter Barnes' laboratory at the National Heart and Lung Institute, Brompton Hospital, London, UK.

Dr Baraniuk returned to Washington, DC, and Georgetown University, where he is currently Associate Professor with Tenure in the Department of Medicine.

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## **IIMEC9 ABSTRACT: PROFESSOR JAMES BARANIUK**

### **BRAIN IMAGING AND ME**

The following was taken from the IIMEC9 Conference Report made by Dr Ros Vallings of New Zealand [<http://www.investinme.eu/report.html>]

Discusses work with MRI and victims of Gulf War Illness (GWI). He has explored a model sub-group dating back to 1990-91. Many had experienced acute illness, possibly as a result of sarin exposure. There has been chronic progression of illness over 20 years. Up to 25% of Gulf War veterans were affected. There are resulting problems with the brain, its functions and networks. i.e. "The pain is in the brain". This results in problems with fatigue, attention, working memory, pain, anxiety, tenderness and exertional exhaustion.

Many types of MRI are now available: Voxel-based, diffusion tensor imaging, BOLD (measures oxygenation of blood in brain), fMRI (at rest and during tasks), functional connectivity, structural connectivity, cerebral blood flow and concentrations of brain chemicals. He has been interested in looking at cortical thickness, and grey and white matter intensities and lucencies. He has looked at the white matter volume and fatigue duration. The white matter is decreased in ME. There is shrinkage of 1% per year. There is also volume loss in the superior cerebellar peducles, pons and medulla in GWI. Also some brain stem atrophy.

Using BOLD and fMRI, these measures are blood oxygenation level dependant and the areas that are functioning can be identified. Brain blood flow is regulated from the neuron, which releases glutamate, affecting NMDA, which then activates astrocytes to produce D-serine, which releases nitric oxide, which relaxes the arterioles and thus increases the blood flow. The fMRI shows differences in GWI leading to more errors.

He then discussed resting state brain networks. When the mind is wandering, it is rehearsing and/or debriefing. A default network starts. When you stop a task, there is functional connectivity. Patterns of resting state networks may be indicative of specific diseases. He also talked about the differences in easy and difficult tasks, and also what happens when you switch tasks. Different parts of the brain function depending on difficulty. You may go into default mode if you need to switch tasks.

If a person has post-exertional malaise, there are differences in cognitive function identified also. In a 2 day exercise test, healthy controls experienced some fatigue and switched to default mode, but those with GWI found symptoms came on, and there was basal ganglia activation for cognitive compensation. In a second test everything went down and additional brain areas were recruited. The GWI patients could be divided into phenotypes according to their response to exercise. There were START and STOPP groups. In the former exercise caused autonomic dysfunction. In the STOPP group there was phantom perception.

He finished by saying that these new brain scanning studies will redefine psychiatry. For example, in depression the amygdala has a central role and has dysfunction, while the cerebellum is shown to be involved in emotional processing and fibres have connection with amygdala and areas of atrophy

## PROFESSOR JULIA NEWTON

### Julia Newton MD PhD

Institution: Institute for Ageing and Health, Newcastle University, UK  
Title: Professor  
Position Held: Dean for Clinical Medicine  
Clinical Professor of Ageing and Medicine and Honorary Consultant Physician, Royal Victoria Infirmary, UK

Professor Newton's research programme focuses upon the integrity of the autonomic nervous system in health and disease, specifically the role of autonomic dysfunction in the pathogenesis of fatigue and its clinical consequences, namely cognitive impairment.

Examining the integrity of the ANS in humans is established in her physiology laboratory using relatively simple, inexpensive, non-invasive technologies that allow evaluation of a wide range of parameters that will within the foreseeable future be readily transferable into therapeutic interventions for patients.

### IIMEC9 ABSTRACT: PROFESSOR JULIA NEWTON:

#### AUTONOMIC DYSFUNCTION & ME

The autonomic nervous system controls all of those functions that go on in the human body outside conscious control. Studies have confirmed that problems with the autonomic nervous system (autonomic dysfunction (AD)) are a common occurrence in those with ME, with almost 90% of sufferers describing postural dizziness, syncope (blackouts) and a range of other autonomic symptoms. Formal testing has confirmed the presence of objectively measured autonomic dysfunction in ME with conditions such as neurally mediated hypotension and positional tachycardia syndrome recognised at significantly increased prevalence compared to matched control populations.

