



# *Invest in ME*

PO Box 561, Eastleigh SO50 0GQ, Hampshire, UK

Telephone: 02380 251719 – 07759 349743

Web: [www.investinme.org](http://www.investinme.org)

Email: [info@investinme.org](mailto:info@investinme.org)

## 10<sup>th</sup> Invest in ME International ME Conference

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### INVEST IN ME – 10<sup>th</sup> International Conference

29<sup>th</sup> May 2015, London

Rosamund Vallings MB BS

I was privileged to attend the 10<sup>th</sup> Invest in ME conference in London on 29<sup>th</sup> May 2015 following on from the 2-day colloquium attended by 60 invited delegates from around the world.

Participants from 17 countries were welcomed to the conference opening by **Invest in ME** and the chair was then taken by **Dr Ian Gibson**.

The keynote speech was given by **Professor Ian Charles** (Norwich, UK). He has recently been appointed by the Institute of Food Research to lead the programme to develop the UK's new centre for Food and Health based at Norwich Research Park. This is a large complex incorporating: The Institute of Food Research, The University of East Anglia, the Norfolk and Norwich University Hospital and the Genome Analysis Centre. There will be interdisciplinary approaches to address many complex problems.

He discussed the gut microbiome, explaining that we have ten times more bacteria than cells. He asked the questions: "Do alterations in intestinal barrier integrity and microbiota exist in ME?" and "Is there evidence of immune exposure and reactivity to commensal microbes in ME patients?" He will be working within an interdisciplinary model, which will become an international hub for food and health research, with top class scientists appointed. Many departments will be working together.

This new approach will be holistic, systematic and integrated to deliver faster innovation. It will be a site of excellence and will liaise with government. The aim is to lead to personalized nutrition to benefit the individual microbiome.

The first presentation was given by **Mady Hornig** (Columbia, USA). She discussed markers of immunity and metabolism in ME. She described a 3-strikes hypothesis regarding development of the illness, involving genes, environment and timing. These affect brain outcomes, and she discussed the effects of the mother's own immune system on the developing foetal brain. Her cytokine profile could be implicated in the risks of the infant developing nervous system disorders, even years later. The microbiome of the mother also influences the offspring's immune system with potential risks. Many disorders of the nervous system may stem from immune-mediated pathogenesis.

She then described how there is an increase in plasma levels of pro-inflammatory cytokines associated with recent illness in ME, and as the illness progresses, these levels fall. A striking finding is the very high level of IFN-gamma in short duration illness. It is possible that different cytokine profiles may affect the potential benefit of different types of therapies. Therapies may need to be different at different stages of the illness.

Looking at the cerebrospinal fluid (CSF) comparing ME, MS and controls, there were some similarities between ME and MS but the controls had very different immune signatures. The patterns of immune molecules in the CSF of ME subjects, who largely had been ill for many years, were similar to those



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observed in Hornig et al.'s immune profiling studies using blood from ME subjects of long-standing duration.

Discussing metabolomics, she then described 7 classes of 180 metabolites. Alterations were found in a wide range of metabolites in ME, including ADMA, which is associated with nitrosative stress, and in tryptophan and serotonin. These metabolomic changes were found to be correlated with changes in cytokines.

In the gut, there may be imbalances due to foods leading to bacterial fermentation. Probiotics and faecal transfers do have potential, as have been found to prevent encephalopathy in cirrhosis of the liver.

A question was asked as to whether the effects of SSRIs may be affected by the serotonin levels and whether the duration of the illness could be implicated here. It may be that patients will need to be categorized according to illness duration, and there may be a subgroup who will respond. But serotonin levels are not the only mechanism. It is likely to be more complex than that.

**Jonas Berquist** (Uppsala, Sweden) describing himself as an analytical chemist, discussed the Proteomics in ME/CFS. The first ever analytical chemist was Tobern Olaf Bergman from Sweden. So there is a strong Swedish tradition in this field. Berquist's lab does general research and uses mass spectrometry looking at endogenous analytes. He described proteomics as life's molecular machines – i.e. proteins which carry out all functions of the body.

