One Event Can Change Everything

The

# JOURNAL of IiME

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## IiME Conference DVDs

The Invest in ME conference DVDs are professionally filmed and authored DVD sets consisting of four discs in Dolby stereo and in PAL (European) or NTSC (USA/Canada) format.
They contain all of the presentations from Invest in ME International ME/CFS Conferences (2006 – 2014). Also included in the DVD sets are interviews with ME presenters, news stories and round-table discussions.
The Invest in ME conference DVDs have been sold in over 20 countries and are available as an educational tool – useful for healthcare staff, researchers, scientists, educational specialists, media, ME support groups and people with ME and their carers/parents.
Full details can be found at -
http://www.investinme.org/DVD.html
or via emailing Invest in ME at
mailto:info@investinme.org

## Inside This Issue




**Invest in ME**
**PO BOX 561**
**Eastleigh SO50 0GQ**
**Hampshire, UK**
**E-mail: info@investinme.org**
**www.investinme.org**


**Member of European ME Alliance**




## Welcome to the 9th Invest in ME International ME Conference 2014 in London – IIMEC9

Invest in ME was established in 2005 by Kathleen McCall and became a UK charity in 2006. The charity trustees are composed of ME patients and parents of children with myalgic encephalomyelitis - ME.
The aim of the charity is to raise the profile of ME by improving the education of healthcare professionals about the disease, by raising awareness of the disease amongst the public and media and by facilitating and enabling an international strategy of biomedical research into the disease.

Everyone working for and with the charity is a volunteer and nobody is paid a salary.

At our last conference the theme was Mainstreaming ME Research –reflecting our view that after eight years of constant effort we could begin to see the change in emphasis about ME. Now even moribund establishment organisations are being forced to take ME more seriously.
The IiME conferences have formed a crucial part of this education.
Since our 2013 conference we have seen dramatic progress with our objectives.

Our foundation project has begun at University of East Anglia and the Institute of Food Research. This three year studentship will analyse gut microbiota in ME patients.

At the 2012 conference we stated that we were working on an attempt to set up a rituximab clinical trial. Following our Biomedical Research into ME Colloquium in London last year we have made rapid progress by partnering UCL in setting up the planned UK rituximab clinical trial.

*(continued..)*

### *Disclaimer*

The views expressed in this Journal by contributors and others do not necessarily represent those of Invest in ME. No medical recommendations are given or implied. Patients with any illness are recommended to consult their personal physician at all times.

Thanks to the great proactivity of Professor Jonathan Edwards and Dr Jo Cambridge we have been able to develop the means to initiate the clinical trial and the initial B-cell preliminary study has now passed internal UCL checks and has gained ethical approval. IiME have now signed the contract with UCL.

In addition we have been discussing with Dr Amolak Bansal a new study surrounding the hypothalamus. The charity is also planning on funding medical students to participate in research.

In our ninth year as a charity we can say each year has been a stepping stone in breaking the mould and bringing ME into mainstream in research and media.
Funding is scarce and the efforts of our supporters to make up what has been lacking from government agencies and research funding organisations have been awe-inspiring.
Patients have worked tirelessly and imaginatively to raise funds for the research proposed by IiME and this has created a force for change.
Currently Invest in ME and our supporters are actually initiating, organising and funding possibly the two most important ME research studies currently in the UK - the gut microbiome project at UEA and the IiME/UCL rituximab clinical trial.

With the power of social media the charity and our supporters have been able to crowd source funding for these projects.

Translational biomedical research - an iterative feedback of information between the basic and clinical research domains in order to accelerate knowledge translation from the lab to the bedside and back to the lab again - needs to be implemented to translate the findings of basic research more quickly and efficiently into medical practice. This will produce more meaningful health outcomes and facilitate the sharing of repositories and research-based facilities and laboratories. This is the model IiME are attempting to promote in the proposal for an examination and research facility.

The change in the dynamics of research – certainly in the UK – has been affected by patients, those who have viewed with dismay the continued apathy to proper research which has been shown by establishment organisations. The success of the IiME/Let's Do It For ME crowd sourcing campaigns has meant that patients can effectively enable the research that is required to be considered rather than research that unrepresentative establishment organisations decide they want.

It is this that has forced progress.
Progress is a fine word but change is its motivator – and people with ME and this charity have made that happen.

Supporters have set up many Just Giving pages listing many imaginative ways of raising funds ranging from walking, running, cycling, swimming etc to dog sitting, crocheting, and cutting of hair


A supporter's song was put on iTunes.
YouTube has been used for awareness videos.
The Big Sleep has had an amazing range of ideas and events based around one theme.
The ZZZ Factor Comedy Club used to humour to raise awareness.
The 92 for ME football club tour was especially effective in getting publicity and reaching an entirely new audience and an article from the team's leader, Mike Harley, appears in this Journal.
There are close to 100 Just Giving pages set up to support Invest in ME in contrast just to a handful when we signed up to it with the help of a supporter paying the first year's fee.
The charity took part in Direct Debit competition again this year and won the first £2000 price – all of which has gone to funding biomedical research.

All of these ideas and events belie the crass misinformation about the disease which has been allowed to be propagated. IiME events all show patients and their families in a positive light – people who just wish to get better.
The success in fundraising lies in active support from passionate volunteer fundraisers with the visionary Let's Do it for ME team spearheading this change and leading the field.
Yet even with all of the magnificent efforts of patients, carers, families and friends it is still a huge task to compete with the reserves of organisations such as the MRC – which ought to be accountable to patients but which has failed to develop any sensible or scientific approach to research into ME, until forced to do so.
So just one slice of luck, a fortuitous coincidence or a benevolent act may be the difference between slow and rapid progress.
As our poster states, One Event Can Change Everything.
One such event has seen the charity receiving a £25,000 matched donation and later a further pledge of £200 000 in memory of the late Roger Heindry who sadly passed away in March 2013. This has enabled the charity to make a huge commitment to fund the rituximab clinical trial.

***So just one slice of luck, a fortuitous coincidence or a benevolent act may be the difference between slow and rapid progress.***

Social media has opened up new avenues of participation and publicity. It helps improve education – and also awareness.
It also allows us to become aware of those who are no longer with us due to this awful disease.
The loss of Robert Doyle 30, in July 2013 was a sad moment for many internet users as Rob was a well known and active member of the ME forum community. There are too many cases like this. The abuse of ME patients, based on ignorance and vested interests, extends beyond the UK – such has been the ability of some to fabricate and spin misinformation about ME.
We continue to try to help where possible .
Invest in ME have invited those in Denmark responsible for the treatment of Karina Hansen to the conference events and have written to the Danish health minister. We are also supporting other cases, in UK and Germany.
In order to emphasise these situations and continue our commitment to help severely affected people with ME, we have invited Dr Nigel Speight to present our pre-conference dinner speech. Dr Speight is a paediatrician who has been involved in helping many severely ill young people in the UK and abroad.
Millions of patients are suffering around the world and the ratio of money being spent on this disease to the economic and societal losses it causes is at odds with any scientific, economic or moral viewpoint.
It is organisations such as the MRC and the NIH in the USA that need to take most of the blame for this. It is the attitudes of people in these organisations that have been the problem.
We actually agree with the remarks attributed to Professor Stephen Holgate of the MRC last year when he stated that we are bathing in a sea of ignorance regarding ME. It is rather disingenuous, though, of those who have been involved in controlling funding for ME research and have been aware of the lack of results from the psychosocial approach to ME to talk of ignorance. Organisations such as the MRC and the NIH have been filling the bath of research for ME patients for all these years and patients have been drowning in the effects of ignorance rather than bathing.
How else can one explain the lack of funding for biomedical research especially into causes of ME? Experienced researchers such as Professors Ron Davis and Ian Lipkin are willing to study the disease but cannot get NIH funding. Surely the often-used excuse of lack of good quality research applications does not apply here.
It is obvious that there has been, and still is something profoundly wrong with the peer reviewing system within these organisations regarding research applications from those who focus on biomedical into ME - something IiME has mentioned frequently over the years. It is vital that

***"We have all been frustrated over the years by the attitude of the MRC to CFS/ME."***

these organisations address this as a matter of urgency. Perhaps it requires governmental select committee scrutiny to change things.
The policies of these organisations seem to affect other countries also - and so we have situations like that of Karina Hansen, where blind ignorance of the effects of ME and a lack of proper research may endanger patients' lives.
Professor Holgate himself has been head of the CFS/ME Programme at the MRC for many years and was also a member of recently demised CFS Research Foundation's research committee. In a newsletter produced many years ago by the CFS

Research Foundation the lack of action by the Medical Research Council was highlighted –

> "We have all been frustrated over the years by the attitude of the MRC to CFS/ME. They have assured us that they felt this was an important area of research, but grant applications were turned down. Dr (Jonathan) Kerr and the Foundation submitted three applications all of which went to the Neuroscience and Mental Health Board. These applications were dealing with neither neuroscience nor mental health. In spite of protests from the Foundation the MRC refused to remove our grant applications to a more appropriate board."

Indeed, the same newsletter spoke of Professor Holgate being chair of a forthcoming MRC panel for ME. That was 2008!
In fact the newsletter went on to state –

> '..it is anticipated by the end of 2008 that the MRC will have an agenda …'

In fact the response by the MRC lasted another five years and many years on from that article the sea of ignorance had been allowed to build into a tsunami. Now, belatedly and due to the example and the efforts and results of IiME supporters who are finding/funding a proper base of research, the MRC has actually been forced into at least appearing to act. Yet even their latest initiative, which proposes to join all researchers and organisations, no matter what their beliefs about ME or their interests, cannot agree on the basics – with no view or agreement on the correct way to diagnose ME nor even on the prevalence figure - with more than one MRC representative stating in the past year that the number of people suffering from ME was over 600,000, a magical and dramatic increase of 300% over previously assumed figures). If this really were the case then there certainly is an epidemic of ME which would warrant government intervention immediately. But this indicates the futility underlying this manoeuvring. And so the farcical continues.
It is a strange policy to manipulate statistics in this way at a time when social media is liberating patients by allowing easier communication, more information, better education and the means to challenge the establishment PR organisations such as the Science Media Centre with robust and correct critiques of flawed science.
Funding of research into ME is the key issue and it is a wonder to patients how key funding agencies can get it so wrong.

In reality it seems that there is no shortage of funds available for studies which fit government policy. And this shames those who issue statements talking of funding being available for high-quality studies or of ignorance about ME.
It would indeed be a sad indictment of the society that we ourselves are paying for if what matters is who one knows rather than what one does when it comes to research funding granted for ME.

So what of the real research required - the right stuff?
As mentioned in our article which was published at the beginning of April research into ME needs a strategic approach - but it may be destined to fail completely by attempting to establish the way forward on foundations which include so much of what has been wrong in the past.

***..a strange policy to manipulate statistics in this way at a time when social media is liberating patients by allowing easier communication, more information, better education and the means to challenge the establishment PR organisations such as the Science Media Centre with robust and correct critiques of flawed science.***

We have written in the past that we feel it is impossible to marry the views of those who believe in the deconditioning or behavioural/wrong illness belief model of ME with those from the biomedical side.
The failed and flawed PACE Trial, for all the spin and waste of scarce funding, did prove one point emphatically - that the behavioural view of ME cannot deliver and should not continue to command more funding.

There is another, better way forward for ME research - a clear case to be made for segregating the biomedical from the psychosocial. This could then force a separation of fatigue research from ME research.
A strategy of biomedical research into ME with a research group being formed consisting of biomedical researchers, using resources and facilities across continents - hooked up to share research and data and crowd fund new research.
Future research into ME must be based on collaboration - but not collaboration at any cost. It would seem quite meaningless to base the strategy on those failed policies and directions of the past -

which have served patients so poorly and caused such suffering.

***This full day closed researcher meeting was designed to encourage collaboration and sharing of experience and to bring in new ideas and knowledge from outside the field of ME.***
***A small charity with a BIG cause can achieve this.***

**Colloquium**
Such is the meaning behind our Invest in ME Biomedical Research into ME Collaborative meetings which have been organised by Invest in ME and which precede our annual research conference.

These aim to interest other researchers to the field of biomedical research into ME, assist those who are undertaking research or planning research into ME, and look for future collaborative projects and funding which could be generated by new ideas.
This Colloquium, now in its fourth year and which has now attracted almost fifty delegates from ten countries, is a full day closed researcher meeting designed to encourage collaboration and sharing of experience and to bring in new ideas and knowledge from outside the field of ME.

A small charity with a BIG cause can achieve this.
The government, their organisations and the media have a lot of catching up to do.
Listen to the patients is still a maxim to which politicians and the media should pay heed.

**Invest in ME Research**
Soon the charity will convert to CIO charity structure – something that has taken a lot of administrative effort over the past year. The name will become Invest in ME Research. But essentially everything continues. Our web address will remain, albeit with a new web design coming soon.
Invest in ME Research will continue to lobby, raise awareness, facilitate, initiate and fund biomedical research into ME, and campaign to help patients and families to receive proper diagnosis, treatment and respect. Our commitment is to biomedical research into ME – something we will not compromise by merging all research into one big pot – a convenient but ill-fated philosophy. There is the wrong way and the right way to progress research into ME.

**The Journal**
The Journal of IiME and forms part of each delegate's conference pack at the 9th Invest in ME International ME/CFS Conference 2014.
The Journal of IiME was created as a means of providing a broad spectrum of information on ME/CFS, combining biomedical research, information, news, views, stories and other articles relating to myalgic encephalomyelitis (ME/CFS).
Our aim has been to distribute this for free four times a year. However, due to the resource and financial limitations of IiME we can only provide a snapshot of the wealth of experience which already exists and continues to increase and currently we are only able to publish a maximum of two copies a year.

Biomedical Research into ME
Colloquium 4

We hope to change that in the future.
For this version of the Journal we have included some interesting articles on other research areas as a way to help research into ME. So articles by Dr Jo Cambridge and Professor Steven Tracy will not specifically deal with ME but we hope, nonetheless, will be useful.
From the USA columnist and producer Llewellyn King has contributed our letter from America article. Llewellyn's comments the lack of action by governments and establishment organisations chime with ours.

**The Conference**
And so to the conference.

Our programme has always been planned so as to move the field forward and not just provide one presentation after another without thinking how they might join together or lead the field forward.

