June 2, 2013 / Simon

Mainstreaming ME Research: The 8th Invest in ME International ME Conference, 2013

Mark Berry reports from London on the 8th Invest in ME International ME Conference.

This was only my second year at the Invest in ME conference, but already I feel right at home! The presentations you're about to read about are only half the story; the opportunity to mingle and network with a family (yes it really does feel like a family!) of top researchers, physicians, campaigners and patients from all over the world, is absolutely priceless. And this year, the new spirit of hope and togetherness in the air was a joy to behold.

The title this year was "Mainstreaming ME Research: Infections, Immunity and Myalgic Encephalomyelitis", and the twin themes – an emerging consensus around a 'paradigm shift' to thinking about ME as an autoimmune disorder, and a focus on strategies for effective research and a breakthrough into the scientific mainstream – fit together perfectly. For it's the growing recognition that immune treatments like Rituximab and Ampligen are having dramatic effects on many patients who were once bedbound and without hope, together with two decades of often confusing but highly suggestive research

findings of immune dysfunction in ME patients, that is now threatening to propel ME from the backwaters of science right into the limelight.

A key part of that process has been Invest in ME's Clinical Autoimmunity Working Group, formed last year – a group of researchers which meets before the main conference to discuss the latest scientific developments. The creation of international collaborative networks is surely valuable in any field of science, but in a field that has been so neglected and so under-resourced for so long, it's even more important to maximize resources.

Once the working group has done its thing, next comes the pre-conference dinner – the Patient Advocate reports on Linda Tannenbaum's pre-conference dinner presentation here.

And then it's on with the main event: time for conference-goers to pick up their copy of the Conference Journal, mingle and chat with old friends over coffee for a while, and settle down for the first item on the Agenda….

Of course, sadly many of us can't hope to make it to a day like this, and I'm acutely aware of that and wish for the day when they can, so for those who've been relying on Jorgen Jelstad and his excellent conference tweets, here's my summary of the day…as a teaser for the far more comprehensive conference DVD…

Conference Highlights

- **Dr Ian Gibson announces new PhD studentship in Norwich looking at gut bacteria**. "Things are beginning to pop, across the nation and across the world…There's a new spirit loose, I think, in the ME field".
- **Dr Peterson keynote: "It's time to stop querying patients and begin developing new diagnostics"**. We need both clear endpoints and clear populations for successful research.
- **Dr Kogelnik: Medicine is at a crossroads, and ME will be "key disease"** in coming "health/disease revolution": technology enables the 'Quantified Self' and personalized medicine. Govt agencies "not the enemy", it's "their ignorance and our lack of data" – our job is to bring them the data so it can't be ignored.

- **Dr Rakib Rayhan: In Gulf War Illness, Baraniuk et al believe their brain scans after exercise challenge produced a "quite robust biomarker"**, and they want to extend to ME/CFS. New study out in a couple of weeks finds 2 subgroups for pain and fatigue post-exercise.
- **Professor Greg Towers puts XMRV saga to bed**: valuable lessons learned mean this kind of situation should never happen again.
- **Professor Mady Hornig: Final analysis of cerebrospinal fluid now underway**; possible finding of 'different patterns of cytokine associative networks' and 'potential novel candidate' in CSF still needs to be confirmed.
- **Dr Clare Gerada steps into the lions' den and "tells it straight"** – attempts to "build a bridge between the largest Royal College and a very important problem" – hopes to "be better able to work with you to improve the care you receive from my profession".
- **Dr Donald Staines stands in for Professor Sonya Marshall-Gradisnik. Publications expected in next weeks and months**; still finding "sustained, demonstrable, significant impairment in NK cell function", "highly confident" of up-regulation of T-reg cells; "clear derangement in the immune system…it's irrefutable", and "anyone who suggests that this might be fixed by exercise therapy should probably be de-registered I think".
- **Dr Amolak Bansal senses a "paradigm shift" towards model of subtle form of autoimmunity in ME**; suspects patients' B cells are failing to mature properly and producing low avidity antibodies; lasting response to B-cell depletion therapy may require clearing the viruses responsible in addition to 'rebooting' the B cells.
- **Norwegian ME Association presents awards to Invest in ME founders Richard and Pia Simpson, and to Professor Malcolm Hooper** for "untiring and exceptional contribution to the ME cause". Hooper accepts with his shortest ever speech.
- **Carmen Scheibenbogen and her team at Charite are finding similar immune dysfunction** and share many of the same theories as Bansal, Fluge and Mella. They're trying to develop a diagnostic test, investigating EBV infections in depth, and seeing 3 immune subtypes of CFS. Hoping for solid data in about 6 months.
- **Professor Mella and Dr Fluge are closing in on publication of their follow-up study on Rituximab therapy.** Some details were presented, along with a fascinating hypothesis, but that's all embargoed awaiting publication, so if you're curious about that, you'd better order the conference DVD right away…my lips are sealed!

Dr Ian Gibson: Welcome

Dr Ian Gibson

Ian Gibson welcomed conference-goers back to 1 Birdcage Walk – the home of Invest in ME's annual conference since 2006 – by joking that he "dreams about this place". But really, said Gibson, the idea is to **stop** people dreaming…"because the thing about dreams is, then you wake up!". Gibson seemed to feel the same sense of hope and excitement that many of the people I spoke to at the conference expressed: "Things are beginning to pop," he enthused, "across the nation and across the world". The sort of positive developments we've seen recently "don't just happen", he added, hinting at the hours of hard work and lobbying behind the scenes that slowly but surely result in progress.

Gibson then announced the funding of a new PhD studentship in Norwich that will be looking at gut bacteria in ME/CFS (presumably in connection with IiME's foundation biomedical research project for ME, which will be carried out at the University of East Anglia). He reminded delegates that in science there's no telling where the next major development might come from. "Somebody is going to make a breakthrough which shatters us all," he predicted, and that makes all the work that went before look irrelevant.

Encouraging the audience to persevere and think broadly and open-mindedly, he acknowledged that political campaigning and lobbying can be a frustrating business, but suggested that local projects might provide more easily achievable objectives that can make a big difference – "politicians…they don't quite understand the issues…we keep on at them, but what happened in Norwich can happen anywhere, and we want to build that elsewhere too".

Gibson was upbeat and sensed a 'paradigm shift': "There's a new spirit loose, I think, in the ME field" and people say to him "Do you remember what it was like 10 years ago?" – a helpful reminder, when road-blocks cause frustration, to think back and realize that the progress made is very real, even if it doesn't always come as quickly as we might like.