He looked at when, where, how proteins are expressed. Post-translational modifications (PTMs) occur. This can be measured using 3D gel electrophoresis, but nowadays “shotgun” proteomics is used to separate them out. Many instruments are used and some of them are very big machines, using high resolution mass spectrometry. It is important to use the correct samples from serum and tissues. The tests are extremely sensitive. He compared the small concentrations measurable with these techniques as the amount found if a cup of coffee is poured into a swimming pool.

When looking at the CSF, the total volume is about 150ml and 5-600ml daily is produced. Sample handling needs to be extremely careful. His labs have produced a 776 page list of the peptides in the CSF. There are different ranges with overlaps in different conditions. The study gives meaningful insights into the biological processes in ME/CFS. There are significantly changed proteins involved in neurologic, metabolic and immune diseases. He has looked at upstream and downstream analysis.

The conclusion is that this work could lead to biomarkers, which maybe diagnostic, prognostic and therapeutic.

**Luis Nacul** (London, UK) reviewed the epidemiological evidence on ME/CFS looking at the current status and implications for research and service delivery. He described it as a jigsaw coming together. He felt that the symptoms of encephalitis were very similar to the symptoms of ME, which may therefore be indicative of neuro-inflammation. He said that the diagnosis of ME should be distinguished from that of chronic fatigue syndrome, as usually the term ME was indicative of more symptoms. He mentioned a variance in prevalence rates, with females more commonly affected than males. Overall population estimates are between 0.1% and 0.7%. Young adulthood is the commonest age of incidence. In patients with ME/CFS, activity is significantly diminished. He stressed that we need to look at specificity and sensitivity, and risk ratio and risk difference. Specificity should take precedence over sensitivity for validity.

The NICE guidelines on management were mentioned. There are limited effects shown in the clinical response to CBT. But the results may not be valid as studies used in the meta- analyses are of poor quality and a large proportion patients did not complete a trial, and therefore results may not be valid. It could be described as an additional “coping” therapy, which should not distract us from finding specific treatments for me.



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We need to concentrate on biomarkers for the future, with case stratification and intervention strategies. The current UK biobank has 500 participants, with 17,000 aliquots stored as of March 2015.

**Amolak Bansal** (Surrey, UK) gave an overview of the diagnosis and differential diagnosis on ME. He explained how fatigue occurs in many illnesses, but is the cardinal feature of ME/CFS. He said the post-exertional malaise is hard to explain. He then went through the various criteria being used to diagnose the illness. He discussed the differences between the criteria (CDC, ICC etc.). He thinks that the term SEID may be too simple. He talked of exclusion criteria, including temporary exclusion criteria, such as hypothyroidism and morbid obesity leading to sleep apnoea; and psychiatric exclusion criteria. He mentioned comparisons which are made between the terms CFS and ME.

He then went through the Sutton scoring system developed at his clinic. The main symptoms have a “loaded” score: e.g. PEM scores 3 points, sleep problems 2 and all other symptoms 1 point. 8 or more points out of 13 points is needed for a diagnosis. All patients must have post exertional malaise. For subjects involved in research he uses a score of 10+ from 13 to ensure a critically well-defined population. Subjects with a significant depression or anxiety are excluded from research but can still be diagnosed with ME/CFS for management purposes if they have sufficient points and the depression and anxiety is secondary to the ME/CFS. Treating the depression, anxiety and ME/CFS are all critical to improvement in these people. It is important to note that sensitivity to medication, and alcohol intolerance are very common in ME/CFS. Fewer than 10% patients can tolerate alcohol. Another unusual sign in 60 % patients is altered pupillary reflexes (alternating dilatation and contraction while a light is shined) and sighing respirations. Other physical signs include: joint hypermobility (20%), increased respiratory rate (80%), coldness of peripheries (70%). Conditions that can cause symptoms similar to ME/CFS include: hypothyroidism, Addison’s disease, pituitary dysfunction, Sjogren’s syndrome, gluten sensitivity, persistent anxiety, primary sleep disorder, Ehlers Danlos Syndrome joint/hypermobility type, cardiac dysfunction, Parkinson’s disease and temporo-mandibular joint disorder.