The underlying cause of this frequently found AD is as yet not understood. Studies will be described confirming muscle, cardiac and brain abnormalities the severity of which associates with the underlying AD.

## PROFESSOR MAUREEN HANSON

### Maureen Hanson PhD

Institution: Cornell University, New York, USA  
Title: Professor  
Position Held: Liberty Hyde Bailey Professor

Maureen Hanson is Liberty Hyde Bailey Professor in the Department of Molecular Biology and Genetics at Cornell University in Ithaca, NY.

Previously she was on the faculty of the Department of Biology at the University of Virginia in Charlottesville and an NIH NRSA postdoctoral fellow at Harvard, where she also completed her Ph.D. degree.

While most of her prior research has concerned cell and molecular biology in plant cells, she began a research program on ME/CFS after noting at a 2007 IACFS meeting the paucity of molecular biologists studying the illness.

Her lab was part of the 2012 multicenter study organized by Ian Lipkin's group at Columbia University to assess the actual role of XMRV in ME/CFS.

Dr. Hanson has a current project to examine the microbiome of ME/CFS patients and controls, in collaboration with Dr. Ruth Ley (Cornell Microbiology) and Susan Levine, M.D. (Manhattan, NY).

Dr Levine is also collaborating with Dr. Hanson on an immune cell gene expression project that involves Dr. Fabien Campagne and Dr. Rita Shakhovich at Weill Cornell Medical School in New York City.

Dr. Hanson's third project concerns analysis of blood samples from individuals performing a two-day cardiopulmonary exercise test at Ithaca College under the supervision of Dr. Betsy Keller.

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## **IIMEC9 ABSTRACT: PROFESSOR MAUREEN HANSON**

### **MARKERS OF POST-EXERTIONAL MALAISE**

<sup>1</sup>Maureen R. Hanson, <sup>1</sup>Ludovic Giloteaux, <sup>2</sup>Xiaoqing Lu, <sup>2</sup>Jason W. Locasale, <sup>3</sup>Betsy A. Keller

<sup>1</sup>Department of Molecular Biology and Genetics, Cornell University, Ithaca, NY, USA

<sup>2</sup>Division of Nutritional Sciences, Cornell University, Ithaca, NY, USA

<sup>3</sup>Department of Exercise & Sport Sciences, Ithaca College Ithaca, NY, USA

ME/CFS patients often report an increase in symptoms following levels of physical or cognitive activity that would not be challenging to healthy subjects, a problem which is termed post-exertional malaise. Reports have demonstrated that healthy subjects, as well as subjects with heart or renal failure or lung diseases, are able to reproduce their maximum oxygen consumption ( $VO_2\text{max}$ ) and/or  $VO_2$  at ventilatory threshold (VT) when they undergo repeated cardiopulmonary exercise tests (CPET). In contrast, detrimental effects of an exercise challenge on the physiology of individuals with ME/CFS can be documented by objective measures obtained during two CPETs. Because subjects cannot willfully alter the maximum amount of oxygen they inhale nor the amount of carbon dioxide they exhale, measurement of these parameters provides an objective indicator of an individual's physiological function that cannot be explained by deliberate malingering or by psychiatric illness.

After induction of post-exertional malaise by an initial CPET, ME/CFS patients often exhibit abnormal physiological and/or autonomic nervous system responses and are usually unable to repeat either their  $VO_2\text{max}$  and/or VT, which is a measure of the anaerobic threshold, or they show symptoms of autonomic dysfunction. Anaerobic threshold is the exercise intensity at which metabolism transitions to anaerobic energy production, which is less efficient and results in accumulation of lactic acid. We have observed patients with ME/CFS who become

prematurely “anaerobic” at low work levels. After an exercise challenge, even modest activities, such as lying quietly while watching television or sitting and eating, require some patients to use anaerobic metabolism. Other patients exhibit Metabolic Equivalent of Task (MET) levels at maximal exertion of 4.0 or less, while 4.0 METs are required to do such simple activities as hanging laundry, sweeping a sidewalk or climbing stairs slowly.

A simple strategy can be used to discern biochemical and metabolic abnormalities in individuals experiencing post-exertional malaise.