He finished by setting the scene for the exchange of information and ideas that was to come: he always told people, he said: "do your own thing, but talk to other people too"…sometimes in science you do 'go down the wrong road', so continued communication is very important. And with that positive introduction, the presentations began…

Dr Daniel Peterson: Key Note Speech: "The Mainstreaming of ME Research"

Dr. Peterson began by reflecting on the past history of ME/CFS. He said that, in his view, there is now a need for a single set of diagnostic criteria accepted worldwide by researchers and clinicians and to "forget nomenclature", seemingly suggesting that we may be reaching a turning point where the emerging scientific consensus enables us all to put the multiple sets of criteria and arguments over names behind us.

Peterson's short race through history began in the 1980s, with a series of outbreaks of disease; in the 80s and 90s, the focus was on fatigue, resulting in the definitions at that time. Since then, however, the focus of research has been on neurological, endocrine and immune dysfunction, and on Post-Exertional Malaise (PEM) – aspects of the illness which most researchers consider critical to diagnosis. The old criteria, he pointed out, have been around for 25 years: it's "time to stop querying patients and begin developing new diagnostics".

Dr Daniel Peterson

Outlining the scale of the problem, he noted that the prevalence of ME/CFS in the US is around 1 million – 'not rare by any means'. Looking at the picture worldwide, he added, one finds a similar story for all patients: they are in a position of enormous socioeconomic disadvantage, with unmet medical and social needs. The direct financial cost of the disease in the US is estimated at $9 billion, and with indirect costs included the estimate rises to $51 billion. Considering the scale of the problem "sometimes brings us all to a paralyzed state".

Problems with Diagnosis

Showing a brief model of disease progression, where genetic predisposition followed by triggers (including infection, trauma, stress, toxins, and immunization) provokes a complex range of mediators to induce chronic illness (ME/CFS), Peterson considered why this pattern is problematic for traditional medical diagnosis. The US FDA, he said, uses the four steps of traditional differential diagnosis (gather information and create a symptoms list; make a list of all possible causes; prioritize the list with the most urgently dangerous condition at the top; and work down the list of causes treating or ruling them out with tests). This model doesn't fit well with ME/CFS, he explained, because we have a heterogeneous population, there are no clear-cut validated

biomarkers, there are multiple clinical definitions, no drug is licensed for treatment, and there is no universal surrogate marker. Symptomatic therapy can alleviate symptoms and improve quality of life, he said, but it has never returned a patient to full cognitive and physical functioning.

FDA Stakeholders Meeting

Turning to a review of the FDA Stakeholders Meeting, Peterson noted that the FDA had been completely unenlightened with respect to the nature of ME/CFS, the extent of the problem, the lack of treatments, and the amount of research being carried out. But for him, the take-home message from the workshop was a positive one: drug approval does **not** require a biomarker if there are other means to define endpoints. Drug development, however, typically takes 8-15 years, and it's driven by market potential. For the FDA's purposes, it needs validated, reproducible endpoints, which can be surrogate markers.

A Look Ahead

Having outlined the background, Peterson brought up an Invest in ME slide and said: "Along comes my favorite small charity with a big cause". Looking ahead at the presentations to come, he highlighted some key headings. **Computational analysis and bioinformatics**, he said, is a new and exciting advancement, and the CFIDS Association had used these tools to help in its drug re-purposing project (suggesting a way around that 8-15 year drug development timeframe). Looking ahead to Mady Hornig's presentation, Columbia Center for Infection and Immunity's **pathogen discovery project** had started in 2012, the final analysis of the study of spinal fluid in 60 ME patients and 60 controls is now under way, and they now have a large repository of samples and data to work with. **Immune biomarkers** are critical to diagnosis, they can define subsets, and Natural Killer (NK) cell function and enumeration is his favorite biomarker for ME/CFS: there's a large literature on NK cells and it's a field with lots of agreement around the world.

Enabling Drug Development and Approval

Peterson continued his focus on issues critical to drug development and approval. **Endpoint evaluation** is a key issue: in January 2013 the FDA had declined to approve Ampligen, largely

because of the lack of availability of objective endpoints that could be used. The PACE trial had used the 6 minute walking test to define an endpoint, but this was not a good candidate: it's not generally considered to be an objective endpoint and would be rejected in the US. VO2 max or Cardio-pulmonary exercise testing (CPET) could be acceptable though. Finally, **large numbers** of patients are needed for useful and meaningful studies; smaller studies are only useful if there is a very homogeneous population being studied. So we need both clear endpoints and clear populations for successful research.

So: to drive drug development and conduct effective clinical trials, we need large multi-site clinical studies, with clear endpoints, studying a well-defined population – and an appropriate level of funding is of course essential for this.

Peterson summed up: Worldwide collaboration is necessary, to define subsets based on accepted biomarkers, to define the exact pathogenesis, to design interventional strategies, and to create centers of excellence.

Dr Andreas Kogelnik: Key Note Speech: "Making ME Mainstream: Strategies for ME Research and Collaboration"

Dr. Kogelnik is founder and director of the Open Medicine Institute (look out for a Phoenix Rising article on the OMI in a couple of weeks). Kogelnik's exciting key note presentation introduced "The Changing World of Medicine", where the IT revolution, the Social Information revolution, and the Biotechnology revolution are all leading, Kogelnik predicted, to a Health/Disease revolution. ME, he suggested, is now coming to the point where it will be a key disease in moving that process forward.

Dr Andreas Kogelnik

Kogelnik illustrated the dramatic changes that are taking place, building on the huge growth in processing power and storage capacity by developing personal technology solutions that enable the concept of the "Quantified Self". Gadgets that turn your mobile phone into an ECG, quantify sleep, continuously measure activity levels and enable you to monitor your vital signs to see what changes when you try a particular drug or treatment, are just as important to the individual as to the physician or researcher, he said. Costs of full genome sequencing are dropping at a spectacular rate: 5 years

ago it cost a billion dollars to sequence the human genome for the first time; now you can sequence your own for about $2,000 and that price is set to drop below $500 very soon.

Medicine is at a crossroads, Kogelnik believes, and he predicts that we will transition from a paradigm of generic 'evidence-based' guidelines to a model of medicine driven by genomics and personalized, precision medicine. Evidence will still be important, but the kind of evidence has changed.