He then compared ME/CFS with depression and anxiety. The sleep disturbance in ME/CFS is different to that in depression and the former are also markedly hypersensitive to psychoactive medications. Functionally those with ME/CFS can start a task, but then trend downwards while those with depression cannot start a task as they have reduced motivation, but once started they can often manage to complete it. Those with ME/CFS rarely resort to alcohol, while those with depression do frequently. However chronic anxiety associated with ME/CFS will deplete energy further, contribute to faintness, cognitive difficulties and increased respiration.

He then talked about appropriate investigations. The basic blood workup should be done as for all fatiguing illnesses and these are sufficient to exclude other causes for chronic fatigue in the majority of patients. Things to add in depending on history and symptoms may be: ANA, CK, calcium, magnesium, tests for Addisons and on rare occasions infection serology (Lyme, viral) and neurological abnormalities (MRI, fMRI, PET scans). Other tests that are occasionally considered include tilt table, ECG monitoring and neuropsychological tests. Unfortunately in the UK searching for triggering infections, such as viral, bacterial (incl spirochaetes), protozoa and fungi (no evidence for involvement of candida) is rarely rewarding in terms of offering specific therapeutic options. History of immunisations on rare occasions may suggest a possible trigger and there is recent controversy about the HPV vaccine.

Quite often it is a difficult question of how far to delve into issues such as life events, stress, physical injuries, environmental toxins and childhood trauma as there is at least some evidence that they may all play a cofactor role in precipitating ME/CFS. He then discussed the importance of the control population in ongoing ME/CFS



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research. Although the ideal control group would be family members this is often difficult and perhaps monitoring people with ME/CFS through several periods of relapse and remission would be best way forward.

**Sonya Marshall-Gradisnik and Don Staines** (Griffith University, Gold Coast, Australia) presented their work on biomarkers in ME/CFS. They had had two recent papers published –

<http://www.la-press.com/examination-of-single-nucleotide-polymorphisms-snps-in-transient-recept-article-a4824>

and

<http://www.la-press.com/examination-of-single-nucleotide-polymorphisms-in-acetylcholine-recept-article-a4862>

The two researchers highlighted these papers are from a series of papers that will be released in the coming months.

These two papers discussed this important work on single nucleotide polymorphisms (SNPs) in both transient receptor potential (TRP) ion channel genes and acetylcholine (AChR) receptor genes. TRP and AChR are part of the ancient or innate immune system. The TRP ion channels respond to environmental threats, temperature, chemicals etc. They are distributed throughout virtually all cells of the body. The range of threats may lead to widespread symptoms. Imposed physical activity is the wrong thing to be doing as it will likely exacerbate adverse signaling in patients expressing these SNPs.

Acetyl choline is a major neurotransmitter seen throughout the entire peripheral, autonomic and central nervous systems and is also part of the non-neuronal signaling mechanisms of the ancient immune system.

SNPs may cause change in protein structure of translated protein and therefore possibly change in function of these ion channels or receptors.

280 people were recruited and screened using the CDC criteria and exclusion criteria. 115 had ME/CFS, 90 were non-fatigued and 75 were excluded. Those included were given questionnaires (SF36, FSS, KPS), and included housebound patients. Bloods were taken for testing.

13 SNPs were associated with ME/CFS compared to controls (9 – TRPM3, 2 – TRPA1, 2 – TRPC4). TRPA1 is activated by exogenous and endogenous inflammatory agents, leading to pain and inflammation.

It regulates neuropeptides and is a multiple chemical receptor. It is associated with changes in neuropeptide receptors and inflammatory cytokine profiles. TRPM3 is located on the pancreatic $\beta$  cells and in the CNS. It is associated with pain. TRPC4 is associated with vasomotor function and smooth muscle function.