By collecting blood samples before an exercise challenge and 24 hours afterwards, assays can be performed to determine which molecules have changed in concentration. We will discuss the data that is currently available about exercise-induced changes in amounts of plasma molecules.

## DR ANDREAS KOGELNIK

### Andreas Kogelnik MD PhD

Institution: Open Medicine Institute, USA  
Title: Dr  
Position Held: Director  
Director of the Open Medicine Institute, USA

Dr Andreas Kogelnik is the Founding Director of the Open Medicine Institute, a collaborative, community-based translational research institute dedicated to personalized medicine with a human touch while using the latest advances in medicine, informatics, genomics, and biotechnology. The Institute works closely with the Open Medicine Clinic and other clinics to conduct research and apply new knowledge back into clinical practice.

Dr. Kogelnik received his M.D. from Emory University School of Medicine in Atlanta and his Ph.D. in bioengineering/bioinformatics from the Georgia Institute of Technology. Subsequently, he completed his residency in Internal Medicine and a Fellowship in Infectious Diseases at Stanford University and its affiliated hospitals. Following his clinical training, he remained at Stanford with NIH funding to engage in post-doctoral research in microbiology, immunology and bioinformatics with Dr. Ellen Jo Baron and Dr. Stanley Falkow, where he explored host-response profiles in severely ill patients.

Together with Dr. José Montoya, he was instrumental in the conception, design, and execution of the EVOLVE study - a placebo-controlled, double-blind study of a subset of chronic fatigue syndrome patients with evidence of viral infection. Dr. Kogelnik worked with Dr. Atul Butte in translational informatics to determine patterns that indicated a high risk for adverse events in paediatric patients at Lucille Packard Children's Hospital.

He is the Medical Director of the Open Medicine Clinic - a community-based research clinic focussed on chronic infectious diseases, neuroimmune disease, and immunology. Dr. Kogelnik has published numerous scientific papers and book chapters, is an Editor of *Computers in Medicine and Biology*, and is a Consulting Assistant Professor at Stanford University. With the Open Medicine Institute, he has led the formation of CFS and Lyme Registries and Biobanks as well as creating an infrastructure for providers to collect better data and implement clinical trials across a network of sites.

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## **IIMEC9 ABSTRACT: DR ANDREAS KOGELNIK**

### **DIAGNOSIS/TREATMENTS AND ME IN USA**

An update of OMI collaborative projects current and planned will be given, including the Population Survey of Cognition in ME/CFS, The effect of the MTHFR gene on the treatment of ME/CFS, and the OpenMedNet longitudinal survey study.

The Population Survey of Cognition and ME/CFS is a large-scale survey of scientific measures of cognitive function across the spectrum of ME/CFS with subgroups being evaluated before and after treatment (n=4000). The MTHFR study is evaluating the effect of treatment of ME/CFS patients with MTHFR gene abnormalities with methyl folate and methyl B12 (n=120).

OpenMedNet Survey study is giving us insight into the distribution of the disease and natural course of disease (n=100,000). We will summarize upcoming directions and how the ME/CFS community can participate.

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## **DR AMOLAK BANSAL**

### **Amolak Bansal MD**

Institution: Epsom and St Helier Hospital, Surrey, UK  
Title: Dr  
Position Held: Consultant Clinical Immunology and Immunopathology, Epsom and St. Helier University Hospitals NHS Trust, Surrey, UK

Dr. Bansal trained in immunology and allergy from 1989 to 1993 at St. Mary's Hospital in Manchester and at Hope Hospital in Salford. From here he spent five years (1993-1997) as Senior Lecturer and Consultant in Clinical Immunology in the Department of Medicine at the Princess Alexandra Hospital in Brisbane, Australia.

From 1997 to the present date Dr. Bansal has worked as a Consultant in Clinical Immunology and Immunopathology at Epsom and St Helier University Hospital.

Dr Bansal's key interests lie in allergy, autoimmunity, CFS/ME and immunodeficiency.

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## **IIMEC9 ABSTRACT: DR AMAOLAK BANSAL**

### **DIAGNOSIS/TREATMENTS AND ME IN UK**

The diagnosis of CFS/ME is often challenging as the symptoms do not fit commonly encountered conditions and there are no diagnostic tests currently.