ME/CFS has been easy to ignore while there hasn't been enough data, Kogelnik explained; researchers have been gathering that data in order to gain leverage. Agencies like the FDA are "not an enemy" – it's more an issue of "their ignorance and our lack of data": our job is to bring that data to them so that it can't be ignored. So in order to mainstream ME/CFS, we need broad and deep measurement, and we need to encourage greater engagement of people.

Kogelnik also quickly summarized the OMI-Merit (ME Roundtable on Immunology and Treatment) Priority Projects: you can see those 10 projects listed in more detail here.

The Open Medicine Institute's Open MedNet project – an ME/CFS patient data repository which you can now pre-register for – is due to go online in the next month or two, and when it does we'll be urging all our members and readers to help it reach its target of tens of thousands of individuals. I'm also hoping to report on Kogelnik's inspiring presentation in more detail later this week.

Dr Rakib Rayhan: "The Role of the Brain and ME"

Rakib Rayhan is a colleague of Professor James Baraniuk, who was unable to attend the Invest in ME conference this year, but sent his regards. Rayhan's presentation focused mainly on Gulf War Illness, covering some of its history, some subjective analysis, markers of the disease, and some of his recent research findings with Baraniuk's group.

About 30% of the troops in the first Gulf War have now registered in the American Legion gulf war illness database, and those stricken with the illness have had a tough time getting acceptance of their illness. With no diagnostic code,

Dr Rakib Rayhan

and skepticism from physicians, many are still fighting for benefits after 10-15 years.

There are so many potential causes of GWI – oil wells, smoke, combustion, vaccinations, etc – that 20 years later, the exact causal relationships may be difficult to find, Rayhan said – but he offered to shed light on the pathophysiological mechanisms in his presentation. He focused attention on the huge munitions dump in Khamisiyah where sarin gas and other nerve toxins are thought to have been released into the atmosphere when it was destroyed. Sarin is a potent acetylcholinesterase inhibitor, he noted, with similar mechanisms to various kinds of insecticides.

The Post-Traumatic Stress Disorder (PTSD) theories have been done away with, he argued, and pointed to a study by Steele, Sastre, Gerkovich and Cook which shows associations with other factors that put veterans at risk, such as taking bromide pills, periods of less than 4 hours sleep, being near pesticides, and wearing treated uniforms – maybe all these factors worked in combination.

Reminiscent of the ME/CFS history, Rayhan noted that there are many definitions for GWI as well, including the Fukuda and Kansus definitions, and he spoke of the potential for a new consensus criteria for GWI. Baraniuk is not alone in noting the similarities between GWI and ME/CFS, and he has hypothesized that central nervous system (CNS) dysfunction could cause all the symptoms we see in both. The group have been measuring VO2 max and conducting brain scans before and after exercise stress tests, looking for blood flow and structural changes, in an attempt to see what the brain is doing when PEM occurs (veterans complain about that too as a a prominent part of their disease state).

CNS Dysfunction

Baranuik and Rayahn have used a new technology (Diffusion Tensor Imaging) to enhance standard fMRI techniques, so that they can probe the functioning of bundles of nerve fibers. With this technique, they found anomalies in the nerve fibers that interpret pain signals in Gulf War veterans.

They are particularly excited by the details because their brain imaging work is highlighting a pathway that connects 2 regions of the brain associated with pain and fatigue processing and pain and fatigue perception. They've found other potential biomarkers in other areas of the brain as well.

They believe, Rayhan said, that this work has produced a "quite robust biomarker" to distinguish GWI patients from controls, and their findings indicate "some kind of central nervous system dysfunction".

Studying veterans using fMRI and cardiovascular indices before and after 2 bicycle exercise tests, they found the veterans showed either increased or decreased working memory scores, while the controls were unaffected, and later found that the 'increasers' had lower cerebral lactate (associated with mitochondrial dysfunction, leading to the hypothesis that the brain may have used lactate rather than glucose as an alternate sugar source) whereas the 'decreasers' had a higher glutamine/glutamate ratio.

Piece de Resistance

Rayhan then moved on to the group's 'piece de resistance', which should be out in the next couple of weeks, he said. They've been looking at the change in heart rate following exercise, and they're finding two subgroups. One group, with increased tachycardia throughout the two exercises which went away after 4 nights of rest, they are terming the "Stress Test Associated Reversible Tachycardia Phenotype" (START). The other saw an increase in pain perception, which they're terming "Stress Test Originated Phantom Perception (STOPP). They are also seeing different areas of compensatory brain activity in the two groups. We'll be reporting in more detail when that study is published.

Summarizing, Rayhan concluded that exposure to acetylcholine may have led to damage to the central nervous system, and suggested that their approach to exercise stress-testing offered a potential model to study overlapping syndromes, which may be of use in the case of ME/CFS.

Questions

Ian Gibson now invited questions from the audience on the presentations so far.

Dr Peterson was asked for advice about vertigo and some other symptoms by a severely affected patient. Peterson said that he tended to have all-day meetings with patients such as this, and there was no simple answer. They are an overlooked group of people who largely can't access care, he said; in the old days they used to be looked after in hospital, but sadly that's no longer economic.

Charles Shepherd was pleased to see the PEM study, and asked Rayhan how far along they were in conducting similar studies on ME/CFS. Answer: they haven't started yet; it's a difficult funding environment but they're hoping to do it.

Malcolm Hooper asked Rayhan whether the vets they had studied were deployed or non-deployed; hearing that all but 2 were non-deployed, Hooper cautioned that the two groups' circumstances were quite different, and reminded him to look at that: the non-deployed veterans didn't get the chemical exposures, just the vaccines.

A questioner from the audience wanted to highlight hypo-pituitary syndrome, which can arise after brain injury damages the pituitary gland: between 500,000 and 1 million with this condition are believed to be undiagnosed in the UK today, and she was wondering why people with ME aren't tested for that. The ME experts said it's well known that the pituitary is turned down in ME, and there are many other causes for that so it's important to exclude such people. It's quite an involved process to diagnose HPS, using imaging and dynamic tests, but good endocrinologists won't miss pituitary dysfunction. Correct diagnosis of ME does indeed involve excluding such conditions, and that's very important.

Another questioner felt that there was an important category missing in the study of ME/CFS: people who have had diagnosed ME, with full symptoms, who are now fully recovered. This might be an interesting subgroup to study; these stories might be valuable for research. Kogelnik was very positive in response to that: he sees that as "the low-hanging fruit", and said that the MedLine database will allow patients to diarise their symptoms then, now, and next, and tell their stories from a medical perspective – he invited past patients to do that, and add their medical history under the healthy control section.