This year we are very pleased to announce the presence a number of new presenters such as Professors Angela Vincent, Jonathan Edwards, Maureen Hanson, Jonas Blomberg and Drs Saul Berkowitz and Julian Blanco.
We welcome again Professors Simon Carding, Mady Hornig, Sonya Marshall-Gradisnik, James Baraniuk, Julia Newton and Drs Amolak Bansal and Andy Kogelnik.
It is a positive thing that we are able to interest researchers from outside the field of ME.

The conference agenda is at the back of the Journal. We feel this is perhaps the best conference yet – reflecting a maturity which is beginning to develop in the field of ME research.
We have at last managed to mainstream ME research – thus attracting new researchers, new funding and forcing established organisations into action in order not to appear outdated and redundant.

Much of this change has been caused by patients – and although that should have been unnecessary it is, on all accounts, a salutary achievement showing courage, resilience and determination.

Dr Ian Gibson, former cancer researcher and Dean of Biological Sciences at UEA and MP, will be chairing this year's conference.
Dr Gibson has been instrumental in helping Invest in ME initiate negotiations to set up an examinations and research facility in Norwich using the excellent resources the Norwich Research Park has on offer.

The conference is focal point for research and networking but there is a great deal of work behind the scenes.
At the Invest in ME conferences there always seems to be a happy mixture of wanting, needing to learn, optimism and hope that things will improve.
At the conference there will be researchers, clinicians, nurses, patient groups and patients, advocates and, we always hope, a sprinkling of politicians, journalists and others whom Invest in ME self-fund.

The people working for and with Invest in ME are advocates of better education regarding ME.
The IiME conference is not only a platform for proper, high-quality science – it is also a platform for the hopes of millions of people around the world.

Let the Science Do The Talking.

Enjoy the Journal. Enjoy the conference.

# Our Sponsors for IIMEC9

Invest in ME wish to thank the following organisations for helping by sponsoring the 9th Invest in ME International ME Conference 2014. Both organisations are fellow members of the European ME Alliance.

### The Irish ME Trust

The Irish ME Trust has sponsored a speaker at all of our conferences and we would like to thank them for their continued support.

### Norges ME Forening


Norway's ME Association (Norges ME Forening) is sponsoring the IIMEC9 conference.
Norges ME Forening has been a long standing supporter of IiME we are very grateful for this kind donation.

# *Extemporaneous Notes from IIMEC8*
# *Severe ME*

The situation of severely ill bedbound ME patients was discussed by some of the presenters at the 2013 Invest in ME International ME conference – IIMEC8.
Dr Peterson said that the healthcare system is not geared for these types of patients. In the past these patients would have been cared for in hospitals with alimentary treatments but now the cost is prohibitive.
Dr Staines said the situation is bizarre as normally the most severe patients in any illness get most attention and are hospitalized but in ME the situation seems to be reverse.
The Australian Marshall-Gradisnik research group has included severe ME patients in their studies but have not found any differences in the immune system parameters in groups rated according to severity.
Dr Staines pointed out that ME is, however, a multisystem illness and the immune system is only one part of it.
The Griffiths University, where the Marshall-Gradisnik group is located, also has beds for patients so that they can include severely ill patients in their studies as well as monitor patients for 24 hours or more.
This is something that should be possible elsewhere too.

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

After the conference Dr Bansal added the following especially for Invest in ME for a forthcoming news article (which subsequently was not used), explaining severe ME in the following way -

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

How this occurs is unknown but there are counterparts in certain newly described autoimmune conditions and viral infections of the nervous system.
In addition to a direct stimulation of neurones in different parts of the brain and spinal cord there is also an impaired filtering function of the brain stem and a reduced threshold for neurones to fire off.
This allows external stimuli such as movement, light, sounds, touch and sometimes even worrying thoughts to produce widespread neuronal activation with ultimate excitotoxic damage to these cells.

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

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

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

**ME STORY**

***Rob had "asked that he didn't die in vain".***

***His sister Rachael created a JustGivingfundraising page and Facebook group and Rob's wonderful family, including sister Jo Ann, niece Lucy, and their friends set about a number of ways to raise funds for Invest in ME.***
***This included selling the Christmas cards and calendars produced by our campaign in support of Invest in ME, wristbands, running raffles and collections at family events and, "anything else I can think of to make money for such a deserving cause, we just want to do something for others who suffer just like Rob"***

***- Diane***

# Invest in ME Research Grants Policy

Invest in ME supports high quality, biomedical research into myalgic encephalomyelitis (ME).

The following paragraphs detail our policy and procedures for applying for funding for such research.

The charity welcomes applications for grants for projects of 6 months - 3 years duration.

Anyone wishing to apply for a grant from the charity should use the form on the web site to apply (links are below), having first appraised oneself of the conditions for grant applications.

It is emphasised that Invest in ME's ethos is to initiate high-quality biomedical research into ME as an urgent requirement.

Priority will be given to research which maximises the potential to find causality for ME and/or which promises to provide the greatest improvement for people with ME.
Our priorities are steered by the unequivocal belief that ME is of organic origin and requiring a strategy of biomedical research with international collaboration.

## Our Research Priorities

1. Medical research into:

- Research associated with Causality
- Translational biomedical research to provide effective treatments for ME
- Accurate and comprehensive diagnosis
- Improved education of healthcare professionals about the disease
- Telemedicine for use with and by ME patients and their physicians
- Raising awareness amongst the public, the media and academia

## Collaboration

Collaboration has been one of the central tenets of Invest in ME's policy since our 2007 international ME conference in London. As a founding member of the
European ME Alliance we work with international colleagues (advocates, researchers, research organisations and physicians) to make rapid progress in finding the cause of ME and providing treatments for all.
Funding applications will be considered from outside of the UK though we do prefer to use collaborations with UK and European organisations and researchers.

## Our Research Funding Opportunities

Invest in ME Research is committed to funding high-quality biomedical research into myalgic encephalomyelitis (ME).
This is a fundamental part of our strategy for ME which includes creating a UK/European Centre of Excellence for ME (CoE) [1].
The CoE influences our choice of looking for translational biomedical research which can discover causality and provide treatments – in a direct and expeditious way. This therefore means that we are looking for biomedical research applications – covering virology, immunology, and endocrinology with particular emphasis on autoimmunity.

Invest in ME Research does not hold large unallocated amounts in a bank for research.
We are not a membership charity as we believe ME patients should have access to free information and we try always to offer our products or services for free or at cost price.
We campaign for the interests of patients and carers to try to ensure that those most vulnerable are not taken advantage of.
We believe it is inappropriate and wasteful to store large amounts of funds which are unused and which just wait for applications.
Instead we believe in identifying valid research which fulfils our strategic aims and then in initiating a funding campaign to attain the required funds.
A list of current opportunities can be seen at this link.

## How Funding is Awarded

Due to the way in which Invest in ME promotes research and seeks a strategic approach to research we prefer to request ideas for research projects or to identify them ourselves and then perform fund-raising campaigns to raise the necessary funds.
The way we promote the search for ideas is via our conferences, our researcher colloquiums and meetings and our newsletters.
Academic institutions most likely to perform the sort of translational biomedical research into ME

# Invest in ME Research Grants Policy

that we require are invited to our research meetings and to our conferences.
We also circulate our newsletter to many different academic institutions.
In this way we believe we build awareness of our requirements and opportunities.
With the gut microbiome research, which is our foundation project for a centre of excellence for ME, we directly sought support and assistance from University of East Anglia as that university plays an important role in the Norwich Research Park, which is the location for our proposed centre.

### Peer Reviewing

The charity has a list of external reviewers whom we will ask to peer review any applications for funding and projects. We will assess all applications based on the relevance and usefulness of the research and in accordance with our research priorities, scientific merit, timescale and cost.

### How to Apply

If potential researchers wish to first enquire informally about a project and grant request then please contact us using the contact details at the end of this article.

Application Forms are available here –
Word http://www.investinme.org/Documents/IIME%20Grant%20Application%20Forms/IIME%20Research%20Grant%20Application%20Form.docx

PDF-
http://www.investinme.org/Documents/IIME%20Grant%20Application%20Forms/IIME%20Research%20Grant%20Application%20Form.pdf

The award of any research grants will be according to Invest in ME's terms and conditions and all decisions regarding acceptance or non-acceptance of research applications are the charity's and will be final.

### Medical Ethics

Projects funded by Invest in ME are to be conducted in accordance with the guidelines and principles described by the Declaration of Helsinki.

It is expected that the research will be verified and approved by the appropriate research & development and ethics committees related to the research team.

### Dedicated Funds

Invest in ME will maintain ring-fenced funds for those projects which require dedicated campaigns to support the fund-raising activities.
Invest in ME also maintains a general Biomedical Research Fund which is used for many activities associated with biomedical research.

### Use of Animals in Medical Research

The projects currently envisaged or being funded by Invest in ME are not, as far as we are aware, involving animals, and the charity currently has no plans to do so.

### Dissemination of results

Results from Invest in ME-funded projects would be expected to be published in professional scientific journals. Invest in ME will expect frequent reports on progress of the research which would be disseminated though our web site, newsletter and Journal.

***ME FACTS***

***"The hypothesis of the present study is that the appearance of cell-specific autoimmune antibodies may define subsets of (ME)CFS. (ME)CFS is clinically similar to several autoimmune disorders that can be diagnosed and characterised by autoantibody profiles. For this reason, we conducted an exhaustive evaluation of 11 ubiquitous nuclear and cellular autoantigens in addition to two neuronal specific antigens.***

***Very few studies have evaluated the presence of autoantibodies in people with (ME)CFS. The findings of this study hint that evaluation of certain autoantibodies may give clues to on-going pathology in subsets of (ME)CFS subjects. Among (ME)CFS subjects, those who had been sick longer had higher rates of autoantibodies"***

***(S Vernon et al. Journal of Autoimmune Diseases May 25th, 2005:2:5).***

## What is Let's Do It for ME?

Let's do it for ME is a campaign to help raise awareness of the work of independent UK charity Invest in ME (Research) and funds for the biomedical research into myalgic encephalomyelitis that the charity is organising and/or funding.
Let's Do It for ME has its own website, Facebook page and blog and is playing a major part in raising funds for Invest in ME's biomedical research projects.
During the ME Awareness month of May 2014 various events organised by Let's Do It For ME and Invest in ME supporters created numerous ways of raising awareness with something to suit all ages, tastes and abilities. These included –

International Event Page

May 1st - 1 Day - £1 - 1st of the month to donate £1 to 1st class IiME research!


LIGHT UP THE NIGHT FOR ME on May 12th – helping IiME have any public buildings lit up blue for ME Awareness on May 12th.

Turn your body blue for M.E - anyone can take part - posting a photo of oneself or a body part in blue and donate to Julieann's JustGiving page.

Selfie Facebook Fundraiser May 12th - based on the idea for cancer awareness - post pictures of yourself on your social networking sites and donate to Clare's JustGiving page.

Sewber Moments Online Fundraising Raffle

Sarah Mozer's Online Charity Fundraising Raffle

The Big Sleep for ME – hugely successful – and fun - and now in its 3rd year and going global! Including -

- Where's Bear competition
- Poetry Competition
- T-shirt design competition - deadline for entries May 31st
- The Princesses and M.E - their first year and what a team! Fancy being a princess for a day?

The Zzz...Factor for IiME Comedy Club - great entertainment in the comfort of your own home.

Walk for ME in its second year with the first walk for IiME already completed.

Walk for ME Isle of Man - wonderful team new on board for 2014 walking this coming weekend.

Mass Observation Diary on May 12th - for the general public in UK but an ideal opportunity to raise ME Awareness given the date.

#May12BlogBomb – for bloggers to write a guest blog for May 12th.

Light a Candle to Remember M.E. A poignant event created on behalf our lovely Rosa Amor.

A Vigil for International Awareness Day on May 12th in aid of Invest in ME Research

Seren's 12hr Crochet Marathon for Invest in M.E. Seren is hoping to reach her £1000 target for IiME

To get in gear for ME Awareness - visit our Shop for Biomedical ME Research

Mama Chill's dizzyjam ME Awareness ranges with all proceeds to Invest in ME

Click here for a variety of other ME Awareness materials.
These events that anyone could take part in – emphasising the spirit of Let's Do It For ME.

Use this link to learn more -
LDIFME websitehttp://ldifme.org

# A Biomarker in Predicting Clinical Response and Disease Activity in Patients with RA and SLE treated with Rituximab

Geraldine Cambridge, PhD,
Principal Investigator, University College London, UK

Maria Leandro, MD PhD,
Consultant Rheumatologist & Senior Lecturer, University College London, UK

Venkat Reddy, MD, Consultant Rheumatologist, University College London, UK

To investigate the potential of soluble CD23 as a biomarker in predicting clinical response and disease activity in patients with RA and SLE treated with Rituximab

**Aim:**

To determine whether a putative measure of B cell differentiation into memory cell phenotype can be used to inform on B cell kinetics and mechanisms of response and relapse during treatment with rituximab.

**Introduction:**

Removal of B cells with rituximab (RTX – a chimaeric monoclonal antibody recognising CD20 antigen)(1) induces clinical remission in a majority of seropositive patients with Rheumatoid arthritis (RA) (2). RTX is also used with reported success off-label in patients with SLE (3, 4). Although a randomised clinical trial in SLE did not provide clear evidence of clinical benefit, there are reasons to doubt the validity of these negative results (5). In both conditions, relapse can occur coincident with B cell return to the periphery, but in some patients may be delayed for many months (6, 7). *Therefore, although B cell return precedes clinical relapse the time interval between B cell repopulation and clinical relapse is variable between patients, thus limiting the utility of B cell repopulation to accurately predict the timing of relapse.*

The clinical use of the B-cell depleting agent RTX in patients with RA was initiated by Professor Jonathan Edwards at UCL in 1998, with results of the first small open study published in 2001 (8). In 2006, RTX was licenced for refractory RA. Patients may be positively selected based on their serostatus as 'good' clinical responses (ACR>50%) are more predictable in patients with seropositive disease (2). Such an approach may limit the use of rituximab for seronegative RA, which may be better treated with alternative biological agents. Adequate B cell depletion in the peripheral blood, arbitrarily defined as CD19+ cells<5/µl, in patients with RA, and also when RTX is used off-label in SLE, is necessary for clinical response (9, 10). On the other hand, removal of the majority of peripheral B cells does not necessarily guarantee attaining a significant clinical benefit. When high sensitivity flow cytometry analysis was used (ie counting >100,000 cells), it was found that the level of depletion required to be even lower in some patients in order to achieve a 'good' clinical response. (11) Mechanisms underlying poor responses, in the face of good peripheral depletion, remain largely unexplored. In conjunction with studies of adequacy of peripheral B cell depletion, analysis of B cell phenotype showed that a persistence of memory B cells (usually CD27+) in peripheral blood in the weeks after rituximab therapy (12) correlated with impaired response rates in patients with RA.