17 SNPs were associated significantly with AChRs in ME/CFS patients (9 – mAChM3, 5 - nACh alpha 10, 1 -AChR alpha 5 and 1 - nAChR alpha 2

Collectively, AChR and TRP SNPs likely influence the gastrointestinal tract involving insulin and glycogen secretion, B and T lymphocyte development and proliferation, and neurological systems associated with sleep, pain and arousal.

This research highlighted the possible role of TRP ion channels and AChRs in the onset of ME/CFS.

**Next Generation:** A panel discussion then ensued involving 4 new student researchers, and it was good to hear their involvement, which bodes well for the future. The students were -



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- Bharat Harbham (UEA/IFR)
- Fane Mensah (UCL)
- Navena Navaneetharaja (UEA/IFR)
- Daniel Vipond (IFR)

**Jo Cambridge** (London, UK) then talked about B cell biology and ME/CFS. She gave some background history explaining that Rituximab had been used in 1998 to treat Rheumatoid Arthritis and SLE. The work of Mella and Fluge then further drove the hypothesis that B cell depletion could be implicated in ME/CFS. Her group looked at B Cell biology, biomarkers for response and relapse and other B cell directed therapies. The B cell has a large number of markers. Markers tell the age of the cell and other expressions. Every new B cell has a different receptor. Adherence is involved. B cells move through plasma cells to make antibodies. Antibodies are a form of B cell receptor, and are released onto surfaces, and bind to help clear macrophages from the body. They are made in the bone marrow and circulate to lymphoid organs. Antibodies recognize the different stages on the target bug. (e.g. antigen). IgM, IgA, IgG are all a different shape, all recognize the same antigen, but bind to cells in different ways. In a normal immune response, IgM is apparent in the first 7-10 days, then IgG. Memory B cells also form to attack recurrent bugs. There is interaction with T cells causing cytokines to help B cells make the antigen.

Cytokines interleukin8 and interleukin5 are elevated in ME/CFS and interleukin23 is down. There are also early and late effects in this illness leading to different cytokine levels. Antibodies in disease can form to “self” giving rise to immune complexes lodging in tissues leading to inflammation (e.g. lupus, rheumatoid arthritis). The antibodies bind and damage or change cell function. They can interfere with communication between cells.

Rituximab works in diseases where there are antibodies, leading to B cell depletion by recognising CD20 on the B cell. This in turn leads to B cell destruction in the circulation. B cells can regenerate. Changes occur in levels of Anti CCP after a single rituximab course. It is very complicated.

In ME/CFS there were positive results from use of rituximab in Norway. Patients do differ and there is no clear picture of the B cells. The B cell phenotype can be compared to the ME/CFS demographics using flow cytometry. One can look at complex things such as maturation, plasma cells, percentage of B cells in the blood, associated demographics, percentages of memory and naïve B cells etc.

CD24 is present on B cells associated with maturation (mainly on young cells). CD38-CD21 – memory B cell subsets – high expression in controls, less so in ME/CFS. Duration of illness gives different levels, with B cells normalizing over time. There are no differences in classical B cells.

Immune brain communication and relationship to inflammation induced fatigue were discussed by **Neil Harrison** (Sussex, UK). He outlined the symptoms associated with sickness behavior and listed the behavioural changes that occur to protect the body. He explained how cytokines injected into rodents led to symptoms of sickness behavior. Humans given high doses of interferon- $\alpha$  to treat Hepatitis C also develop sickness behavior and often experience severe fatigue. There is immune-brain communication via a number of pathways, and in particular via the vagus nerve. The microglia are also activated leading to brain inflammation.

Typhoid vaccine was used as a bacterial mimic. The fMRI showed activity++, and PET showed increased metabolism particularly within immune-brain communication pathways. Inflammation induced insular activity, which predicts fatigue. Interferon mediated fatigue is a side effect of interferon- $\alpha$  therapy (a viral mimic). MRI scans were done before, and shortly after beginning Interferon-alpha therapy then patients followed up for their 6-month duration of treatment. A challenge with IFN lead to the onset of fatigue and





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MRI changes within 3 hours. One could also use changes observed on MRI to predict which patients would subsequently develop the worst fatigue during their 24 weeks of treatment. There are implications for post-IFN fatigue and post viral fatigue. He asked the question “Do structural brain abnormalities persist post-inflammatory challenge?”.