A final question asked the speakers about the accepted criteria. The CCC and ICC exist. And why is it so hard for physicians to co-ordinate different specialties for a patient; why do we have to do that for them? Answer: At the heart of the problem: we don't agree about what it is. Dr Peterson lamented: "CFSAC has just voted to put off the clinical and research definition question for 2 more years…why would you ever use 25-year old outdated useless criteria?"

Time for a short Refreshment Break!

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Professor Greg Towers: "Retroviruses and ME"

After a short break for refreshments, Professor Greg Towers reprised the XMRV saga. Retrovirologists weren't paying much attention to XMRV, he said, until the Mikovits paper came out, but that paper caught their attention. Firstly because ME was clearly hard to diagnose, but with XMRV, it wouldn't be, and vaccination and treatment would have been feasible. Secondly, the study had suggested that many (maybe 4% of the general population) may have the virus without symptoms, and it may lead to prostate cancer. So it seemed very important to sort this out as quickly as possible.

Professor Greg Towers

But the situation got confusing quickly: the positive studies slacked off, and the negative studies began. The important question remained: is XMRV circulating in the population?

I'll cut a long story short here – followers of the XMRV saga are familiar with the discovery of XMRV in the 22rv1 cell line; the revelation that it has been known for some time that novel combination retroviruses are commonly created inadvertently in laboratories by the repeated passage of cell lines through mice; the comparison of ancestral genetic sequences that found patterns of variation suggestive of a common laboratory source rather than an actively circulating virus; and the discovery of common integration sites that further suggested a contamination explanation.

One revelation was new to me, though: when tracking down this detective mystery, the team had hit a wall when they tried to get hold of samples of the 22Rv1 plasmid used in Cleveland. This problem was circumvented, Towers explained, when they discovered that Vinnie Pathak's brother in law happened to know somebody who worked in the Cleveland lab; they called him up and got hold of the necessary samples! They were then able to show the XMRV sequence there to be a recombinant of 2 others in the mouse genome – 'preX1' and 'preX2'. The final closure came with the Lipkin study, when he sent samples blinded to Lo, and to Ruscetti, and they didn't detect any viruses with their method. That study puts this story to bed, said Towers.

Valuable lessons had been learned along the way though. PCR is very sensitive – that was well known, and this investigation confirmed just how sensitive it can be. But retrovirologists learned that it is essential to manage it in such a way that you are able to fully understand the possible sources of contamination. They didn't think before that it mattered, but now they know that you mustn't prepare a virus-encoding plasmid in the same laboratory that contains the samples you're testing against; if you do, you can't test sensitively without a risk of contamination. This situation should never happen again, said Towers: the papers published since should show how to prevent this kind of situation happening in future.

Professor Mady Hornig: "Pathogen discovery in ME"

Professor Mady Hornig is Director of Translational Research at Ian Lipkin's Center for Infection and Immunity (CII), Columbia University, and her goal is to understand illnesses where brain and immunity are believed to take centre stage. This is an ideal fit for ME/CFS, given that most researchers suspect that the brain and/or immunity play a central role in the illness.

Professor Mady Hornig

Hopes for a sneak peak at some early findings from the world's largest ever ME/CFS biomedical study were largely dashed...there were a couple of bits of very preliminary news, but we're going to have to wait a little longer for the findings. The hunt by Mady Hornig, Ian Lipkin and colleagues for a virus or other pathogen that may cause our illness, and their investigation of signs of immune abnormalities (as opposed to specific pathogens) has already been described here on Phoenix Rising, in Simon McGrath's articles Lipkin & Hornig go hunting for ME/CFS pathogens and Mady Hornig: How do you solve a problem like CFS? Hornig's presentation at Invest in ME covered very similar ground, and I can't hope to describe it as well as Simon did!

She did mention an additional study of some 'unusual cases' provided by Dr Peterson though, and offered a glimpse of the type of data they are collecting in their cerebrospinal fluid work: a promising slide showed very different patterns of cytokine associative networks in the ME/CFS patients as compared with controls, with the cytokines in the patients more tightly associated. They are perhaps beginning to see here how the immune system functions in a very different way to the controls, but we'll have to wait a little longer for these findings to be confirmed.

We got a few clues as to how far they have progressed: they've completed the initial peripheral blood work, and she estimates they're about 80% through the lab work on that. The bioinformatics work is ongoing, and they think they may have found a 'potential novel candidate' in the spinal fluid, though that needs to be confirmed (is that the network association, or something else? We'll just have to wait and see…) The other studies (including the microbiome investigation) are just gearing up now. This is painstaking work, and science of the highest caliber: although we must wait a little longer, the up side is that the results of this study are sure to be very widely respected, and we have good reason to hope that, when they are published, they will take the field of ME/CFS research forward significantly.

Mady threw in a couple of fine quotes as well. Her opening slide cited Esquirol on Insanity: "Many authors assure us that mental alienation is epidemic. It is certain that there are years, when, independently of moral causes, insanity seems suddenly to extend to a great number of individuals". At times, she added in her introduction, the approach has seemed "almost as if we've had a decapitated body" – where the head has been thought to function independently of biology and physics. I think we can be confident from this that Hornig leans rather more towards the biomedical than to the biopsychosocial…

And to emphasize the ever-changing nature of science at the frontier, she ended again with her great Einstein quote:

Student: Dr. Einstein, Aren't these the same questions as last year's [physics] final exam?
Dr. Einstein: Yes; But this year the answers are different.

Lunch Time!

Yum! That looks delicious!

While I'm tucking in, here are some fun links for you to play with...

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Dr Clare Gerada: "Govt NHS Reforms: Implications for long term chronic conditions such as ME – for GPs and Patients"

Nobody wanted to be back late from lunch! We started the afternoon "with a highlight of the conference," said Ian Gibson, introducing Dr Clare Gerada, "I enjoy listening to Clare because she tells it straight". The audience applauded warmly as Gerada stepped bravely into the lions' den...

Dr Clare Gerada

Dr Clare Gerada was elected to lead the Royal College of General Practitioners in 2011, and now represents over 40,000 doctors; she recently announced that she will be stepping down from the position in November. She trained in psychiatry and maintains an interest in the treatment of patients with addiction problems.