The analysis of B-cell phenotype has also been explored in order to suggest possible biomarkers to predict response. Several studies have now concluded that evolution of B cells towards an immunoglobulin-producing phenotype was related to whether the patient is going to respond well or not to rituximab and also whether periods of remission are going to be relatively short-lived (13-15). In addition, higher percentages of switched memory B-cells in the circulation after rituximab have been associated with earlier relapse (15-17). This was supported by studies of the genetic phenotype which were possibly predictive for the strength of clinical response. In the REFLEX trial of rituximab in inadequate responders to anti-TNFα therapies, a 25% subgroup of treated subjects with elevated baseline mRNA levels of IgJ (a marker for antibody-secreting plasmablasts), showed reduced clinical response rates. There were no significant efficacy differences in the placebo arm subjects stratified by this marker. Prospective testing of IgJ, and strong IFNα signature pre-treatment in the DANCER and SERENE rituximab clinical trial cohorts confirmed the ability of these genetic markers to

predict poor response to anti-CD20 therapy (18, 19). In patients with SLE, we have shown that high serum BAFF levels and possession of autoantibodies with ENA specificity indicated shorter clinical response(<6 months) to RTX (20). *Thus, current evidence suggests that tracking of memory B cell- and plasma cell activity are both important in predicting clinical relapse/response. Whereas serum immunoglobulin levels including autoantibody levels are used to identify plasma cell activity there are no biomarkers that may predict the formation of memory B cells.*

Our early studies of the kinetics of autoantibody levels following RTX showed a correlation with the 'delayed' onset of clinical response (often approximately 1-2 months after B cell depletion induced), characteristic of RTX treatment in patients with RA. Studies by Immunohistochemical studies of synovial biopsies after RTX by Thurlings and colleagues (21) showed that the reduction of plasma cells at 16 weeks post-RTX was the best predictor of clinical improvement at 24 week follow-up. Although B cell numbers in synovium were also reduced at 16 weeks, they were not correlated with response. The results from studies of biopsied joints following RTX therefore supported our hypothesis that the clinical response to RTX was due at least in part to an indirect effect on plasmablasts/plasma cells associated with autoantibody production (22). Rituximab was therefore possibly working by preventing recruitment of activated autoreactive B cells into secondary lymphoid tissue and to joints by removing circulating B cells.

Re-establishment of disease involves the re-engagement of pro-inflammatory pathways, which are absent or greatly diminished during the period of B-cell depletion. Relapse after RTX has been found to follow B cell return to the periphery in patients with RA, but this relationship is less clear in patients with SLE. B cell return after RTX mirrors ontogeny with transitional and naïve B cells, many expressing CD5, exiting the bone marrow and expanding in the periphery. Recovery of B cell numbers to within the normal range varies enormously between patients and can be very protracted. Maturation to memory phenotype, and restoration of the normal ratio between naïve and memory B cell compartments is not often achieved for many months or even years in either condition(23, 24). Differentiation towards memory phenotype after B cell return, most commonly associated (but not always) with gaining CD27+ status (25), may however herald relapse (14). Our observations also suggest that rises in IgM-RhF are closely associated with impending relapse (26).

Therefore, relatively long periods of B cell depletion in the peripheral blood (6-9 months in patients with RA) are associated with reduction in symptoms after RTX. The trigger for relapse can either coincide with, or follow by periods of some months, the exit of new B cells from the bone marrow. The time-course and B cell kinetics during the RTX treatment cycle therefore suggest that pathogenic plasmablasts/plasma cells are mostly short-lived and their removal is necessary for induction of remission. The strong association of rises in autoantibodies, rather that B cell numbers, with clinical relapse, suggests that naïve B cells or resistent memory B cell populations (perhaps expanded by by-stander help as a consequence of T cell dependent or independent pathways), are differentiating into Ig-producing cells.

**Studies leading to this project:**

Preliminary studies in our laboratory suggested that the measurement of a serum factor released from B cells as they undergo differentiation to memory phenotype (soluble CD23) , may be a useful surrogate of a) relative rate of differentiation of naïve B cells to a memory phenotype (CD27+) following RTX (Cambridge et al, submitted 2013) and b) a potential biomarker for depletion/response to RTX in RA and SLE patients (preliminary data, Figure 1 attached). Briefly, we found that in 23 RA patients treated with RTX, baseline levels of serum sCD23 were generally within normal limits, decreasing to below the normal range at depletion, demonstrating that most serum sCD23 was derived from B cells. It has previously been shown that sCD23 levels may correlate with disease activity in patients with SLE and SS (27, 28). CD23, the low affinity FcεR, is expressed on mature naïve B cells, lost from germinal centre cells and is expressed only on a low proportion of IgD+ memory B cells and possibly some transitional B cells (29). Expression of CD27 following antigen encounter induces cleavage of CD23 and the soluble receptor, sCD23 is released into the circulation. CD23 and CD27 expression appears to be virtually mutually exclusive; with both antigens possibly only transiently expressed on the same cell. sCD23 is released from the membrane expressed molecule by the action of endogenous αdisintegrin and metalloprotease10. Cleavage from the cell surface can be induced following stimulation *in vitro* with IL4 and CD40-L. Serum levels above normal limits (>2000ng/ml) in vivo are associated with allergy and atopy. It has recently

been shown that the soluble molecule can positively control IgE synthesis (30, 31). *Therefore, sCD23 levels would serve as a potential biomarker of memory cell formation, the detection of which in peripheral circulation is predictive of clinical relapse.*

## Experimental plan:

**RA:** As the relationship between B cell kinetics and relapse after RTX is highly variable between patients, we identified 4 key time points in each cycle for analysis: Baseline (pre-RTX in each cycle); when B-cell depleted (CD19+B-cells <5/□l); at B-cell return (CD19+B-cells ≥5/□l); clinical relapse (ΔDAS28>1.2).

**SLE:** The relationship between B cell return and disease flare is also highly variable in these patients and the kinetics of the clinical response differs from RA. We will therefore use length of time to flare after treatment either (<6 months) and between 6-12 months to determine efficacy of treatment, as we have previously described (32, 33). Therefore we will include samples collected at baseline (prior to RTX) and at 3, 6, 9 and 12 month intervals. Determination of disease activity and flare will be assessed by BILAG2004(34).

## Protocol

**Patients:** Stored serum samples are available from patients treated with RTX over the last 12 years (from our cohorts of >250 patients with RA; 100 patients with SLE). Clinical data will be collected retrospectively and samples from the same patients tested concurrently. Levels of soluble CD23 will be measured using ELISA (R and D systems). Isotypes of Rheumatoid factors (RhF) and anti-cyclic citrullinated peptides (CCP) will be measured using ELISA kits (from Axis Sheild, Dundee, UK). We aim to include samples from 30 patients with RA and 20 with SLE. Differences between time points will be assessed following log transformation and T-test with significance level set at 1%. Correlations between variables (sCD23, autoantibodies) will be by linear regression. Multivariate analysis will be used to determine relationships between serum sCD23 levels, levels of autoantibodies and duration of clinical response, assessed by EULAR response criteria for RA patients; flare< or ≥ 6 months; and SLE responder index for SLE.

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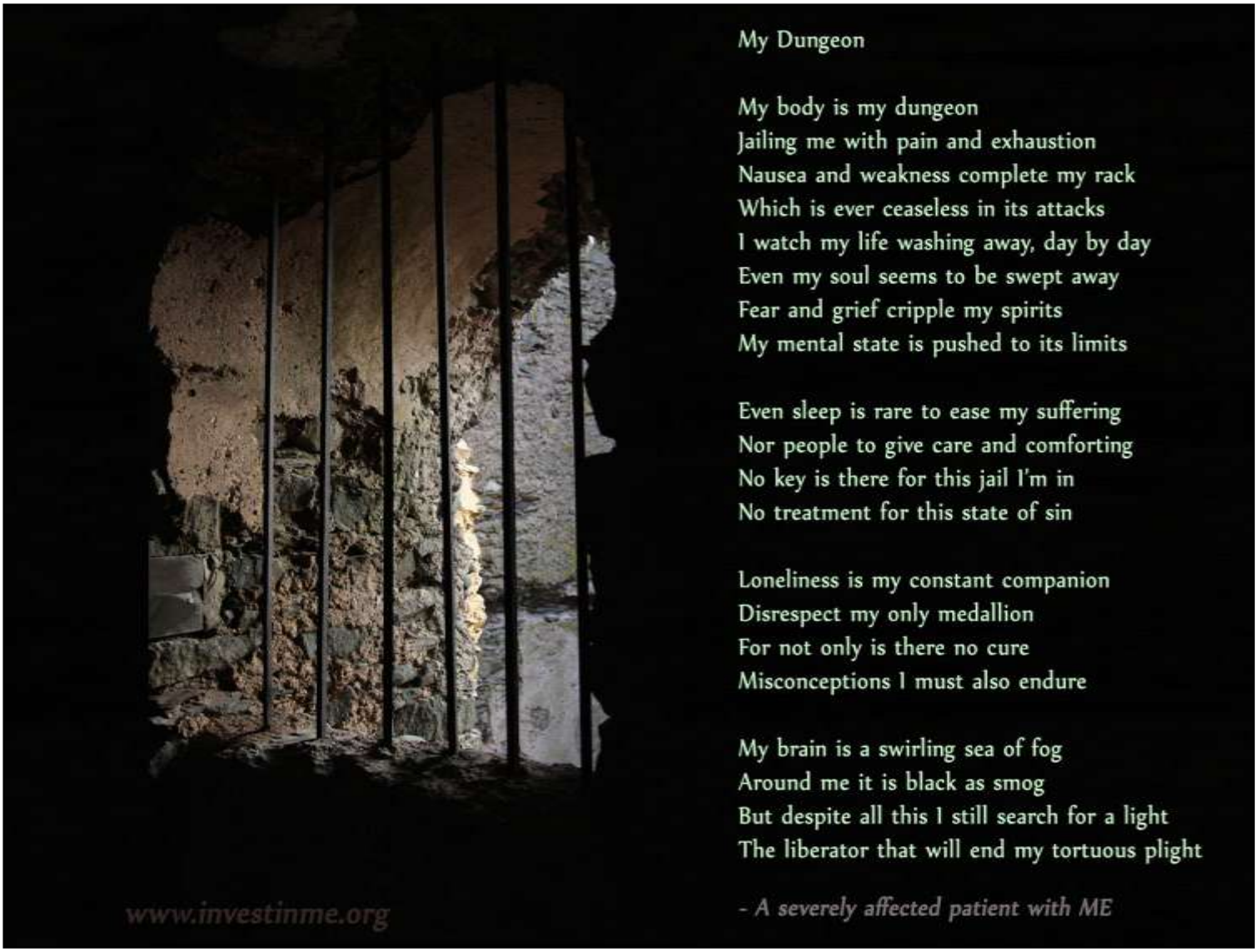
# A Poem for ME Awareness Month

## by a severely affected young person with ME




The world of ME has many hurdles for patients - one of the greatest being isolation.
It is too infrequent an occurrence for friends, and sometimes even relatives of someone with ME to stay in contact, let alone actively do something to help.
Many ME patients can feel isolated and abandoned by their friends and even family members due to the ignorance and effects of the disease.

So Invest in ME were amazed at the reaction and spirit of a group of four friends who created a scheme to visit all 92 English Football League Stadiums in under 92 hours in support of Invest in ME and in order to raise money and awareness for the Rituximab Trial.
They did this to help their friend who has ME.

The event lasted six days in April 14.
The charity and our supporters are indebted to this group of four who are did such an amazing job of raising awareness for ME. Football clubs, hotels, TV companies helped in building huge interest and this positive way of raising awareness and funds for ME has increased the exposure of the work the charity is trying to do.
The blog of the event is here http://92in92.blogspot.co.uk and one can still make donations to support the amazing event
The charity had a flag especially made for the tour and this was shown in photographs made at every football ground and used for photo opportunities at all of the clubs.

On 16th of April 2014, my wife, Cat, and two good mates; Mike and Raz started a six day challenge to drive to all 92 English Football League Grounds in under 92 travelling hours for Invest In ME.
I wanted to do something to raise funds and awareness for ME sufferers as one of my best friends from school in Cornwall, Ian, has suffered from ME for over 7 years and been unable to work or lead a normal life. Throughout this period he has always amazed me with his positivity about one day recovering and he told me about the Rituximab trial and its success in Norway. From hearing about it and doing some research online it appears that the drug could represent a very real breakthrough for treating and hopefully curing the illness and I was determined to get involved and do as much as we could to support bringing it to the UK. Ian and I have always talked for hours about football (him being a Liverpool fan, myself being a Man Utd fan) and once we'd come up with the idea to visit all 92 clubs it became really obvious that this could be a huge event in raising awareness. We began writing off to all of the clubs for support, football magazines, over 150 newspapers UK wide and various radio/TV to try and get as much attention as possible. In the end over 70 clubs pledged their support for the challenge which was pretty amazing and over 30 newspapers began calling me for info and agreeing to feature us. The challenge itself had been done by 3 other groups in the weeks running up to its start date so we found that a lot of the clubs were unable to support us with

donations or signed items. We changed tactics therefore and asked them for a small feature in their match day programmes which we hoped would be seen by thousands of supporters per game and also their websites and social media. We were in effect giving them free content and asking them to promote us and themselves with the view of raising awareness which for the most part they were more than happy to do. This meant that we acquired hundreds of followers and an army of supporters who in turn wrote off to their local clubs and media demanding support!


In some cases we were able to secure signed items which we are due to auction very soon including match tickets, signed pennants and other items but the most important aspect of the trip was to try and dispel the myth that ME is purely a psychological/non-physical condition and required funded biological research. We had fantastic support from Invest In ME who not only helped with emailing the clubs but were influential in creating flyers which we handed out at the grounds and working with us to design our huge flag which we took to be photographed with at all of the stadiums. We wrote off to local hotels to stop at during the trip and were given some fantastic discounts mainly from the Holiday Inn and also secured a cash donation from Enterprise Rent-a-car who would play a key part in our success later on in the story….