**John Chia** (California, USA) updated us on his work with enteroviruses. He explained that there are many illnesses associated with enteroviruses. Most doctors are not trained to diagnose enterovirus infection. They are difficult to recognize. In 1995 41% CFS patients had positive serum enterovirus. He presented his research up to the present. He worked initially with blood samples, but moved onto tissue samples. In patients with persistent gastrointestinal symptoms, there was no evidence of H Pylori. But there were positive abdominal tender points, and focal gastritis on endoscopy (often mild). 135 out of 165 patients were positive for VPI within the parietal cells, compared to 7 out of 34 controls. He tried to culture the viruses, but none survived. In 2008, viruses were found in biopsies (Enterovirus capsid protein) 81% showed VPI and 91% dRNA. Work with SCID mice showed effects of enterovirus infection after injection. (66% positive compared to 10% controls). He says that initial infection in the stomach is not controlled by the immune response. Enteroviruses travel via the vagus to the brainstem.

**Claire Hutchinson** (Leicester, UK) had looked at visual processing in ME. She talked about how visual symptoms were commonly reported in the 63 patients studied, using questionnaires and free report of symptoms. She wanted to map anomalous visual behavior onto the visual pathway, and to provide evidence to support symptom reports. There was experimental for the existence of visual stress/pattern glare in 20 patients compared to controls, which may reflect cortical hyperexcitability. In a study looking at visual attention and the ability to ignore background information (29 patients, 29 controls), found basic visual processing speed was normal, but both divided attention and selective attention were slow. She also presented data showing that, under some conditions, eye movements are less accurate in people with ME.

**Betsy Keller** (Ithaca, USA) went through activity guidelines to avoid symptom flares. This was an active talk incorporating audience participation. She talked about energy currency and post-exertional malaise (PEM), describing short term anaerobic, long term anaerobic and aerobic stages (>2 minutes) - the latter not being suitable for a person with ME/CFS because this energy system fails to recover normally. She described the abnormal recovery response, with ME/CFS patients taking 3 days or longer to recover from 5-10 minutes on a treadmill. PEM is the defining quality of this illness. It is easier to avoid it than to recover from it. Her advice is to pre-empt PEM with scheduled rest periods, do not wait for a crash, pace carefully, know your triggers and avoid or minimize them. Exercise should be redefined with focus on quality of life and use of the short-term energy systems that do work. Yoga and Tai Chi are suitable forms of exercise. The strategy for physical activity should use functional movement that is restorative, with a goal to improve. Aim should be to use the anaerobic energy systems with a work/rest ratio of 1:3, 1:4 or more if needed. That is, ‘work’ for 30 seconds, recover for 90 seconds (1:3).

She went on to explain the importance of core stability to conserve energy. The core includes muscles, bones, connective tissue of the trunk from the neck to hips- it connects the extremities. She explained the weight of the head and how it increases if one slouches (using extra energy unnecessarily). Warm up should begin with focused, square or nose-breathing (4 sec inhale, 6-8 exhale). This will often help symptoms too by better oxygenating the tissues.

5 steps to align core: 1) Contract pelvic floor (contract muscles that stop flow of urine or Kegel), 2) draw in umbilicus (draw belly button toward spine), 3) raise ribcage (rib cage points up toward ceiling or umbrella diaphragm). 4) Lift shoulders up to ears then back and let drop down, 5) retract chin. (Some of these exercises can be done lying down). Back extension is important (lying on floor on belly). She then ran through some exercises on the floor or Swiss ball straightening arms and legs - alternate and opposite sides. These exercises strengthen the core. It is important to assess how one feels the next day to determine if the work/rest ratio is sufficient. If structured activity works, core stability improves, movement