It is therefore a diagnosis of exclusion.

However, the delayed post-exertion malaise after physical and mental overactivity as well as the hypersensitivity to sounds and lights and the neurocognitive dysfunction are rarely if ever seen collectively in any other condition. Unfortunately, the precise mechanism for these highly disabling symptoms remains unclear.

The criteria used to confirm CFS/ME in research and particularly the operationalisation of these criteria has been the subject of much controversy. The deficits in the early criteria appear to have been eliminated but at the expense of additional complexity.

The need to assess the frequency and severity of each of the symptom sets is an important step forward and will hopefully improve the diagnostic certainty for primary and secondary care physicians. The Sutton CFS/ME service has used a diagnostic scoring system for the last 6 years which has been found easy to use and reliable (see [Appendix 2](#)). This will be discussed in the broader context of the various diagnostic CFS/ME criteria and certain unusual clinical findings noted by this service.

## DR ØYSTEIN FLUGE

### Øystein Fluge MD PhD

Institution: Dept. of Oncology and Medical Physics, Haukeland University Hospital and University of Bergen, Norway  
Title: Dr  
Position Held: Chief Physician Cancer Department

## PROFESSOR OLAV MELLA

### Olav Mella MD PhD

Institution: Dept. of Oncology and Medical Physics, Haukeland University Hospital and University of Bergen, Norway  
Title: Professor  
Position Held: Department Director Cancer Department

### IIMEC8 2013 CONFERENCE ABSTRACT:

#### DR ØYSTEIN FLUGE/PROFESSOR OLAV MELLA

#### B-CELL DEPLETION THERAPY USING RITUXIMAB IN ME/CFS

Professor Mella and Dr Fluge have published a paper "Benefit from B-Lymphocyte Depletion Using the Anti-CD20 Antibody Rituximab in Chronic Fatigue Syndrome. A Double-Blind and Placebo-Controlled Study" -

<http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0026358>

#### **Intervention and maintenance treatment with the B-lymphocyte depleting monoclonal anti-CD20 antibody Rituximab in ME patients. A Phase II study.**

We have previously published a case series and a small double blind, placebo-controlled study using immune manipulation with the B-lymphocyte depleting, monoclonal anti-CD20 antibody Rituximab (Rtx). These studies showed that Rtx yielded clinically meaningful responses, with symptom alleviation, although usually transiently, in the majority of patients. Patients in the double-blinded study having received placebo were according to protocol offered inclusion into an open-label Phase II with Rtx treatment. This study pursued the concept of repeated Rtx infusions to see if responses were more durable than in the randomized study, and to estimate side effects of the drug including adverse effects of prolonged B-cell depletion.

28 patients (including 2 pilot patients) were treated with Rtx 500 mg/m<sup>2</sup> day 1 and 15 (as in the randomized study) and with maintenance Rtx infusions at 3, 6, 10 and 15 mths. Patients in slow responses were offered additional infusions up to 24 mths. Study endpoints were predefined according to the criteria defined in the randomized study. The main endpoint defining response was change in Fatigue score during the observation period, although improvements in fatigue were generally followed also by decrease in other ME-symptoms. Follow-up is a minimum of 28 mths in all patients.

Two patients had serious allergic reactions and had to stop Rtx treatment (one responding patient given alternative B-cell depleting agent with new response). Two had repeated airway infections and were given antibiotics and eventually gamma globulin. Seven had transient ME-symptom increase shortly after Rtx infusion. Two had late onset neutropenia of short duration.

20 of the 28 patients had moderate or major response to treatment. 7 of the 9 placebo patients from the randomized study (without response) responded in the present study. Median self-estimated level of functioning, compared to completely healthy condition, was changed from 10% at baseline to 78% at 18-24 mths after inclusion in responders, and from 15 to 18% in non-responders. Response durations were evidently longer than in the randomized study. However, later than 24 mths into the study, 9 of 20 responding patients have had ME-symptom recurrences. We conclude that the present Phase II study supports previous data on good clinical responses to immune manipulation with Rtx in ME-patients and that maintenance treatment seems to prolong responses.