Taking to the road we stopped at Plymouth the night before and visited Plymouth Argyle where I met the Chief Executive of the club who told me that he himself had overcome ME –he'd come in on his day off to support us and opened up the ground for us to be filmed for ITV which was a fantastic gesture. Donations and requests for information began to flood in and we began the event in high spirits with a real feeling that we'd be able to change people's perceptions of ME and make a difference. Day one was eventful and although we got caught up in heavy holiday traffic we made it to our final club at 10pm with pitch side photos at Plymouth, Exeter, Yeovil, Bristol Rovers, Cardiff and Swansea under our belts. Twitter support from these clubs and web features also came in which further increased our followers and sponsorship. Day two was a huge one, beginning in Bournemouth, going along to Brighton and then up into the 12 London clubs was always going to be tough at the start of the bank holiday weekend. But luckily we had some amazing support from Arsenal who ushered us onto the pitch for photos and put us in two match day programmes! Another pitch side photo at Tottenham and some great support from the other London clubs followed and we were humbled by the support that we had from some ME sufferers who met us at the grounds and wished us well.

Day three was extremely hard as we arrived at Colchester just before the kick off for their home game and my clutch gave out. The staff and police at the ground were fantastic and Invest In ME helped us secure an Enterprise hire car to finish the leg as I travelled with the car back to Bristol on a very slow recovery truck. I hopped in another car and drove through the night to Milton Keynes ready to start the fourth day back with the team. As our car lay stationary in the car park outside the ground we had what is now infamously being called 'The Colchester Silence' –a two minute pause as reality sunk in that we might not complete the event. Don't worry this and much

more has all been captured on video which we are furiously editing ready for view! The team met with Richard from Invest In ME who had been such a huge help and we had another fantastic food parcel! With a man down and a midnight finish we decided that there was no way we wanted to let everyone down and no matter the cost or effort, we were going to finish the event.


Day four was actually pretty enjoyable despite covering a huge distance and over 24 clubs. These including pitch side photos at Aston Villa and with yet more club and paper support but we had become a well-oiled machine running on a diet of ghastly energy drinks and service station sandwiches. It was tough physically and mentally to keep going with just two drivers and the 'media team' in the back trying to keep up with messaging and posting to our social media which had become such an important part of the event. We met up with James Smith at Burton Albion whose mum suffers from ME and he came with us onto the pitch just before kick off at their home game and with one of their players we were photographed for the local papers –this was again another huge highlight for us and his mum baked us some delicious cakes! After a feature on Radio 5Live a lady from Scunthorpe drove over to the ground especially to make a donation which again was simply an amazing feeling for us.


Day five included a start at York City where someone at the club got wind of the club's initial refusal to support us and he contacted us to apologise, taking matters into his own hands he actually opened up the ground bringing one of the players along for a photo as well as featuring us on their website and match day programme. We moved on towards Bradford and met one of our supporters whose partner suffers from ME and he came along especially with the local newspaper to give us a cash donation. Again we were incredibly moved and meet-ups like this really kept us going.

Later in the day Manchester United not only allowed us onto the pitch but their fantastic staff showed us the dressing rooms and players lounge which was a fantastic bonus. More programme features, papers and twitter support followed as we broke through the £3K mark. Ending up in Carlisle at 10pm we knew that the final day would be a lot easier with just 7 clubs left to go. On day six we met up with Paul Kayes from 'Lets Do It For ME' at Middlesbrough and he was a real inspiration to us (as he had been throughout the entire project) as well as other ME sufferers we met there who had contacted the club to open their doors to us. A fantastic welcome from the club and another signed pennant as we left for our final two clubs. We finally finished at Leicester City (which we had moved from day four) and were thoroughly shattered but enormously delighted to have completed the challenge in what was just over 80 travelling hours.

It's an incredibly unfair and seemingly indiscriminate condition and we're all passionately behind any event that sees a move towards a cure or better treatment.

We targeted ourselves on reaching an audience of 10 million people which with the help of being featured on ITV news in 10 regions, BBC Radio 5 Live, the 30+ newspapers and over 70 clubs we feel that we have more than achieved this.

The sheer volume of anonymous donations that have come in prove that there is a real clamour to get this illness properly researched and a

cure/prevention found. We have another event to raise awareness in the pipeline (top secret) and we'll do everything we can to support Invest In ME and bring the Rituximab trial to the UK. Just by the trial even happening we hope that it will open the door to more trials and biological research which can only be a good thing for Ian and the other 250,000 we hope will one day benefit.

If you'd like to find out more about our event please go to www.92in92.blogspot.co.uk –all photos, football club support and media features can be found here. To sponsor us please visit www.justgiving.com/teams/strobl


***"We're pretty happy with the reach that we had with regard to highlighting the need for clinical research and feel that if we inspire just 100 people to select the charity as the beneficiary for their next sponsored event then that will be a fantastic achievement.***

***What struck us as we recovered from the lack of sleep and rehydrated ourselves was that we're all fit and well, the people that have supported us throughout the run up to the challenge and throughout all still have ME and need our help. The young children we met who suffered from the illness have left a lasting impression on all of us."***


I consider this a manifesto for the ME/CFS community. These are my thoughts, after nearly five years of watching the anguish and the neglect that surrounds this disease.
The manifesto states what I think should be done now.

And "now" is an important word.

There is a story that Winston Churchill, when he was very old and sick, summoned the gardener at his beloved country home in Kent, Chartwell, and asked him to plant an oak tree in an open space.

The gardener, looking at his enfeebled employer, swallowed and said,

"But, sir, an oak tree takes a hundred years to grow."

"Then you'd better plant it now, hadn't you?" said Churchill.

During World War II, Churchill used this same execution imperative approach to work. Churchill used to stick little, pre-printed notes — long before the days of Post-it notes -- on his paperwork for staff that read, "Action This Day."

One of the first things that struck me about ME/CFS, when I started writing and broadcasting on the subject, was how slow the pace of progress was, even as the suffering suggested the need for immediate action.
The second was how stingy public and private funding for research was then and is now.

I want my friends and loves, who are in the grip of a relentless affliction, whose days are torn from the calendar of hell, to be cured in my lifetime -- and I am 74. I want to be able to hold them as whole happy people; the people they were before they were struck down by an enemy they did not provoke, a monster they do not deserve, an unseen captor, a malicious jailer that takes daily life and makes it into a tool of torture and punishment.

One year, the CFIDS Association of America was able to declare proudly that it had raised $2 million.
The National Institutes of Health, a federal agency that should be pushing research, granted a paltry $5 million for ME/CFS in 2013. By comparison, in that same year, I learned that a consortium of foundations was sponsoring a green power marketing initiative at $6 million a year.

I have spent nearly 50 years writing about federal funding for energy, science and technology, and the sums of money spent has been in the tens of billions of dollars. One company gets more than

***Llewellyn King***
***A ME/CFS Manifesto***

Invest in ME contacted Llewellyn King to ask for permission to republish this article – as it chimes so well with the views of the charity regarding progress, obstructions to progress, and the need begin sowing the seeds of change.

Llewellyn King is executive producer and host of "White House Chronicle" on PBS, a columnist for the Hearst-New York Times Syndicate and a commentator on SiriusXM Satellite Radio.
He is the co-host of ME/CFS Alert on YouTube. king@kingpublishing.com

# Letter from America

$60 million year-in a year-out for nuclear fusion research -- and I see nothing wrong with that.

But when I look at the federal funding for ME/CFS research, I am aghast: It is not funded at a level that can be expected to produce results. It is, to my mind, a crime against the sick; morally, if not criminally, indictable.

To allow the scale of suffering that attends ME/CFS, without making research on the disease a national priority, is close to wilful neglect; an abrogation of the high purposes of Hippocrates' calling.
Other governments are not free of guilt for the suffering – and the United Kingdom stands out among the many offenders.
These governments have been seduced by the fraudulent blandishments of the psychiatric lobby. If a ME/CFS patient refuses to accept a psychiatric diagnosis, he or she can either be imprisoned or forced to suffer the insinuation that they are not physically sick, even if they cannot get out of bed. There are cases in Europe where patients refusing the prescribed psychiatric treatment have been imprisoned, as happened most recently to Karina Hansen in Denmark.

The United States is experiencing a boom in natural gas production and the deployment of solar panels on rooftops.
These successes are the manifestation of substantial research money committed in the 1970s, and sustained since then.
Science needs certainty of support, both political and financial, to triumph.

The key is sustained funding; a splash here and a dash there just won't do -- it won't do anything. ME/CFS researchers need to concentrate on their work, wherever that work takes them, free from the stress of insecure funding.
ME/CFS deserves the level of effort that might lead to success. It is not getting it now, and it never has had it.

It is appalling that Dr. Ian Lipkin, the highly respected virus hunter, is trying to raise $1.27 million through crowd funding to investigate the role of microbiome in ME/CFS. What we are seeing is a scientist forced to beg.

Yet this fundamental research, with application for diseases beyond ME/CFS, is at the frontier of biomedical science.

If we, as a nation, are to believe that we are in the forefront of science, we must be in the forefront of biomedical research as well as the forefront of computers, telecommunications, materials and physics.
We almost humbled polio, and developed powerful drug therapies for AIDS.

***Other governments are not free of guilt for the suffering – and the United Kingdom stands out among the many offenders.***

We can transplant vital organs and gave hope to the leper. The advances came neither cheaply nor easily, but they have saved lives beyond counting and eased suffering beyond enumeration.
Why not for ME/CFS? Why not?

There is eloquence in the voices of the community. But they are widely distributed and, sadly, they fall mostly on ears of those who already know them — the sick, their families and their advocates.

The voices need to be heard widely, need to be channelled and need to be focused. A million points of light won't do it. A laser, a great beam, will do it.

There are three principal reasons why these voices are not heard by those who need to hear them:

1. ME/CFS is a hard story for the media to grasp.
2. ME/CFS has no celebrity doing what Elizabeth Taylor did for AIDS, what Jerry Lewis did for Multiple Sclerosis, or what Michael J. Fox is doing for Parkinson's Disease.
3. ME/CFS has no presence in Washington.

Of the three, the last is the most critical to act on, and it is the one that would produce the most measurable result. Simply stated: Being on the ground in Washington every day is the essential step the community has to take.

# Letter from America

To get results in Washington, you need to-see-and-be-seen in the daily life there. Letters and petitions do not have nearly the impact as a Washington denizen talking to a decision-maker in person.

Happily this would amount to one very visible person, who strolls the halls of Congress, lunches at the clubs and restaurants, like the Cosmos or Metropolitan clubs, or the Monocle Restaurant on Capitol Hill. Once, I was mentioned in the Wonkette blog because I was spotted entering Bistro B, a favourite restaurant of the powerful, and those who think they are powerful.
If your children attend one of the power schools, like St. Alban's or Sidwell Friends, contacts can be made and deals can be done at the events.
A friend of mine enlisted President Bill Clinton's help for a cause because their children went to the same school.

It may strike you as banal, but it is the Washington political game.
Learn to play it.

Washington is a society of people who are impressed with each other.
It is important to be known. If you are invited to the annual White House Correspondents' Association or Alfalfa Club dinners, you are known. The next step is to be known for ME/CFS advocacy.
Once known, the perfect advocate/lobbyist will morph into a resource, a voice for others in Washington: a source of information for congressional aides trying to understand the budget requests of agencies, and a source of information for reporters writing about diseases of the immune system.

A voice in Washington puts pressure on government agencies to do the right thing, and on members of Congress to authorize and appropriate money.
The advocate/lobbyist can learn, through the hearing process, about the diligence and transparency of the agencies and the quality of their operations; to see if they are doing the job or treading water, to see how transparent their operations are and the quality of professionals operating programs.

Another salutary source of pressure in Washington is the press corps. It covers not just politics but also the functioning of government.
The pinnacle of power in the corps are still The Washington Post, The New York Times and The Wall Street Journal.
But the news agencies, The Associated Press, Bloomberg and Reuters, followed by a veritable media army that cover politics and programs, including Politico, The Hill, Roll Call, National Journal, and the specialized medical publications also play important roles.

Fifty years ago, the center of media activity was New York. Now it is Washington. A professional advocate for ME/CFS needs to cultivate the media and to be comfortable with the currency of Washington and to trade in it.

That currency is information.

Washington is a great information market. The successful lobbyist/advocate is, by the nature of the city and its functioning, an information broker.

The sums of money that will be needed to accelerate research cannot be calculated and could be very substantial.

Research funding, above all, needs to be sustained at predictable levels.

The pharmaceutical industry figures that a new drug can cost upwards of $1.2 billion. I mention it only to hint at the vast amount of money needed for drug research and development.

How much ME/CFS will need and for how long is an existential question?

Money stimulates research, attracts new young minds to the field and leads to success. Right now, there is so little money funding so few researchers in ME/CFS.

In the United States, that success may be a long time in coming – too long for those for whom today will be a living hell, as yesterday was and tomorrow will be.

I figure that for as little as $1 million, a start toward a Washington presence can be made. That would

cover one advocate/lobbyist, one office and one assistant for one year; not a smidgeon of attention from a giant lobbying firm, but a dedicated ME/CFS standard-bearer. Funding should grow within a year, as the ME/CFS cause comes out of the shadows.

I operated a small business in Washington for 33 years, and I am confident that a new ME/CFS presence there will reverse the disease's funding fortunes at NIH, increase media awareness, and cause the big foundations to sit up and take notice. It would give ME/CFS the kind of presence that other diseases with active advocates – COPD, ALS, MS and others -- have in Washingon and the nation.

If this is not done the government will continue to ignore the case for ME/CFS. Worse, the new billionaires who are beginning to throw real money into biomedical research will not know about ME/CFS. It will be hidden in plain sight much as it has been from the wider public.