Following her father into general practice, her career as a GP began in 1991 at the Hurley Clinic, Lambeth. She has been concerned with improving the support available to drug-users from their GPs and in 2000 she was awarded an MBE for services to medicine and the wellbeing of drug-users. She has served as Director of Primary Care for the National Clinical Governance Team and Senior Medical Advisor to the Department of Health.

She also happens to be married to Simon Wessely.

A Controversial Choice

The decision to invite Gerada to the Invest in ME conference raised more than a few eyebrows; her strong biopsychosocial views and her appearance in a training video advising GPs how to treat ME patients (playing the role of a GP advising a patient that 'exercise has been shown to be safe') made her a controversial and surprising choice to say the least. But Invest in ME defended their decision to invite her robustly, and their call for the audience "to use this opportunity wisely and politely to move the ME cause forward" was very much heeded: no demonstrations, cat-calling or walkouts here.

Building a Bridge

Indeed, Gerada was applauded as warmly when she left the lecture theatre as she was when she was introduced, and while the questioning at the end of her talk was intense, the conversation was enlightening and constructive. The bravery of Gerada's attempt to "build a bridge between the largest royal college and a very important problem" won respect from the audience, as did her robust and forthright defence of GPs "under strain…blamed for problems in everything from dementia to Accident and Emergency…battered by political leaders, the press, and sometimes the patients we serve…bearing the brunt of cuts, and the inability to deliver personalised care at supermarket prices…".

The audience were treated to an insight into the realities of general practice which put the experience of ME patients in the UK into some context, as she spoke of the huge problems with "models of care for chronic illnesses" in general and defended GPs' admitted ignorance of ME by insisting that general practitioners, as generalists, "cannot know a lot about everything" and when faced with a "chronic disease with such levels of disability" can only refer their patients to a specialist. GPs simply cannot provide the care that ME patients need, she explained, "That takes skills, and resources, and where are the experts? How, if there are no specialists" can GPs provide for the needs of ME patients?

"I'm not disputing whether it's physical, neurological, or jelly…I want to move on from that…", she said: the patients' disability needs to be managed with kindness but "we need specialist services: we need you to lobby for that". And when challenged with stories of GPs advising patients to "go to a gym", or stating that they "don't believe in ME", she was clear that while she did not expect a

GP to understand the complexities of ME, she "would expect him not to make such comments". "I don't know what causes motor neurone disease, but I can still treat those patients with compassion" – she doesn't know the cause of illness for many or most patients, but for the GP the important thing is the "ability to handle patients kindly, with compassion – that's the point".

NHS Re-organisation

Gerada's talk focused not on ME, but on the challenges and problems the NHS is now facing, with a minimum of £20bn more cuts to come in the next 4 years; she warned that the re-organisation in the last few years has "dismantled every existing structure on social care that we had" and rebuilt them at breakneck speed while losing 16% of the staff, and she explained the importance for patients of lobbying the new commissioning groups to answer "what they are doing, and when, for ME – otherwise you will be left out".

Two Conflicting Paradigms

Clare Gerada's appearance at an Invest in ME conference was never going to resolve the differences between what an audience member called "two conflicting paradigms" – but it did show that respectful and worthwhile communication is possible across that divide. I, for one, learned a great deal about the current transformation of the NHS, the pressures faced by general practitioners, and the reality of where the gaping hole in provision for ME patients should properly be filled. While I, like most of those present, remain convinced that the guidance being provided to GPs is still inappropriate and frequently harmful to ME patients, and that remains a huge problem, I gained a greater appreciation that this situation is not the fault of GPs.

Common Ground?

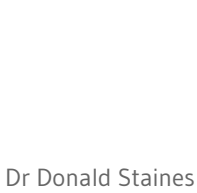
There was even one point on which all those present appeared to find common ground: the real gap in provision is the complete lack of specialist care for ME, and the way forward for ME care has to come from the provision of integrative, specialist services. So in the end, we communicated, we learned, we expressed our concerns, we were respectful and we applauded Gerada's passion and her bravery in speaking to us, and we can only hope that Gerada learned something in the process as well. We even found what looked like points of agreement, and as a football fan (that's soccer, for you Americans), trying to remain objective, I saw the match as a game played in a positive spirit ending in a score draw. Whether a bridge was built, as Gerada hoped, only time will

tell, but there is at least a glimmer of a chance that Gerada will get her wish to "be better able to work with you to improve the care you receive from my profession".

Coming soon on Phoenix Rising, we'll have a full report on Dr. Clare Gerada's talk.

Dr. Donald Staines: "Current Knowledge of Immunological Biomarkers"

Dr. Don Staines was standing in for Professor Sonya Marshall-Gradisnik, who was unfortunately unable to attend due to ill health. (A get well soon card for one of the world's most important ME/CFS researchers may perhaps be in order!). Stains is a member of Marshall-Gradisnik's research team at Griffith University in Queensland, Australia.



Dr Donald Staines

Staines introduced himself as a public health physician, responsible for supporting GPs in understanding disease outbreaks and how to deal with them in the community. Addressing first some of the issues raised in the previous debate, he said he had some perspective on prevalence and incidence. Part of the design of the research unit at Griffith University, he said, was a dedicated clinical and research capacity, with a dedicated 3-bed unit with 24-hour care, enabling them to observe patients over a period of time. It was a very integrated system, he said, and a "really simple idea", and he didn't know why it's "not picking up momentum here as well".

As a primary care physician, said Staines, it was "very important to find immunological and molecular markers". Clearly, he continued, there are factors in ME/CFS throughout the body, but they are focusing on the immunological factors, and in particular the bridge between the innate and adaptive (acquired) immune system.

Natural Killer Cells and CD8 Cell Lysis

Starting with what is already known regarding NK cells and CD8 cell lysis, he explained that NK cells release granzymes, which attack target cells; in ME/CFS, a consistent reduction in NK cell lysis (the breaking down of cells by granzymes) has been found by them and by others. This observation is "not a flash in the pan", it's a "sustained, demonstrable, significant impairment in

NK cell function". They see CD107a degranulation, and big differences in expression. Staines showed how granzymes do their work to assassinate cells. In their studies, they find that this job breaks down in the granzyme B group (not so much in granzyme A or perforin). In CD56 glycoproteins (binding glycoproteins expressed on the surface of NK cells), they find that a specific subset is affected, the CD56 'bright' and not the CD56 'dim'. In the NK cell receptors, they see a change in the KIR3DL receptor. All of these are responsible for attacking and immobilizing an invading infection, and so there are several aspects of impaired function.