Based on the studies, we have sought financial support for a Norwegian multicenter, double-blinded and placebo-controlled study of Rtx given at day 1 and 15, and at 3, 6, 9 and 12 mths, with 24 mths observation time. This study will also include prospective analyses of bio bank material and physical tests to verify the subjective measures that are the prime endpoints.

Parallel to the clinical studies, we have performed multiple analyses to get a better understanding of the mechanisms that trigger and maintain the symptoms in ME. Although preliminary, this has given us a candidate system we presently are investigating as a possible effector system in the body that may explain the symptoms and responses to interventions in ME-patients. What could be a possible link between such a system and the immune manipulation that Rtx induces? Dr. Fluge will cover this aspect of our studies in his presentation at the (IIMEC8) meeting.

Supported by the Kavli Foundation and the Western Norway Health Authority.

## **DR JULIAN BLANCO**

### **Julià Blanco PhD**

Institution: Cell Virology and Immunology Research Group, Irsi Caixa Research Institute, Barcelona, Spain  
Title: Dr  
Position Held: Lead Researcher  
Leader of the Irsi Caixa Research Institute's Cell Virology and Immunology Research Group, Barcelona, Spain

The Irsi Caixa Institute for AIDS Research IRSI Caixa works alongside the most prestigious international research centres, and its publications are among those with the most impact in their field.

Dr Blanco has vast experience in HIV related research but has also been involved in ME/CFS research as in 2013 his group published the paper , Screening NK-, B- and T-cell phenotype and function in patients suffering from Chronic Fatigue Syndrome, Curriu et al. Journal of Translational Medicine 2013, 11:68.

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## **IIMEC9 ABSTRACT: DR JULIAN BLANCO**

### **EXTERNAL VIEW OF ME RESEARCH STRATEGY**

When ME/CFS knocked the door of biomedical research, most teams were already working in other life threatening diseases, and little attention was paid to this disease.

Reversing this situation to take advantage of the massive work and exceptional advances that biomedical research has made in the last decade, should be a major goal. The advances in the clinical definition of ME, the undeniable data on the prevalence of the disease are major players contributing to push ME towards the frontline of biomedical research.

What will ME/CFS find in the current research landscape?

Most of diseases can now be approached from a completely different scientific perspective that could be approached ten years ago. New technologies and new analysis tools generating and managing million of data are now available. This information will inform us on the genetic basis of the disease and the implication of intestinal microbiota or the immune system in its pathophysiology.

However all this powerful arsenal of technology will be useless in the absence of a proper choice of patients.

Clinical efforts in diagnosis and in the definition of clinical trials will be therefore determinant to achieve the final goal.

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## INVEST IN ME RESEARCH CONTACT DETAILS

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## FURTHER INFORMATION

Invest in ME (Research)

<http://www.investinme.org>

Invest in ME International ME Conferences

<http://www.investinme.org/IIME%20International%20ME%20Conferences.htm>

Invest in ME Conference DVDs

<http://www.investinme.org/InfoCentre%20Education%20Homepage.htm>

More details of IIMEC9 conference

[www.investinme.eu](http://www.investinme.eu)

Invest in ME Current Research

<http://www.investinme.org/ldr.htm>

Invest in ME/UCL Rituximab Clinical Trial

<http://www.ukrituximabtrial.org>

Caring for seriously ill ME-patients: A small survey

<http://bit.ly/THS87c>

Caring for seriously ill ME-patients: A small survey

<http://bit.ly/THS87c>

A Clinical Case Definition and Guidelines for Medical Practitioners

[http://www.investinme.org/InfoCentre%20Guidelines.htm#Canadian\\_Criteria](http://www.investinme.org/InfoCentre%20Guidelines.htm#Canadian_Criteria)

## ***Severe ME***

The situation of severely ill bedbound ME patients was discussed by some of the presenters at the 2013 Invest in ME International ME conference – IIMEC8.

Dr Daniel Peterson (Director Simmaron Research, USA) said that the healthcare system is not geared for these types of patients. In the past these patients would have been cared for in hospitals with alimentary treatments but now the cost is prohibitive.

Dr Don Staines (Public Health Medical Officer, Queensland Health, Australia) said the situation is bizarre as normally the most severe patients in any illness get most attention and are hospitalized but in ME the situation seems to be reverse.