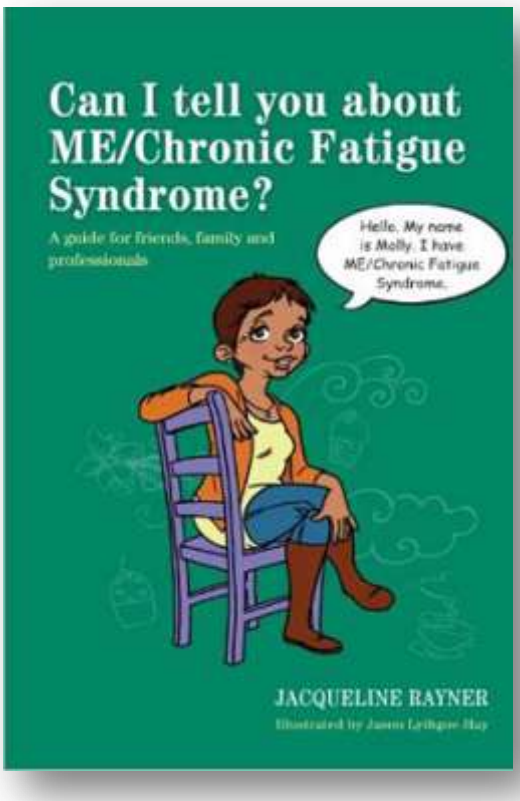
ME/CFS needs a place on the national agenda if it is to be understood and cured in reasonable time, and if the very best minds are to be attracted to the task and to stay with it. That Churchill oak needs to be planted now, and in sight of the U.S. Capitol.

# Can I Tell you about ME/Chronic Fatigue Syndrome?

This is a book by Jac Rayner.

IiME chairman Kathleen McCall has reviewed the book for the publisher and included the following comments -

> "This book is very clear and easy to read. It is a great resource that can be used by ME patients and their carers to explain and inform others what it is like to be affected by ME/CFS.
>
> Not only children but adult relatives, friends and teachers would learn a great deal from this book."




Available on Amazon at this link http://www.amazon.co.uk/tell-about-Chronic-Fatigue-Syndrome/dp/1849054525

Jac's book is also to be translated into Norwegian.

# Arctic Marathon - Fundraising for Invest in ME


Marathons are no mean feat to accomplish - for anyone. An extreme way of raising awareness of ME and much-needed funding for biomedical research into ME has now been set in motion by Mike Shepherd. Mike is taking on the North Pole Marathon.

As Mike writes on his web site

> -This is the challenge of a lifetime and it is the result of my daughter having ME since September 2008. I have seen first hand how damaging ME can be to a person's life, their prospects and their family
> http://www.shepherdfitness.co.uk

Donations and sponsorship can be made/discussed with Mike using the web link above.

# MY A-Z OF M.E. (Myalgic Encephalomyelitis)

by Ros Lemarchand

Do you feel that no one understands you?
Do you feel alone with this illness?
Do you find it hard to express how you feel?

Ros Lemarchand's book of poems about life with M.E. is a must for you.

MY A-Z OF M.E. (Myalgic Encephalomyelitis) is available in both Kindle and paperback editions
http://www.amazon.co.uk/.../dp/1492735116/ref=sr_1_6
Ros also has a YouTube video about the book -
http://www.youtube.com/watch?v=4GotabFQVjI

# Human Enteroviruses and Type 1 Diabetes

## by Steven Tracy[1]

***Following on from our 2009 article by the same author***

***Illustrating the complexities of translating basic research into clinical practice***

For some years now Invest in ME has been trying to interest other researchers to work within the areas of ME – partly to mainstream ME research and allow it to overcome the misinformation that has been allowed to be propagated over a generation, but also partly to use the great experience from other research which must be brought in and applied to ME research in order for progress to be made.

The link between enteroviruses and ME has existed for many years but the lack of funding from establishment organisations has forced this to be banished to the sidelines, with just the work of Dr John Chia keeping alive the research in this area. Invest in ME has had Dr. Chia presenting at many of our conferences.

We have also had Dr Nora Chapman from University of Nebraska presenting at our conference.

Professor Steven Tracy is an expert on diabetes and enteroviruses. He wrote an article for IIME – Human Enteroviruses and Chronic Infectious Disease

He has kindly given us permission to reproduce this article in our Journal. This is a good article to illustrate the amount of research that has gone into understanding the role of enteroviruses in T1D.

We could not agree more with the conclusion of this article.


***[1] Professor Steven Tracy Ph.D.***

Department of Pathology and Microbiology,
University of Nebraska Medical Center, Omaha NE 68198-6495;
stracy@unmc.edu; 402-559-7747

Primary research interest: Molecular biology and pathogenesis of the group B coxsackieviruses since the early 1980s

http://www.unmc.edu/pathology/type1_diabetes.htm

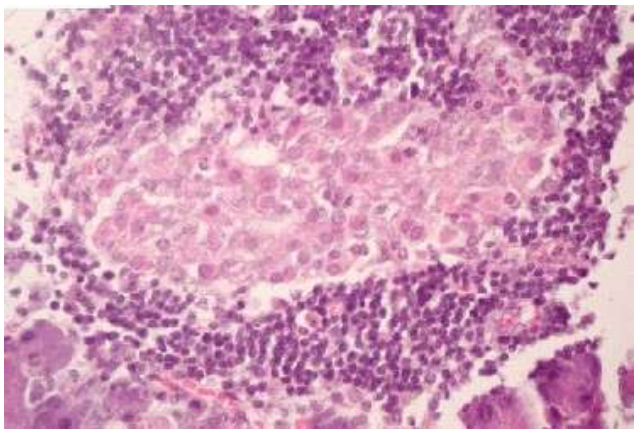

## Type1 Diabetes

Our laboratories have been working with the CVB since the early 1980s to understand how the viruses induce human inflammatory heart disease (myocarditis). It was therefore a natural extension of our work to examine the putative connection between CVB infection and type 1 diabetes (T1D) onset.

We use the nonobese diabetic (NOD) mouse as the animal model in which to study T1D onset. This is a well-established model used throughout the world for T1D research and one which is very useful for studying aspects of the virus-host relationship. Female NOD mice develop T1D at an incidence of between 70-100% of mice by 6 months of age: this means that for every 10 mice studied, 7-10 will naturally develop T1D by 6 months of age. Examination of the pancreatic islets in these mice shows that when mice are very young, no insulitis is apparent but by 6-8 weeks of age, insulitis has started to develop. Insulitis is inflammation of the islets, the places in the pancreas where beta cells are found. Beta cells produce insulin. When enough beta cells are destroyed, T1D occurs. Islet

# Human Enteroviruses and Type 1 Diabetes

inflammation is autoimmune, which is to say, it is a naturally occurring inflammation that targets the host itself. By 12-15 weeks, insulitis is extensive in nearly every islet and it is at this age that the mice begin to develop outright T1D. This is easily observed by measuring the level of glucose (sugar) in the mouse' urine: when normal, there is no glucose detectable but once diabetic, the mice shed more than 20 grams per liter of urine (equal to about an ounce per quart).



(A picture of a NOD mouse pancreatic islet that is dying due to the infiltration of autoimmune lymphocytes. The pathogenic lymphocytes are the dark cells surrounding the interior, lighter area, which is the remaining intact islet, still able to produce insulin. But not for long...)

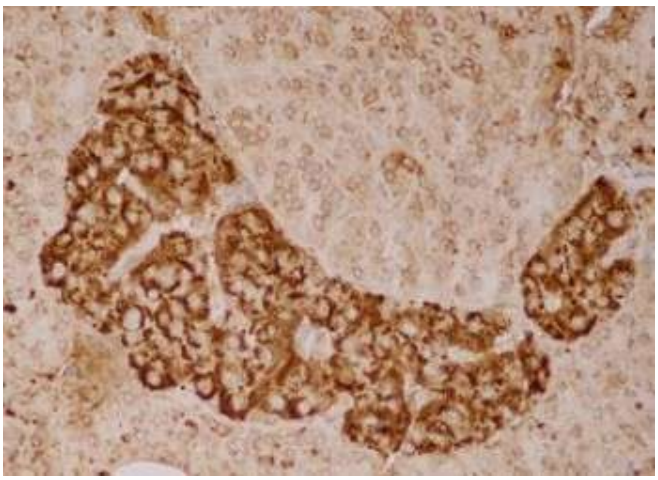
Our laboratory has a collection of different CVB strains for its studies. A serotype of CVB classifies a group of CVB; we use predominantly the CVB3 because we have spent most of our research characterizing this specific serotype. However, many different enteroviruses are likely able to cause T1D in humans, not just the CVB. It is often mentioned that only CVB4 causes T1D: this is simply not true. Now, within any CVB serotype, there are numerous strains of viruses, which all differ genetically from each other. You can think of a virus strain as a variation on a single theme. Our use of the CVB3 strains has permitted a deeper understanding of how relatively minor variations in the viral genetics can have huge impact on the outcomes of virus infections. We have derived molecular clones of several CVB3 genomes so that we can manipulate the viral genetic stuff in the test tube, then resurrect infectious virus in cell cultures, and use such viruses to study their biologies. This is a technique called reverse genetics and uses another key technique, molecular cloning. We have discovered several new aspects of the virus/T1D relationship using the mouse model, all of which are consistent with that which is known from others' human studies.

**1. The CVB protect diabetes prone mice from developing T1D.**

Because the CVB are often mentioned as primary infectious causes of human T1D, we asked the simple question: if we inoculate the virus into young, healthy NOD mice, what happens? Does T1D immediately occur? The answer? No! Such CVB-inoculated mice enjoyed a significantly diminished chance of developing T1D compared to control mice (mice which were not inoculated with virus and develop T1D normally)[1]. In some cases following CVB inoculation, no mice developed T1D through 10 months of life. This finding showed that there is no simple link between these viruses and T1D. The NOD mouse is very prone to developing T1D: these data showed, however, that a common virus infection, one linked to human T1D onset, could actually protect these mice. There is the criticism that nearly any treatment of NOD mice will suppress T1D and in large part, this is true. However, this criticism ignores the important fact that alone of all the treatments experimentally used in NOD mice to suppress T1D, inoculation with CVB represents a test of an agent suspected to be the cause - not the cure - of T1D. Our work demonstrated that, in effect, we can vaccinate NOD mice so that they do not develop T1D. This in turn suggests the intriguing possibility that one might be able to be vaccinated against developing T1D. Indeed, we strongly believe that T1D was rare in humans before about 100-200 years ago, simply because humans were commonly exposed naturally to numerous enterovirus infections as a natural part of growing up in a world of contaminated water and poor or absent hygiene [1]. [This was recently reviewed: Enteroviruses, type 1 diabetes, and hygiene: a complex relationship. S. Tracy et al., Reviews in Medical Virology 20:106-116, 2010.]

# Human Enteroviruses and Type 1 Diabetes

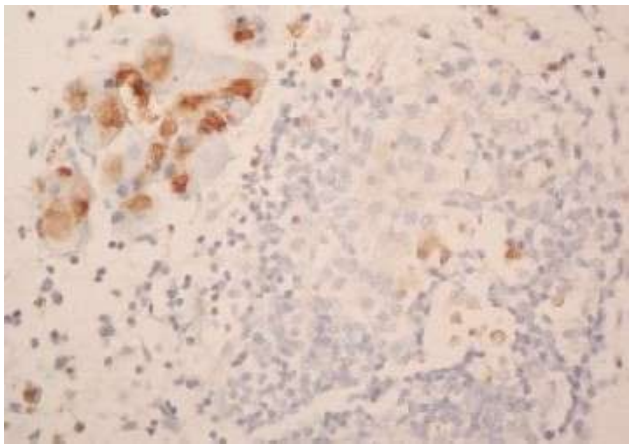
**2. The CVB do not invade and destroy islet cells of healthy mice.**
Viruses generally destroy cells by direct infection: viruses enter a cell, take it over, replicate themselves and in the process, kill the cell, releasing newly-created progeny virus to repeat this process. If enteroviruses such as the CVB are to be considered causes of T1D, then - most simply - the viruses must be able to destroy the insulin-producing beta cells in the pancreatic Islets of Langerhans. We observed that no virus was detectable within the islets of young, healthy NOD mice, even though we could detect the receptor protein that the CVB uses to gain entrance to cells. Receptors are like doors to rooms: a virus has to have a receptor in order to gain entrance to a host cell. Thus, even though we showed the receptor is present in islets, the 'door' appears somehow barred to effective CVB entry. This observation was consistent with our failure to observe that CVB cause T1D in young, healthy mice: if the virus cannot kill islet cells, then one would suspect the virus cannot induce T1D, either. In fact, this is what we observed.



(This is a picture of a human pancreatic islet that was stained for the expression of a protein, called CAR, the receptor which the coxsackie B viruses require in order to enter a cell to replicate. The dark brown is the islet to which an antibody against CAR is bound. Clearly, human islets, like mouse islets, express CAR and so, should be able to be infected under the right circumstances.)

**3. However, if the islet microenvironment is altered in specific ways, CVB can enter the islets.**
Other workers have suggested that the islets defend themselves against virus entry through a mechanism called the innate immune response and production of specific antiviral protein molecules called interferons. Using a CVB3 strain that we developed in the laboratory which was bioengineered to produce a mouse immune protein (cytokine) called interleukin-4 (or IL-4), we showed that this virus did gain entry to islets in young, healthy NOD mice. This experiment was important for two reasons. One, it showed that the expression of the virus receptor meant that CVB could gain access to islet cells. While this was logical, it had not been shown before in the mouse itself, only in a special condition (cell culture). Secondly, it showed that by changing the local microenvironment of the islet by the virus-induced production of IL-4, the virus could replicate successfully in the islets.

We also noticed two more things of importance. One, this type of virus infection caused no insulitis: the virus which produced IL-4 did not induce the mouse to attack the islets with its anti-viral immune response. Two, mice inoculated with this strain of virus had a better chance of never developing T1D than mice which did not get the virus infection. This surprising finding meant that despite intraislet replication of this bioengineered virus, this group of mice developed fewer cases of T1D than did mice without the virus injection. This observation showed that in some cases, virus infection of islets does not lead to more T1D or rapid onset T1D and therefore, the story was not quite so simple [2].



Islets in older NOD mice naturally become massively inflamed with autoimmune lymphocytes. This kills beta cells and the islet then loses the ability to produce insulin. Here you can see the residual small areas in such an islet in which

# Human Enteroviruses and Type 1 Diabetes

coxsackie B virus is replicating (shown by the brown color in the upper left corner primarily). The light blue in the remaining area are pathogenic autoimmune lymphocytes. Virus only replicates in the remaining healthy tissue, thus speeding T1D onset by killing insulin-producing beta cells.