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becomes more efficient and less energy draining. Activities need to be monitored and modified. The exercises should be very brief e.g. 30 seconds of activity, 90 seconds of rest, 3 times. The heart rate (HR) can be monitored and should not exceed the anaerobic threshold, and watch to see which exercises work at what HR. There is a perceived exertion scale and the aim should be to stay at the bottom level. She described structured activity as empowering, improving quality of life, giving a sense of control and being off the rollercoaster. Energy conservation involves pacing, body position, joint protection and activity planning. There is need to think circularly not linearly (use a work/rest ratio all day), acknowledge limitations, aim for core stability and structure physical activity. She then outlined 10 simple energy-saving tips shared with her by Staci Stevens of the Workwell Foundation:

- Make bed while you are in it or not at all
- Take things around the house in a back pack.
- Shower sitting down
- Simplify clothes and hair
- Use an answering machine
- Pack groceries smartly ready for unpacking
- Cook ahead
- Get disabled car park
- Prioritize chores
- Learn to say No and Yes

**Olav Mella** (Bergen, Norway) brought us up to date discussing the Phase 2 and 3 studies of the rituximab trial. The Phase 2 study will be published shortly. 20% patients had a transient worsening of symptoms. There was marked improvement of physical function in 6 of 9 previous placebo patients. Half of the original responders were still responding at the end of follow up (36 months). The quality of life of the responders was very good. Only 5 patients were as low as 30%. During the trial levels of function were tested using a bicycle on a ramp. Experience with measuring endothelial dysfunction was gained. Maintenance therapy may sustain response

A new study is now underway. Patients recruited have been ill for 2-15 years. The Canadian criteria were used for diagnosis. 4 university hospitals and a community hospital were involved. Patients were given information and filled in the De Paul questionnaire. Biobank material was withdrawn and frozen. Patients undergoing the ramp test may need to wait 3 months before start of treatment to get back to their normal level. The study is randomized, double blinded, placebo-controlled. Study period will be 24 months, so results will be available in summer 2017, unless there are serious side effects. There will be no access to randomisation. All monitoring will be external. The physicians concerned will not see the patients. Rituximab 500mg/m<sup>2</sup> will be given on days 0 and 15, and then 500mg at 3, 6, 9 and 12 months. Patients will monitor themselves. SF36 will be used every 3 months and FSS at zero, 6, 12, 18 and 24 months. Electronic activity will be assessed at zero and 18 months, using a wrist band. Blood samples will be drawn regularly for biobank freezing. The primary endpoint will be the level of fatigue over 24 months. The secondary endpoint will be changes in QOL, and any effects of toxicity. Sub-studies will include endothelial dysfunction (large vessels - ultrasound and microvessels - PORH analysis) – Is there correlation between endothelial dysfunction and ME and improvement parallel to endothelial dysfunction? Ergo spirometry can be used, if patient is able, to see if there are changes in the anaerobic threshold. Another sub-study will look at gastro-intestinal function.



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These are high quality studies hoping for good clinical response. One must expect up to 20% placebo response, and hope for a 50% rituximab response. One needs to look at clinical characteristics of the responders. There may be a 4-5 month delayed response. The biobank will be useful. There may be political impact. Another multicenter trial elsewhere is needed. Toxicity also needs to be considered. Some patients cannot tolerate the treatment.

A further new study using cyclophosphamide started in March 2015. This is a cheaper immune-modulating drug. It shows major improvement in treatment for breast cancer. 40 ME patients have been recruited with 6 infusions to be given every 4 weeks. There are 3 groups of patients: those not treated with rituximab, previous non-responders to rituximab and those who have recurred after rituximab. Patients with mild to moderate illness are recruited and the trial will last 2 years. It does not include young patients or those at risk of pregnancy. It will be tried later on for 20 more severe patients.

The conference concluded with thanks to all speakers and closing remarks from **Dr Ian Gibson** and **Invest in ME**, and all agreed it had been the very best yet.

I would like to thank Invest in ME and ANZMES for making it possible for me to attend this excellent event.

**Rosamund Vallings MNZM, MBBS**



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