Looking at the CD8 transmembrane glycoprotein (a co-receptor for the T cell receptor), they see consistent changes over time: they have studied this at several time points through the year and find that the CD8 itself is compromised. Staines next explained the function of neutrophils, a type of phagocyte (white blood cells that protect the body by ingesting foreign particles) – an essential part of the innate immune system. They migrate through the bloodstream towards sites of inflammation, target the cells they want to immobilize, and trigger several pathways to create a toxic environment within the targeted cell, and are therefore very important in defending the body from invaders. In ME, when they look at the respiratory burst, they find that it is profoundly reduced. This is a significant abnormality, and they are finding that the human neutrophil antigens HNA-2 and HNA-5 are abnormal. More strength for these results would be required to provide an exclusive diagnosis, however.

MicroRNAs, T-regs and pDCs

Turning to MicroRNAs, Staines explained that they are made in the nucleus, exported to the cytoplasm, and work from then on as 'messenger RNAs'. There are about 2000 of them in humans, of which only 200 are known, and still less is understood about them. They have found quite a number of MicroRNAs with significant differences in ME/CFS patients, but they will need to perform studies with other conditions before they can say whether these differences are unique to ME/CFS, or shared with other conditions.

In the adaptive immune system, as they reported at Invest in ME 2012, they have found subsets of T-regulatory cells which are up-regulated, in particular, FOXP3, which is seen as a 'master regulator' in the development of T-regulatory cells. The up-regulation of these cells is probably in order to suppress some inflammatory mechanism and they are "highly confident" of this up-regulation.

They've looked at gamma and delta T-cells, which straddle the adaptive and innate immune systems, but although they observed something there, it wasn't statistically significant. Looking at subtypes of B cells, they found deficits in immature cells, and an increase in memory and plasma cells (but the latter finding has also not yet been found at statistically significant levels). They have also found high levels of plasmocytoid dendritic cells (pDCs).

Summary

Summing up, Staines went through the immune defence process: a pathogen enters the body, recognition starts, and innate and adaptive immune responses then begin. In ME/CFS patients, they find that the innate immune response shows changes in neutrophils, NK cells, gdT, pDC, and nitric oxide. In the adaptive response, they find disorder in B cells, T cells (including T-reg cells), CD4, granzymes, micro RNAs, CD8 and more. They conclude, then, that in ME/CFS, dysregulation is initiated and maintained throughout NK and CD8 cells, B and T cells, T-regulatory cells, and Th1 and Th2 response.
These findings, says Staines, suggest the potential hallmarks of autoimmunity, and "anyone who suggests that this might be fixed by exercise therapy should probably be de-registered I think".

Questions

Challenged that these findings wouldn't differentiate between the "biologic" and "psychiatric", Staines accepted that his phrasing was a "shorthand paradigm" – the key thing, though, was that there was "clear derangement in the immune system, in so many compartments – it's irrefutable".

A researcher from Spain (IrsiCaixa?) said his research group had tried to correlate their similar findings with severity, but have not yet found any clear association. Did they find any association with severity?

An excellent question, said Staines: they did look at this. The severely affected group are very abandoned. In any other illness, the more severely patients are affected, the more care they receive; with ME, the opposite seems to be the case. So they went into their homes, they took blood samples, and carried out a number of other tests as well, especially with flu vaccines. They found differences both in the response to flu and in the response to flu vaccines. His recommendation based on their findings would be that this makes it especially important for severely ME patients to get the vaccine. But anyway, no they didn't really find differences in the

markers between the moderate and severe patients. But maybe we shouldn't expect there to be, he mused – there are many other systems of the body affected as well in ME/CFS (suggesting that the severity of disease provoked by the immune disorder may be determined by other factors). The short answer, Staines concluded, was that they can't yet explain this, but will be interested to research it further.

Dr Amolak Bansal: "Clinical Immunology and Research on B-cell abnormalities in ME Patients"

Dr Bansal began by joking that he was glad he hadn't begun his presentation with a photo of St Helier Hospital (in the London borough of Sutton); it wouldn't compare well with Griffith University!

Dr Amolak Bansal

But he thinks "we have a hypothesis here", and a "paradigm shift" towards autoimmunity in ME…he would begin by taking a step back and trying to "bring everything together", starting with a look at the evidence for immune dysfunction.

Predisposing Factors

It's well known, said Bansal, that certain predisposing factors are associated with CFS, and people with these kinds of immune and autoimmune conditions (such as EDS) have a very high incidence of CFS, and even if they don't have CFS, they too have chronic fatigue. We know that CFS affects women more than men – just like most other autoimmune conditions. There's a slight tendency for it to run in families, though that could be due to environmental factors. It has been associated with certain personality traits, and black Americans, American Indians, and other groups, are at higher risk. It has also been associated with higher than average IQ, lower social class, and lower income.

We know too, he added, that any form of severe stress causes stress on the immune system – so maybe stress leaves you susceptible to CFS?

Infectious Triggers

Bansal looked quickly at a number of potential infectious triggers. Regarding infections, he noted that EBV, while it may not be 'the cause', has proteins that may encourage autoimmunity. Regarding spirochetes, he said they are not really a significant problem in this country. He didn't

seem to think that fungal triggers are particularly important either, but on vaccinations, he seemed more open, as that does seem feasible. He listed other triggers, including stress, organophosphates, sleep and mood disorders, over- or under-activity, multiple infections, illness beliefs, etc etc…and in the end, he thinks it all comes back to stress.

He finds the known delayed reaction to **mental** over-exertion, in particular, very hard to explain. Speculating, he wondered whether leaking adenosine and ATP might be acting on prurinergic receptors.

Stress and Immune State

But persistent stress, Bansal re-iterated, does have an adverse effect on the immune system, and he thinks that's very important. So his suspicion is that persistent stress can provoke a shift to a type of immune state which promotes autoimmunity and also impairs immune function. And cognitive dysfunction and ANS dysfunction could perhaps be explained by the auto-antibodies binding to one or more CNS sites or neurotransmitters.

So Bansal produced a model: a cyclical graph in which stress causes fatigue and lowered Th1 immune response, leading to increased susceptibility to viral infections, causing worry and more stress, which further reduces Th1 response and impacts on T-regs, which induces more viral illnesses, which causes further stress, and so on back round the cycle. In this way, stress, he suggested, prevents the immune system from regulating itself.

Viral and Immune Observations

Considering the viral and immune observations in CFS patients, very few get rashes, pneumonia, or similar classic consequences of an impaired immune system, so it seems there is a very subtle immune dysregulation involved here. We need to look in much more detail in order to find that, and that's why we haven't found it before, he suggested.