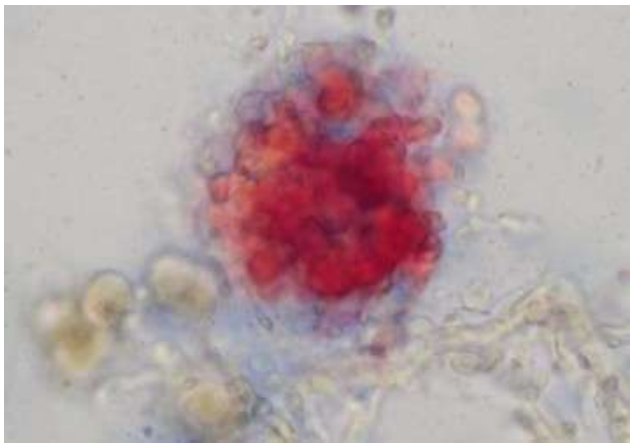
**4. CVB infection of older, prediabetic mice can, however, trigger T1D, an event linked to the alteration of the islet microenvironment.**

Older, pre-diabetic mice show massive insulitis in nearly every islet and not surprisingly, soon begin to become sick with T1D due to loss of insulin production. This naturally occurring, genetically driven autoimmune disease kills cells in the islets, including the beta cells, a process that leads to loss of insulin production and thus, T1D onset.

This inflammation of islets represents a real change in the biology of the islet, a massive naturally-occurring change in the islet microenvironment. We therefore asked another simple question: if CVB does not trigger T1D in young mice but instead, protects them, what happens in mice that are about to develop T1D anyway? We knew that IL-4 could let virus replicate in islets: would inflammation permit the same? The answer was yes!

Young NOD mice are analogous to humans who are genetically predisposed to developing autoimmune T1D but have yet to do so: they may have little or no insulitis present, just like young NOD mice. Based on our results, we suggest that humans with little or no insulitis, are at low risk from CVB-induced T1D. This is because we have shown that CVB (or in humans, we believe other enteroviruses as well) need to have insulitis in place in order to be able to successfully replicate in islets. However, it is quite difficult to say how advanced insulitis is in a human being; even presuming one knows that one is at risk. Humans are not like mice in a key respect: these mice are highly inbred and so, their own genes drive them to develop T1D in a regular, predictable fashion (the very thing that makes them so useful for this research). Every human is genetically distinct and has a different schedule for developing autoimmune insulitis (if indeed they ever do and of course, by far most do not). By modeling this situation in mice, we mimic the case in humans where a virus infection occurs at a time closely prior to the time when that person would develop T1D anyway from his/her own autoimmune disease. In mice, this is a specific age; in humans, it could be any time.

What we found was that pre-diabetic mice - i.e., mice with ongoing insulitis - when inoculated with a virulent strain of CVB, rapidly developed T1D, much faster than the rate of development observed in the control mice in which it is controlled only by the autoimmune disease. When we examined the islets of such mice, we discovered the presence of virus (as shown above). That virus was found replicating within the islets and associated with beta cells prior to the onset of T1D meant that the virus replication was denuding the mouse of intact beta cells, consequently causing early onset T1D[2].



(Stained bright red is an isolated mouse pancreatic islet. It is still associated with some residual pancreatic tissue.)

**5. Findings in mice and how they relate to human T1D: connecting the dots.**

The very great majority of enterovirus infections in humans never trigger T1D, even though enterovirus infections are common in the US from spring through the summer into the fall months and enteroviruses are encountered worldwide. So, if human enteroviruses are causes of human T1D, how is this explained? Using information we have gained by asking key questions of our mouse model and correlating clinical reports of enterovirus-linked T1D, we suggest that there are several reasons.

It is very likely that only certain enteroviruses can induce T1D or for that matter, act to protect one from developing T1D. Clearly in NOD mice, the CVB can either protect mice from developing autoimmune T1D (when they are exposed to the virus when young) or CVB can rapidly trigger T1D

# Human Enteroviruses and Type 1 Diabetes

onset (when older mice with insulitis are exposed to the virus). The CVB belong to one of four human enterovirus species, denoted A-D. Only human enteroviruses of the B species (or HEV-B), and this includes the CVB, have been associated with T1D onset. Poliovirus, for example, which is a species C enterovirus and to which nearly everyone in the world has been exposed (mostly now by clinical inoculations but prior to this due to wild-type infections), has had no impact on T1D incidence. Thus, we propose that the HEV-B species are the key players.

Now, for an enterovirus to 'suddenly' trigger T1D (when T1D occurs shortly after or during, for example, a 'cold' or 'flu-like' illness), we believe the islets have to already be significantly experiencing extensive insulitis through one's own autoimmune disease. That is to say, insulitis has to be present. This might normally, in time, lead to T1D onset or it might not. From the NOD mouse model, we know that islets in young mice that are not inflamed cannot be normally infected by CVB. This does not have to do with the virus receptor, the protein on the cell surface which the virus uses to enter cells. The CVB receptor is well expressed in young and older mice. So, when mice are young and have no insulitis yet, the islets cannot be infected, but when the mice are older and are developing insulitis, CVB can infect remaining healthy islet tissue and if the viral damage is sufficient, T1D ensues shortly after the virus infection. However, the overwhelming majority of people do not have insulitis. Therefore, we postulate that because most enterovirus infections in humans do not induce T1D, by far most people do not have insulitis. Therefore, this is consistent with the observation that the very great majority of enterovirus infections do not trigger T1D onset.

The host (humans or mice) have to "work" with the virus to cause T1D. That is to say, without host-driven (genetically determined) insulitis, the enterovirus cannot replicate productively in beta cells and cause T1D. Viruses are opportunists and will replicate wherever they can. In the case of a normal (not inflamed) islet in the mouse pancreas, CVB can enter cells (because the receptor is present) but cannot successfully replicate. We hypothesize that this is also the case in human beings. Only when the islet is attacked by the host's autoimmune disease do islets' defenses fall, permitting the virus to replicate productively in and kill islet cells. We know this happens in mice and we postulate this is the case in human beings. But this is a contested point. Human islets, isolated from pancreas and placed in culture, can replicate enteroviruses: such infections can kill beta cells in these cultured islets. This observation suggests that human islets might be infectable in the body, whether or not they are inflamed due to the autoimmune process. Currently, this remains an open question.

We also know from our work in mice, that the enterovirus infection has to be due to a strain that replicates quickly in the pancreas. Just like some humans can run faster than others, some virus strains can replicate faster than others (that is, some virus strains make more progeny virus in a shorter length of time than others). We have characterized strains (or variants) of CVB serotypes that replicate more rapidly and to higher titers, than other strains. To initiate T1D in NOD mice, we have shown that as few as 50 virus particles of a rapidly replicating strain of CVB3 can induce T1D, whereas more than 1 million virus particles of a slowly replicating strain are needed to induce T1D. Therefore, the average dose needed to successfully infect a mouse and to cause T1D with a rapidly replicating strain is far lower than for other strains. However, these rapidly replicating strains of enterovirus (which are generally termed 'virulent' strains, due to their capacity to induce disease easily in disease models) which are capable of causing severe disease, circulate relatively rarely. Most CVB strains, for example, do not cause serious disease such as myocarditis when assayed in mice. And even though all CVB strains replicate well in pancreas (thereby showing that these viruses have a predilection for replicating in pancreas tissue), this does not mean, that all are capable of replicating sufficiently well in islets to trigger T1D. The bottom line is this: the average (usual) enterovirus infection is due to a poorly virulent strain at a low dose, two factors that along with the requirement for ongoing insulitis, lower the odds dramatically for a T1D-inducing islet infection.

We also know that enterovirus infections induce protective antiviral immunity in people. This is the same principle by which the poliovirus vaccines have worked so well: inoculation with the vaccine strains of poliovirus induce an immunity that

# Human Enteroviruses and Type 1 Diabetes

dramatically suppresses the replication of polioviruses when the human again is infected, thereby keeping that individual safe from crippling polio. There are more than 100 known enterovirus serotypes and each serotype induces immunity in a person that will protect that person from disease caused by future exposure to that same serotype. This means that if one has already experienced an infection by a specific serotype, for example CVB3, one is immune to disease from all variations (strains) of CVB3 when next one may encounter it. However, type-specific immunity does not protect one from infection by a different serotype; protection is serotype-specific. To continue this example, therefore, CVB3 immunity will not protect one against infection by a strain of CVB1 or CVB4, for instance. Therefore, in order to trigger T1D in humans, an ebterovirus must infect a person who has no pre-existing immunity to that specific virus. So in addition to everything else discussed above, one must also experience a new enterovirus infection, against which one has no immunity, in order for T1D to be triggered. From this argument -knowing the various requirements which we can postulate to exist based on our current knowledge - one can see that having T1D initiated by a enterovirus infection such that it 'suddenly' occurs, would be a rare event.

In order for T1D to be triggered by a enterovirus infection, therefore, a variety of specific conditions have to be met all at the same time: (1) the right enterovirus species (not all can do this, insulitis needs to be present (and most people likely have none), (2) the virus strain should be one that replicates rapidly (because the average natural infectious dose is very low, the virus has to generate enough progeny virus to cause the damage before the host immune response suppresses the infection), (3) the virus infection must be one never before encountered by the person (otherwise, that person is immune to the virus), and (4) the person's islets must have insulitis ongoing (in order to create the environment that supports productive enterovirus replication in the islets). If T1D onset triggered by an enterovirus requires all these requirements, one can understand why the disease is rarely caused by an enterovirus.

**6. What does all of this mean for a cure for T1D?**
Finding a cure for existing T1D or a preventive measure against as-yet-to-occur T1D are two vital missions. Current work suggests that newly diagnosed T1D patients may profit from an antibody treatment that reduces pathogenic T cells, permitting the patient's own regulatory (good) T cells to expand in number to protect the islets from damage. This is wonderful news.

However, we must also stay focused on the issue of preventing T1D completely. We know the value of vaccines: polio, rabies, measles, mumps, rubella and more, all are diseases readily countered and suppressed by vaccine development. Properly designed vaccines work. However, the relationship between enterovirus infections and T1D biology is complex as the foregoing arguments have shown. We can largely prevent T1D in NOD mice with a single injection of CVB at an early age. This means we can prevent the host's own autoimmune disease from killing the beta cells and causing T1D - in most cases. There are those who argue that NOD mice are not a good platform for designing approaches to counteract or suppress T1D, and in most cases, this criticism is valid: nearly every approach that has functioned well in NOD mice does not function in humans.

However, human enteroviruses are human viruses and we know they are involved in human T1D. That they mimic much of what we know or surmise occurs when studied in the NOD mouse, is strongly inferential data in support of the hypothesis that certain human enteroviruses can either protect from, or induce, T1D. Enteroviruses are 'a bird in the hand' argument: we know they are involved in human T1D. So while we wait for clinical studies to produce lists of potential infectious candidates involved in the T1D etiology, we ought to be moving ahead to understand how enteroviruses are involved in the disease process. In the final analysis, no matter what list of potential pathogens that are found to be suspected of causing T1D, the human enteroviruses will be at the top of the list. Waiting is not an option anymore, now that we know this story.

# Human Enteroviruses and Type 1 Diabetes

Can a vaccine be created against enteroviruses which will eliminate T1D and perhaps all other enteroviral diseases as well? Good question. Vaccines usually target at most a few viruses; the polio vaccines targeted three types of poliovirus, for example. A major developmental problem for T1D is that at present, we do not know which enteroviruses cause T1D: there are at least 100 known and many more uncharacterized human enteroviruses. This is far too many to target for a vaccine, especially if some or many play no role in the disease. For a classical vaccine approach to be considered, we must determine which enteroviruses cause T1D, and determine how the viruses cause the disease. That enteroviruses in species B are likely the key players, suggests the relevant field has been winnowed significantly already. Research on this topic should be actively encouraged.

Of course, there is also the question of how many cases of T1D are indeed caused by enteroviral infections. If enteroviruses do not cause many cases, no company would ever make a vaccine because the market would be so small. That is a hard fact: cures are dependent upon the free market. We know that CVB and other species B enteroviruses are involved in T1D induction. However, work is required to identify the viruses that are found in the pancreas tissue of diabetic humans.

That said, we have been speaking so far about a classical vaccine: one which develops protective antiviral immunity against specific virus(es) serotypes that protects one against disease caused by subsequent exposure to the same virus(es) serotypes. There are potentially other approaches to vaccination, ones which may not involve the generation of protective immunity but instead, a generic or pan-enterovirus immunity. The possibility exists that one can induce the immune system to recognize enteroviruses in general, such that when it comes up against an actual virus infection, the immune response will be much more rapid. That may be all that is required and that would be rather readily accomplished. Such an approach is not a "silver bullet" like, for example, the polio vaccines; such an approach would offer a much better chance at suppressing a potentially T1D-causing infection but might protect all people. This, too, is worthy of research support because of its immense potential, not only for T1D but for viral diseases in general. In fact, we now have a large amount of data demonstrating that we can actually vaccinate NOD mice in this way and protect them not only from their own autoimmune T1D but also from CVB-induced T1D later in life. Therefore, we believe that the potential for this approach is huge. In one scenario, using standard and well-understood (from the poliovirus vaccine experience) technologies, a safe, protective anti-enteroviral vaccine could be devised. While it would not completely protect the individual from virus disease in the same manner that the polio vaccines prevent poliomyelitis, such an approach could slow the infection sufficiently so that the immune response would have a vital few extra days to respond and clear the infection. Again, data from the mouse model indicates this slowing of new infections is tightly linked to lowering the chance of developing virus-induced T1D.

***The goal should always be to eradicate the disease, while an acceptable compromise is to greatly reduce the incidence of the disease. To focus primarily on treating people with the disease is unacceptable.***

**7. The importance of basic research to help find the cure to T1D.**

That which we understand about human enteroviruses and their impact upon T1D development has been derived from basic research. As scientists and citizens, we are driven by the need for a cure, but we must temper our approach as we know that if we chase off down a promising but blind alley, we will waste valuable time. Ignoring basic research while emphasizing only clinical palliative efforts will never eradicate or suppress the disease. The goal should always be to eradicate the disease, while an acceptable compromise is to greatly reduce the incidence of the disease. To focus primarily on treating people with the disease is unacceptable.