The Australian Marshall-Gradisnik research group has included severe ME patients in their studies but have not found any differences in the immune system parameters in groups rated according to severity. Dr Staines pointed out that ME is, however, a multisystem illness and the immune system is only one part of it.

The Griffiths University, where the Marshall-Gradisnik group is located, also has beds for patients so that they can include severely ill patients in their studies as well as monitor patients for 24 hours or more. This is something that should be possible elsewhere too.

Doctors simply do not know what to do with these patients so there is an urgent need for education.

After the conference Dr Amolak Bansal (Consultant Clinical Immunology and Immunopathology, Epsom and St. Helier University Hospitals NHS Trust, Surrey) added the following especially for Invest in ME, explaining severe ME in the following way -

“While it is presently very difficult for modern medicine to fully explain all severe ME symptoms, disordered neural function within the brain and spinal cord would come close.

How this occurs is unknown but there are counterparts in certain newly described autoimmune conditions and viral infections of the nervous system.

In addition to a direct stimulation of neurones in different parts of the brain and spinal cord there is also an impaired filtering function of the brain stem and a reduced threshold for neurones to fire off.

This allows external stimuli such as movement, light, sounds, touch and sometimes even worrying thoughts to produce widespread neuronal activation with ultimate excitotoxic damage to these cells.

The consequence is impaired activity of the brain generally but particularly the hypothalamus and prefrontal cortex leading to fatigue, disordered sleep, impaired memory, attention, faintness, palpitations, disordered respiration, temperature dysregulation etc.

Outwardly many patients appear well and routine blood and other investigations are normal. Internally there are severe symptoms which, if unchecked, escalate leading ultimately to immobility and increasing pain and spasms in a proportion of patients.

Clearly a greater understanding of this highly disabling condition is required with a greater focus on disrupted immune and neural pathways and not just psychosocial factors as has previously been the case.”

**APPENDIX 2 – BANSAL SCORE CHART FOR ME/CFS**

Delayed prolonged PEM after Physical, Mental & Emotional excess	3
Non-restorative sleep with difficulty initiating and maintaining sleep	2
Impaired concentration that is reduced further by external stimuli	1
Reduced short term memory with word finding difficulty	1
New headaches (>2/mth & different in character from previous headaches)	1
Sore throat with cervical tenderness/recurrent flu-like episodes	1
Arthralgia affecting several joints (with stiffness >1hr but no swelling)	1
Myalgia affecting multiple groups and exacerbated by mild exertion	1
Postural instability (NMH/POTS) – feeling unstable on standing/sitting	1
Hypersensitivity to sounds and lights (smells as well with nausea)	1

Need 8 or more from 13 points to confirm CFS/ME with an absolute requirement for some form of PEM.

Delayed (>12 hours) prolonged (24hrs+) PEM gives 3 points while an immediate PEM (<3hours) of > 24hours gives 2 points. Immediate PEM (<3 hours) lasting < 24hours gives 1 point.

The fatigue, neurocognitive problems, myalgia, arthralgia, hypersensitivity issues must be significant and cause disability for >50% of the time.

Non-restorative sleep with difficulty initiating and maintaining this at night time and present >5+nights per week gives 2 points. The non-restorative nature of the sleep disturbance must persist with hypnotics.

Non-restorative sleep without difficulty initiating or staying asleep gives 1 point.

Sore throat and flu like sensations must be present 1+/wk

Neurocognitive dysfunction with impaired concentration and memory problems aggravated by overload from excessive visual & auditory stimuli.

Great care when patients have a significant anxiety and/or depression. However, depression and anxiety can complicate CFS and vice versa.

In our research studies all subjects have 10 or more points and we exclude those with significant depression and anxiety. The HADS is partly helpful.

Hypersensitivity to medications is particularly frequent and especially to SSRIs, SNRI's, TCA,s etc.

Alcohol intolerance is also frequent and tolerance of 4 units or more in a single sitting encourages a reevaluation of the diagnosis. Fewer than 10% our patients continue regular alcohol ingestion.

*From a clinical perspective, additional points that may help in suggesting the diagnosis in borderline cases include cold peripheries, alcohol intolerance, drug hypersensitivity, altered pupil reflexes and sighing respiration (3+ = 1 point).*

Dr Amolak S Bansal  
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