Bansal turned next to cytokines: we've seen some are increased, and some are decreased, and a lot has been written about this. To work all that out, it all comes back to autoimmunity. But in CFS, we don't find anything on routine tests for autoimmunity – the standard tests have all showed up negative there: IgG, IgG subclasses, ANCA, C, C4, TPO abs…nothing. A few have increased levels of atypical lymphocytes. There are conflicting reports regarding levels of cytokines, he pointed out.

His research hasn't found reduced functioning or numbers of NK cells, whereas others have. Why? Well, he speculated that this may be due to different case definitions, different test protocols… they may be affected by something like taking samples at different times of day…in the early HIV work, he noted, results from blood taken early in the day looked different to blood taken in the evening.

But we have failed to ask, he said: What is the role of exaggerated receptor solubilisation and cytokine/cytokine receptor autoimmunity? Could it be that patients are making antibodies against cytokines, maybe?

Altered Functional B Cell Subsets

Bansal moved on to discussing his own recent study. Most of his patients were classed as moderate, two were severe. All fulfilled the CCC. All were negative for routine antibodies and none had gluten sensitivity. All were seen at the same time of day; all were assessed in serum for a wide range of exotic antibodies seen in neurological problems: all those tests were negative.

But when they studied B-cell gating, what they found was that levels of **transitional** B cells were increased in CFS. B cells are produced in the bone marrow, and migrate via secondary lymphoid tissues (such as the spleen and the lymph nodes) where they are called transitional B cells, some of which differentiate into mature B lymphocytes. Bansal thinks what may be happening is that some problem in the transition of these cells means that they haven't been through the same 'checkpoints' as normal B cells, meaning that the B cells in CFS patients are more likely to produce low avidity antibodies – antibodies which bind weakly with the antigens they are supposed to attack, perhaps because some of their antigen-binding sites are not functioning properly.

[Interestingly, this hypothesis may connect somehow with the recently-discovered mechanism of Rituximab reported in Cancer last month: Rituximab binds to one side of a diseased B-cell and dramatically increases the success rate of NK cells in destroying the diseased cell. Could Rituximab be assisting somehow with the faulty binding of these low avidity antibodies?]

Bansal also finds that naïve B cells are a higher percentage of all B cells in the CFS patients he studied – these are the cells that haven't undergone the 'checkpoints'. He noted that other results show lowered levels of IL 21,12, and 27 – all of which are involved in the correct maturation of B cells. So it would make sense to him that the B cells aren't undergoing the

correct checkpoint analysis. But then looking at T cells, a number of abnormalities have been reported. The end result: an abnormal interaction between T and B cells, and the B cells are not regulated properly. As the interaction proceeds, Bansal warned, these responses will mature, the avidity gets higher, and the process becomes harder to reverse, which would make early diagnosis particularly important.

Summarising his findings, Bansel re-iterated that he believes he is seeing impaired maturation of B cells, less anti-viral cytokines and especially less of those involved in B cell regulation, resulting in impaired T-Lymphocyte homing receptors.

Conclusions

Bansal therefore proposes that the initial problem in CFS may involve B cell dysregulation, perhaps after a series of viral infections, and especially if the patient is under stress as well at the time of infection. In some people, the B cells then start to make auto-antibodies against neural receptors in the CNS and the periphery. These auto-antibodies contribute to worsened arousal mechanisms, causing sleep dysregulation and autonomic dysfunction. Some may also target mitochondrial proteins and produce delayed PEM.

In perhaps one of the most important take-home messages of the day, Bansal suggested that while removing these auto-antibodies has been found to reduce symptoms, for a lasting response it may also be necessary to suppress the action of certain viruses which encourage the survival of auto-reactive B cells. So we may not only need to 'reboot' the B cells; we may also need to get rid of those viruses as well.

In summary: it's a very complex disease, he said, but he believes we are now entering a 'paradigm shift'. In Bansal's opinion, it is very likely there is a subtle autoimmune phenomenon here, with antibodies targeting CNS proteins.

Questions

I asked Dr Bansal whether this need to clear viruses as well as rebooting the B cells is the reason for the 'combination treatment' arm mentioned in Dr Peterson's proposed multi-site Rituximab + Valcyte study; he confirmed that's the rationale.

Somebody asked where the gut might fit in with all of this. If you have gut inflammation, he answered, that will disrupt digestion in the gut. The initial trauma maybe encourages a loss of tolerance, and thus you end up with increased auto-reactive B cells (this may occur due to food poisoning, salmonella, or with typhoid). Maybe the initial infection targeted T cells, causing a diminished ability to regulate B cells, and then the cycle is underway…

Refreshment Break Time Again!

If you've made it this far, then it looks like you've got your money's worth! Perhaps you'd consider supporting the people who make it all possible? Here are some ways you can help…

How to Help Invest in ME

Sponsor a Health Professional through IiME

Support Phoenix Rising

Volunteer for Phoenix Rising

Award Winners!

Ellen Piro, founder of the Norwegian ME Association (celebrating its 25th year) called forward Richard and Pia Simpson to receive a special award from the Norwegian MEA.

Invest in ME was officially founded in 2006, Ellen explained – and it was those two who were behind it. They created IiME because of their frustration at the lack of progress. They have worked tirelessly, always successful in their choices of topics and speakers, and IiME conferences have

always been exciting and surprising, always at the frontline of research, and an important source for updates and information.

Through this conference, said Ellen, an international network of professionals and communities has been established. Richard and Pia are down to earth, forthright and friendly. They have two children with ME, and they have poured their time and funds into this organization. Without IiME, there would be no ME conference in Europe, and Invest in ME has earned great respect worldwide; they have always been very appreciative of the Norwegian MEA. So on behalf of the Norwegian MEA, Ellen presented the ME Award to Richard and Pia Simpson.

All those present at the conference who were physically able to do so rose to their feet for a round of appreciative applause – and Richard was obliged to say a few words. "You're all doing great work by what you're doing," he said graciously, "here and elsewhere". He praised the "frontline research" in Norway, making "great inroads into a very difficult area," and added that everything that has been achieved is built on the backs of many campaigners and researchers. If researchers and people like Dr Peterson had given up, he asked, where would we be now? "This is the easy part," claimed Richard, "it should actually be us honoring you".