1. Tracy et al. 2002 J Virology 76:12097-12111
2. Drescher et al. 2004 Virology 329: 381-394

# PERVERSELY DARK


A new film from Norway – about severe ME – from Pål Winsents.

It is perverse that many formerly able bodied persons have to lie in complete darkness and isolation. And, indefinitely so.


In each of their respective rooms, in two different places around the greater Oslo, Norway area, lie ME/CFS patients Kristine and Bjørnar sequestered in protective total darkness. In both cases, the tiniest amount of mental, social, or physical effort is detrimental and can completely overwhelm their bodies' minimal energy reserves and function. Consequently, only health care assistants and immediate family are permitted whispered access into their isolation in order to feed, medicate, and tend them.

Film maker Pål Winsents and Fenomen Film remarkably were given access into these patients' dark realms and permitted to 'syphon' some of Kristine and Bjørnar's stories and their precious infinitesmal life energy for the making of this important and unusual film. While medical experts in Norway and internationally debate and test their many theories in attempts to understand and discover a cure for ME/CFS in order to get its patient group up and out into light and life again, many such lives whither way as the many years roll by.

During the six years of filming Kristine and Bjørnar, the Fenomen Film crew was astounded by these patients' non-despairing fortitude, courage, and level of intellectual reflection despite the lack of proper stimuli or external battery life recharging them when confined to be in the dark with a great unknown.

Without giving away too much, ***Perversely Dark*** is also a film about love, perseverance soccer, presents, and Christmas songs, as well as a human transformation one would not believe it if not seen with one's own eyes.

**Director and film company**

***Perversely Dark***, the documentary film by director Pål Winsents from Norway and Fenomen Film, recently premiered at Victoria Movie Theaters in Oslo, Norway on May 12 with 350 people. And the premiere was one of the headlines on National TV Broadcaster the same evening. *Perversely Dark* follows the somber sequestered lives of two ME/CFS patients and their survival struggle to regain health and activity.


*Perversely Dark* is Pål Winsents' ninth documentary film and his second thematic ME/CFS film uniquely exploring the lives of this little known patient group while bringing their stories and voices into society's light.

His first ME/CFS themed film *Få Meg Frisk (Heal Me!)* featured partially functioning Anette Gilje, ME/CFS patient and former General Secretary of the Norwegian ME Association, through her desperate journey for treatment and proactive steps.

In *Perversely Dark* Pål Winsents ventures even further and captures the anguishing worse case stories of two full-time ME/CFS bed ridden patients and their families' struggles over a six year period in which time ME/CFS patients flounder in the unknown about what is happening to their bodies while without treatment or cure available.

The film will have English subtitles added.

**http://www.syktmorkt.no/**

# IiME Research Projects
# UK Centre of Excellence

**Executive Summary for MPs**

This is a summary of the current status regarding Invest in ME's proposal for a Centre of Excellence for ME Research and Treatment

*STATUS UPDATE May 2014*

## Background

- Seriously inadequate standard of medical care for ME patients in UK
- Very little funded UK biomedical research into condition
- Confusion between ME and chronic fatigue has led to unscientific research and ineffective treatment regimes
- NHS resources focus on symptom management therapies whilst underlying condition left untreated
- Medical professionals lack understanding of and training in ME -serious risk of mis-diagnosis and missed diagnoses
- International research has revealed much about biomedical basis of ME
- ME now identified as both highlighted area and high priority by MRC
- ME is leading cause of long-term absence from school due to sickness for students and teachers
- ME is recognised by the Department of Health as a chronic neurological illness

## Project Outline

Biomedical research and treatment institute for ME in East Anglia, based in Norwich within the Norwich Research Park utilising and based on university and institute facilities and resources

Hub of scientific and clinical excellence for ME within Europe

Research arm to be funded initially by private/charitable donations leading to applications to major public research funding bodies such as the NIHR, NIH, MRC etc.

Clinical diagnosis and treatment arm to be funded by CCGs (formerly agreed with Norfolk PCT)

## Service Commissioning

- GP referral, via normal NHS channels
- Consultant physician to diagnose patients according to international scientific criteria
- Based at Norfolk and Norwich University Hospital, subject to agreement
- GPs with special interest to be linked to Institute
- Treatment of patients based on up to date biomedical research findings
- Hub and spoke model: dissemination of expert knowledge to GPs and ME clinics nationwide
- Out of area referrals included
- Correctly identified patient cohorts considered for Institute research projects
- Training opportunities for medical students and other consultants, nurses etc.

## Invest in ME

- UK charity campaigning for biomedical research and treatment of ME
- Founder member and current Chair of European ME Alliance
- Organises annual international CPD-accredited international ME conference
- Organises annual international research colloquium
- Allied to a patient led campaign called Let's Do it for ME to raise funds for Invest in ME research
- Has initiated UK gut microbiome project to study ME as well as a UK rituximab clinical trial
- Holds worldwide contacts with ME organisations, physicians and researchers

## Research

- Based at Norwich Research Park, including University of East Anglia and Institute of Food Research and utilizing other institutes such as The Genome Analysis Centre
- Advanced fundamental research, initially using virology and immunology
- Key component: accurate definition of patient cohort, giving scientific validity to results
- Translational research -potential for direct patient benefit

- Dovetails with national identification of ME as priority area (NIH initiatite and MRC highlight notice)
- Initial projects: “A role for a leaky gut and the intestinal microbiota in the pathophysiology of myalgic encephalomyelitis” The majority of the immune system can be found in the gut and it is therefore highly desirable to study the gut microbiota in ME patients. The gastrointestinal tract contains a microbiota consisting of a vast number of bacteria and viruses
- Includes cooperation with other national/international research facilities (network already in place)

## Benefits


- Unique opportunity to establish European hub of scientific and clinical excellence
- Attraction of international interest and research funding to East Anglia
- Early and correct diagnosis
- Establishment of clinical trials
- Development of effective treatments, leading to highly significant public savings
- Hub and spoke. model to address seriously inadequate levels of clinical service for ME in East Anglia and nationwide
- Development of network of domiciliary services to support severely affected patients (currently seriously neglected)
- Savings on existing consultant referrals and staff -ME examination focused in one area
- Financially viable – Institute can start small and grow as further funding becomes available

## Current status

- All elements of the Institute model are ready to be put in to place with the exception of Norfolk and Norwich University Hospital, which has previously declined to provide a service locally as they do not feel that they “can provide a satisfactory high quality service on the basis proposed” – despite offering no service currently to ME patients
- The healthcare reforms have removed the promise made by Norfolk PCT to perform full examinations on ME patients by a qualified consultant. This now has to be renegotiated with CCGs
- The charity met with one CCG head and Dr Martin McShane – NHS Commissioning Board Authority, Director for Improving the quality of life for people with Long Term Conditions
- Dr Amolak Bansal from Epsom and St Helier CFS clinic in Surrey is providing accurately diagnosed patients for research purposes. He is involved already in the research funded by the charity
- The Foundation project at IFR/UEA examining the gut microbiota in ME patients started in October 2013
- We have been discussing with a paediatrician at N&NUH to become involved in ME and gut microbiota research at IFR/UEA and the charity is exploring that possibility

## Expansion of Scope

In order to augment the concept of a Centre of Excellence for ME the charity has initiated other research to expand the scope of research and form a strategy of international collaboration in biomedical research of ME.

## Rituximab Clinical Trial

Following the charity’s research meetings and cooperation with European ME groups and researchers, especially the Norwegians, an intent was made in 2012 The beginnings of a clinical trial of the rituximab drug for ME where a multi-centre study is about to begin.

- Jonathan Edwards, Emeritus Professor of Connective Tissue Medicine at UCL became the charity's clinical trial advisor in July 2013
- A study looking at B cells in ME patients is ready to start at UCL in London
- Fundraising is ongoing for a clinical trial to treat ME patients with rituximab, a monoclonal antibody used to treat certain types of cancer.
- Over £300K has been raised so far of the initial target of £350K and UCL has expressed interest in performing such a trial
- Professor Edwards has been working with the Norwegian Bergen researchers and the charity set up a visit to Bergen in September 2013

### Hypothalamus Study

- A study looking at antibodies binding hypothalamus has been accepted to be performed by Dr Bansal at St Helier and Epsom NHS Trust Hospital

Invest in ME is therefore asking Norfolk MPs to engage actively with this project with a view to securing this final, and vital, elements of the project.

Further details: Invest in ME
email: info@investinme.org

**FURTHER READING**
**University of East Anglia**
**http://www.foh.uea.ac.uk**

**Institute of Food Research** http://www.ifr.ac.uk

**Norwich Research Park**
http://www.nrp.org.uk/cms.php?pageid=1

**Norfolk and Norwich University Hospital**
http://www.nnuh.nhs.uk

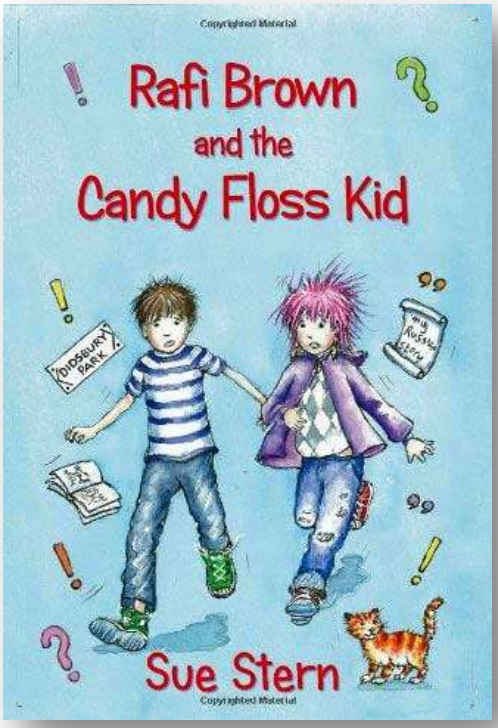
**TGAC - The Genome Analysis Centre**
http://www.tgac.bbsrc.ac.uk

**EDP News Story**
http://www.investinme.org/Medianewspapers.htm

**FAQ September 2011** http://bit.ly/180Iod0

# Rafi Brown and the Candy Floss Kid

Sue Stern has raised over £1000 by taking a MATRIX slot and donating proceeds to IiME from sales of her children's novel last year - just a year ago.

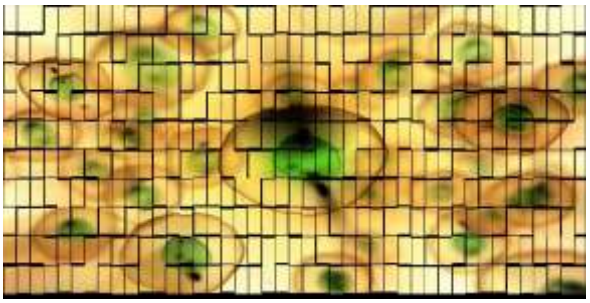



One of Sue's sons has been severely affected by M.E. and other related conditions for many years.

Her book has ISBN code **978-0-9574948-0-0**.

Sue was interviewed by Kath, at Wythenshawe local radio, on her programme, 'Disability Matters'.
As a result of her suggestion, I contacted the Royal National Institute for the Blind, who are now making a large-print version of the book, and when funds allow, a Braille version!

Sue's **MATRIX** slot is here - click here



# PRESENTERS at the 9th INVEST in ME INTERNATIONAL ME CONFERENCE

Bios and Abstracts from the presenters at IIMEC9

## Conference Chair - Dr Ian Gibson

**Former Dean of Biological Sciences, UEA**

Dr Ian Gibson, former Labour MP for Norwich North, worked at University of East Anglia for 32

years, became Dean of the school of biological sciences in 1991 and was head of a cancer research team and set up the Francesca Gunn Leukaemia Laboratory at UEA.
In 2011 Dr Gibson received an honorary doctorate of civil law from UEA.

## Professor Jonathan Edwards

**Emeritus Professor of Connective Tissue Medicine University College London (UCL)**

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

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

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

### IIMEC9 Abstract - Key Note Speech

People with ME may rightly feel that their illness has been neglected by science. However, this 'neglect' may in part simply reflect just how difficult a scientific problem ME poses.
To get a foothold, science needs both reproducible objective findings and well enough structured hypotheses to choose the right questions to ask in further experiments.
For ME these have been hard to pin down.

The recent finding of a response to rituximab in ME patients indicates that at least a proportion of cases may have an autoimmune basis. This suggests that lessons learned in the study of conditions such as rheumatoid arthritis, which led to the initial use of rituximab for autoimmunity, may provide clues for research into ME.
The story of how rituximab came to be used in RA, and the pitfalls encountered both in terms of finding objective disease markers and in formulating a hypothesis for disease mechanism, will be discussed.

Key steps in that process were the recognition that in autoimmune disease external trigger factors may be less important than spontaneous errors within the immune regulatory mechanism itself and that B cell tolerance of self may fail independently of T cell tolerance. It also became clear that there are many ways in which autoantibodies can cause disease and that one should not expect to find a 100% match between traditional antibody findings and disease. Moreover, the use of rituximab has itself proved to be a powerful tool in studying details of disease mechanism and perhaps the same may prove true for ME.

# Professor Angela Vincent

**Emeritus Professor of Neuroimmunology, University of Oxford**

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

Together with colleagues she collaborates with neurologists worldwide.
She was formerly Head of Department of Clinical Neurology (2005-2008), and is a Past President of the International Society of Neuroimmunology, and an Associate Editor of Brain.
She was a co-applicant and group leader of OXION, the Wellcome Trust-funded Integrative Physiology Initiative "Ion channels and Diseases of Electrically Excitable Cells".
She is a member of Faculty of 1000 (Neuroscience, Neurobiology of Disease and Regeneration)
Her major interest is in the role of autoimmunity in neurological diseases, including multiple sclerosis and auto-antibody mediated ion channel and receptor disorders.
Recent advances have included (a) the discovery that maternal antibodies to different fetal proteins can cause rare neuromuscular disorders, and may be involved in some forms of autism or other neurodevelopmental disorders; (b) the definition and characterisation of a new form of myasthenia gravis associated with antibodies to a receptor tyrosine kinase, MuSK, that performs an important maintenance role at the neuromuscular junction; and (c) the recognition that some central nervous system disorders, involving memory loss, seizures, movement disorders, can be caused by antibodies to potassium ion channels and to various receptor proteins.
In these, and several other conditions, new ways are being devised to measure the pathogenic antibodies for better clinical diagnosis, and establishing model in vitro and in vivo systems for investigation of the pathophysiology of the diseases. Her group also works, in collaboration with Profs David Beeson and Nick Willcox, on the genetics of myasthenia and the factors that determine autoimmune responses to the main target, the acetylcholine receptor.