Ellen wasn't done yet though – time for Professor Malcolm Hooper to step forward, to more rapturous applause. Hooper needed no introduction: "A real warrior" in the frontline for years. "He has no personal involvement in this," Ellen pointed out, and yet he's fighting for us. Lecturing, writing, publishing, speaking out about opponents, an active part of Invest in ME and its professional supporter, the Norwegian MEA had often approached him for advice and benefited from his support. So Ellen presented Professor Hooper with the ME award for his "untiring and exceptional contribution to the ME cause".

"Thank you very much," said Hooper.

"The shortest speech I've ever heard him make," remarked Ian Gibson. "Thank you guys, I'll come and see the Northern Lights. Although, you can seem them better in Scotland actually…"

Professor Carmen Scheibenbogen: "Immunological Basis of ME"

Professor Scheibenbogen, from the Charite Institute for Medical Immunology in Berlin, has also noticed that there has been "much progress in recent years". In Germany, she said, they call it

"CFS"; her work is in immune deficiency and she shares many of the same theories as Bansal, Fluge and Mella. It has become obvious that we need to develop a diagnostic test, and this is what she is trying to do.

Professor Carmen Scheibenbogen

Scheibenbogen showed a simple venn diagram of symptoms, somewhat reminiscent of the findings presented by Rakib Rayhan earlier in the day, with Fatigue and Pain either side, and CNS symptoms overlapping with both in the middle. She then reviewed the evidence for ME as an immune-mediated condition.

Firstly, the clinical picture. ME often starts with an infection, and in some patients there is evidence of an ongoing infection; many report ongoing 'flu-like' symptoms. The immune function seems to have changed, with patients experiencing either more or less infections. Secondly, the immune dysfunction is confirmed by the laboratory findings; immune phenotype studies are controversial, but there are clearly elevated T-regs and reduced NK cell cytotoxicity. And thirdly, immunological treatments are now working.

Charite's Immune Diagnosis Study

At Charite, their immune diagnosis study has been looking at T-cell activation, T-cell phenotype, T-cell cytokines, and immunoglobulin elevation.

They found elevated T cell function in about half their patients, divided into three types. They used flow cytometry to analyse the surface of cells and they found some patients with Th1 dominance, more with Th2 dominance, and others with low cytokines, so this again looks like 3 different subtypes to them.

They found polyclonal immunoglobulin elevation is a quarter of the patients (n=286), and think that's a response to ongoing immune activation. Another quarter have immunoglobulin deficiency, and again they think that's a consequence and not a cause.

They also found complete deficiency in MBL (mannan-binding lectin) in 15% of their patients and 7% of healthy controls, which is associated with increased risk of infections and that seems to be confirmed from what the patients say, but that's just one piece of the story...

Herpesviruses

They have been looking really closely at herpesviruses and hope to have solid data in about 6 months time, but Scheibenbogen presented some preliminary results. In the subset of patients with EBV infection, who tend to suffer from recurring herpes lesions, they find they generally improve with valacyclovir, and typically recommend trying that for 8 weeks. HHV1-3, she said, is easy to diagnose from symptoms, whereas EBV is much harder: patients typically get it later in life, EBV copies stay in their blood, and after about a year they are diagnosed with CFS. They don't know yet whether it is the EBV infection that is ongoing or the immune response; nobody can answer this yet.

The data on EBV infection is controversial, with both enhanced and diminished EBV antibodies reported. They are finding some elevated antibody response, but suspect this is just the 'tip of an iceberg'. They have been trying to make a more sensitive assay for antibodies against EBV, evaluating against more than 2000 overlapping peptide libraries; they have support from local government to develop a test based on that. They think they have found some EBV structures that people do or don't respond against. They're now running a study with a multiple sclerosis control group, and hope for clear data on all this in about 6 months time.

Summary

Scheibenbogen summarized their findings so far: they find evidence for immune activation, T cell activation, enhanced antibody production, immune dysfunction and dysregulation, a T cell type 2 shift, antibody and complement deficiency, and altered EBV specific response. Overall, they see chronic immune activation, and think that the infection is not always active but the T cells remain active, perhaps triggered by B cells.

Finally, she presented a diagram summarizing the picture they are seeing: 3 distinct entities, which can be either infection-triggered or adjuvant-triggered:

- Immune activation CFS
- Immune deficiency CFS
- Non-immune CFS (triggered by other agents)

Professor Olav Mella: "B-cell Depletion Therapy Using Rituximab in ME/CFS – Part I"

Dr Oystein Fluge: "B-cell Depletion Therapy Using Rituximab in ME/CFS – Part II"

Saving the best for last (and ensuring that an exhausted audience remained glued to their seats), the last act of the day was the Fluge and Mella show. Unfortunately for you, dear reader, the material presented in this section of the conference has not yet been published, and we are asked not to disclose it in order not to jeopardize the publication process. I most certainly do not want to be the one to do that!

Professor Olav Mella (left) and Dr Oystein Fluge

Norwegian journalist Jorgen Jelstad, however, has a good handle on what to say and what not to say, so I'll refer you to his tweets from the conference, and you'll just have to wait for the follow up to Fluge and Mella's 2011 Plos One Rituximab study. I will say, though, that the picture is encouraging, and the new hypothesis that Fluge presented is indeed fascinating, just as Jorgen says.

As the first study showed, and as some members of the Phoenix Rising forums have found, not everybody is responding to Rituximab, but the progress on exploring the reasons for that – and possible solutions – is encouraging. In particular, see Dr Bansal's comments above regarding the necessity of identifying and clearing any underlying viral infection as well as 'rebooting' the B cells. That's the basis for the proposal for a trial with Valcyte alongside Rituximab, so that theory has clearly been seriously considered for a while, and it makes a lot of sense to me.

On the downside, Bansal also noted that the longer a patient has been ill, the harder it will be to reverse the kind of immune dysregulation he's theorizing, but that's not a reason to give up hope in my opinion. It is still very early days for B cell depletion therapy, and the work on developing therapeutic strategies using Rituximab – and other similar treatments – has only just begun. Assuming it all pans out, the effectiveness of the treatment will surely improve as more studies are done.

Speaking of which, one part of Mella's presentation is no secret: they are pushing hard now to fund a bigger study nationally, and they need to raise enough money for a 140-patient multi-site study. If you're impatient for treatments and possible cures – and who isn't? – then the best thing

for you to do, in my opinion, would be to join the small but dedicated army of volunteers who are raising funds for this and other vital research. Starting with the appropriately-named MEandYou...

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