More information - http://www.clneuro.ox.ac.uk/team/principal-investigators/angela-vincent

**#IIMEC9 - Autoantibodies in different forms of neurological disease: relevance for ME?**

Autoantibodies to a variety of receptors and ion channels on cells of the nervous system can be identified in children and adults with newly acquired neurological diseases. Most of the patients have classical features of myasthenia gravis or central nervous system diseases including loss of memory, seizures, confusion or bizarre movements. The diseases improve with immunotherapies that reduce the levels of the "pathogenic" antibodies. The field is still developing and some antibodies are now being detected in patients with other conditions including first episode psychosis, unexplained epilepsy, sleep disorders or pain.
But the relevance of the antibodies in these disorders is not yet established and some findings may be entirely incidental.

# Professor Jonas Blomberg

**Emeritus Professor of Clinical Virology, Department of Medical Sciences, Uppsala University, Sweden**

Professor Jonas Blomberg is an MD and PhD, graduating at the University of Gothenburg.
Has worked with Lipids at the department of Medical Biochemistry 1965-1972 as a Clinical Virologist in Gothenburg 1972-1979 and as a postDoc at John Stephensons Lab at NCI Frederick on retroviruses 1979-1981. He then worked as a Clinical Virologist in Lund, Sweden 1981-1995 and then as a professor of Clinical Virology in Uppsala 1996- to the present.

His main fields of interest are: Retrovirology, Bioinformatics, Clinical Virology and broadly targeted and multiplex methods for detection of microbial nucleic acid.
He also is interested in evolution and Infection biology.
Professor Blomberg is on the editorial board of Journal of Virology
http://jvi.asm.org/site/misc/edboard.xhtml

**#IIMEC9 Abstract: Infection-induced autoimmunity in ME**

Not available at time of printing – but will be made available on Invest in ME web site.

# Professor Mady Hornig

**Associate Professor Mady Hornig, Center for Infection and Immunity (CII), Columbia University Mailman School of Public Health, New York, USA**

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

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

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

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

She established that there was no association between intestinal measles virus transcripts and autism, and, with Brent Williams and W. Ian Lipkin at CII, has found altered expression of genes relating to carbohydrate metabolism and inflammatory pathways and differences in the bacteria harboured in the intestines of children with autism.
She also leads projects examining the influence of immune molecules on brain development and function and their role in the genesis of schizophrenia, major depression, and cardiovascular disease comorbidity in adults, and directs the Chronic Fatigue initiative Pathogen Discovery and Pathogenesis Project at CII.

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

Her work in ME/CFS is establishing immune profiles and helping to identify pathogens that may be linked to disease.
Her work on the MIND (Microbiology and Immunology of Neuropsychiatric Disorders) Project, one of the largest studies of immune factors in mood disorders and schizophrenia, examines the role of viruses and immune responses in the pathogenesis of these disorders.

**#IIMEC9 Abstract: Pathogen Discovery in ME**

Not available at time of printing – but will be made available on Invest in ME web site.

# Professor Carmen Scheibenbogen

**Professor for Immunology and Deputy Chair, Institute of Medical Immunology, Berlin Charité, Germany**

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

**#IIMEC9 Abstract: Role of EBV and ME/CFS**

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

Late first Epstein-Barr virus (EBV) infection is a frequent trigger of Chronic Fatigue Syndrome (CFS). About 20% of patients have serological or PCR evidence of EBV reactivation. A deficient EBV-specific immune response became evident in more than half of our patients when specific B cell and T cell memory responses were analysed (Löbel M. *et al.*, *Plos One*, January 2014). By analysing the spectrum of EBV-specific antibodies against various proteins we observed a pattern of EBV-specific antibody responses, which could distinguish CFS from healthy controls and patients with multiple sclerosis (Ruprecht K. *et al.*, *J. Neuroimmunology*, April 2014). When comparing EBV load in blood immune cells, we found more frequently low but detectable levels of EBER-DNA in CFS patients compared to healthy controls. However, no evidence of lytic EBV reactivation was observed indicating that no severe defect in T- and NK cell control of EBV exists. In line with this observation we found normal NKG2D expression on NK cells, which is important for killing of EBV-infected B cells. There is accumulating evidence that B cells are dysregulated in CFS. Many patients have alterations of immunoglobulin levels and those with diminished levels often suffer from recurrent respiratory tract infections. Both B cell depletion and high dose immunoglobulin therapy is effective in a subset of patients. Our current research focuses on the detailed characterisation of B cells and the EBV-induced regulation of B cell genes in CFS. Taken together, our findings give evidence for a deficient or dysregulated EBV-specific immune response in many CFS patients. Our data may point to an impaired ability to control early steps of EBV reactivation.

# Professor Simon Carding

**Professor of Mucosal Immunology at University of East Anglia and Institute of Food Research.**

Following his PhD at London he held postdoctoral positions at New York University School of Medicine, New York and at Yale University School of Medicine, New Haven, USA. He then moved to the University of Pennsylvania, Philadelphia, USA as Assistant and

later Associate Professor. He joined University of Leeds as Professor of Molecular Immunology in the Institute of Molecular and Cellular Biology in 1999. His scientific interests are in understanding how the immune response in the gut functions and in particular, is able to distinguish between the commensal microbes that reside in the gut and environmental microbes that cause disease, and in the mechanisms by which the body's immune system no longer ignores or tolerates commensal gut bacteria and how this leads to immune system activation and inflammatory bowel disease.

**#IIMEC9 Abstract: A role for a leaky gut and the intestinal microbiota in the pathophysiology of myalgia encephalomyelitis/ chronic fatigue syndrome?**

Simon R Carding[1,2], Tom Wileman[1], Daniel Vipond[1,2], Bharat Harbham[1], Eleanor Cottam[3] and Amolak Bansal[4]

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

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

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

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

Together these observations suggest that changes in intestinal barrier integrity, which may be driven by or are a consequence of intestinal dysbiosis, as a result, for example, of a gut infection could contribute to ME by driving systemic inflammation and/or influencing the microbiota-gut-brain axis. With support from Invest in ME we have initiated a project to address the hypothesis that alterations in intestinal barrier integrity and the resulting influx of luminal antigens triggers and perpetuates a state of chronic inflammation both locally and systemically that contributes to the pathophysiology of CFS/ME.

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

# Professor Sonya Marshall-Gradisnik

## School of Medical Sciences, Griffith University, Australia

Professor Marshall-Gradisnik is one of Australia's foremost researchers in the area of neuroimmunology and has been instrumental in establishing the Public Health and Neuroimmunology Unit (PHANU) at Bond University, and now at Griffith University. Much of her work relates specifically to autoimmunity in Chronic Fatigue Syndrome sufferers and she is regularly asked to speak to community groups on behalf of Queensland Health and NSW Health.

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

The vital research conducted by Professor Marshall has attracted more than $1 million in grant funding

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

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

**#IIMEC9 Abstract: Innate and Adaptive Immune Cells in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis.**

**Brenu EW[1], Hardcastle SL, Huth, T, Johnston S, Nguyen, T., Ramos SB, Staines DR, Marshall-Gradisnik SM.**
National Centre for Neuroimmunology and Emerging Diseases, Griffith Health Institute, Griffith University, Parklands, Queensland, Australia. Queensland Health, Gold Coast Public Health Unit, Robina, Gold Coast, Queensland, Australia.

Immunological abnormalities are consistent in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) patients, namely reduced Natural Killer (NK) cell cytotoxic activity. However, reports on other basic immune cell parameters are inconsistent in CFS/ME, possibly related to the heterogeneity or variation in severity of the illness.
The purpose of this research was to assess innate and adaptive immune cells that have not been previously examined in CFS/ME in cohorts of both moderate and severely affected patient severities. CFS/ME patients were assessed using the 1994 CDC Case Definition for CFS/ME. Health, mobility and quality of life questionnaires were used to assess all participants and also to further distinguish CFS/ME participants as either moderately or severely affected. Using flow cytometric assays, NK cells, neutrophils, monocytes, T regulatory cells (Tregs), iNKT cells, B cell phenotypes and dendritic cells (DCs) were examined each of these groups.
DC, B, neutrophil and Treg phenotypes were significantly different between the CFS/ME and non-fatigued controls. NK cytotoxic activity was significantly reduced in CFS/ME patients compared to controls and was further reduced in severely affected patients. The severe CFS/ME patients also demonstrated significantly increased DC, B, iNKT and NK phenotypes when compared to both the moderate CFS/ME patients and healthy controls. These results have confirmed previous reports that NK cell cytotoxic activity is consistently reduced in CFS/ME.
This data has further suggested that further immune cells, including DCs, B, Tregs and iNKT cells have immune perturbations related to cytotoxic activity and phenotypes in CFS/ME and this may be contributing to the overall immune profile demonstrated in this illness and other autoimmune disorder.

# Professor James Baraniuk

**Professor of Medicine at Georgetown University Medical Centre**

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


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

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

After 2 years studying neuropeptides, he joined Dr Peter Barnes' laboratory at the National Heart and Lung Institute, Brompton Hospital, London, UK.
Dr Baraniuk returned to Washington, DC, and Georgetown University, where he is currently Associate Professor with Tenure in the Department of Medicine.

**#IIMEC9 Abstract: Brain Imaging and ME**
Not available at time of printing – but will be made available on Invest in ME web site.

# Professor Julia Newton

**Clinical Professor of Ageing and Medicine, Institute for Ageing and Health, Newcastle University and Honorary Consultant Physician, Royal Victoria Infirmary, UK**

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

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


**#IIMEC9 Abstract: ANS and ME Autonomic Dysfunction & ME**

The autonomic nervous system controls all of those functions that go on in the human body outside conscious control. Studies have confirmed that problems with the autonomic nervous system (autonomic dysfunction (AD)) are a common occurrence in those with ME, with almost 90% of sufferers describing postural dizziness, syncope (blackouts) and a range of other autonomic symptoms. Formal testing has confirmed the presence of objectively measured autonomic dysfunction in ME with conditions such as neurally mediated hypotension and positional tachycardia syndrome recognised at significantly increased prevalence compared to matched control populations.
The underlying cause of this frequently found AD is as yet not understood. Studies will be described confirming muscle, cardiac and brain abnormalities the severity of which associates with the underlying AD.

# Professor Maureen Hanson

**Liberty Hyde Bailey Professor, Cornell University**

Maureen Hanson is Liberty Hyde Bailey Professor in the Department of Molecular Biology and Genetics at Cornell University in Ithaca, NY. Previously she was on the faculty of the Department of Biology at the University of Virginia in Charlottesville and an NIH NRSA postdoctoral fellow at Harvard, where she also completed her Ph.D. degree.

While most of her prior research has concerned cell and molecular biology in plant cells, she began a research program on ME/CFS after noting at a 2007 IACFS meeting the paucity of molecular biologists studying the illness.
Her lab was part of the 2012 multicenter study organized by Ian Lipkin's group at Columbia University to assess the actual role of XMRV in ME/CFS.
Dr. Hanson has a current project to examine the microbiome of ME/CFS patients and controls, in collaboration with Dr. Ruth Ley (Cornell Microbiology) and Susan Levine, M.D. (Manhattan, NY).

Dr Levine is also collaborating with Dr. Hanson on an immune cell gene expression project that involves Dr. Fabien Campagne and Dr. Rita Shaknovich at Weill Cornell Medical School in New York City.
Dr. Hanson's third project concerns analysis of blood samples from individuals performing a two-

day cardiopulmonary exercise test at Ithaca College under the supervision of Dr. Betsy Keller.

### #IIMEC9 Abstract: Markers of Post-exertional Malaise

[1]Maureen R. Hanson, [1]Ludovic Giloteaux, [2]Xiaojing Lu, [2]Jason W. Locasale, [3]Betsy A. Keller

[1]Department of Molecular Biology and Genetics, Cornell University, Ithaca, NY, USA
[2]Division of Nutritional Sciences, Cornell University, Ithaca, NY, USA
[3]Department of Exercise & Sport Sciences, Ithaca College Ithaca, NY, USA

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

After induction of post-exertional malaise by an initial CPET, ME/CFS patients often exhibit abnormal physiological and/or autonomic nervous system responses and are usually unable to repeat either their $VO_2$max and/or VT, which is a measure of the anaerobic threshold, or they show symptoms of autonomic dysfunction. Anaerobic threshold is the exercise intensity at which metabolism transitions to anaerobic energy production, which is less efficient and results in accumulation of lactic acid. We have observed patients with ME/CFS who become prematurely "anaerobic" at low work levels. After an exercise challenge, even modest activities, such as lying quietly while watching television or sitting and eating, require some patients to use anaerobic metabolism. Other patients exhibit Metabolic Equivalent of Task (MET) levels at maximal exertion of 4.0 or less, while 4.0 METs are required to do such simple activities as hanging laundry, sweeping a sidewalk or climbing stairs slowly.

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

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

# Dr Andreas Kogelnik

**Director of the Open Medicine Institute, USA**


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

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

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

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

### #IIMEC9 Abstract: Diagnosis/Treatments and ME in USA

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

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

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

# Dr Amolak Bansal

**Consultant Clinical Immunology and Immunopathology, Epsom and St. Helier University Hospitals NHS Trust, Surrey, UK**


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

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

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

### #IIMEC9 Abstract: Diagnosis/Treatments and ME in UK

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

It is therefore a diagnosis of exclusion.

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

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

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

# Dr Saul Berkowitz

**Royal London Hospital for Integrated Medicine, London, UK**

Dr Berkowitz is one of two full-time consultants at the Royal London Hospital for Integrated Medicine. He graduated from Fitzwilliam College, Cambridge in 1989, and from Charing Cross and Westminster Medical School in 1993.

He was the first doctor in the UK to complete a joint training program in both orthodox and complementary medicine, and have recognised postgraduate qualifications in Alllergy, Western herbal medicine (phytotherapy), acupuncture and homeopathy.
Dr Berkowitz treats patients with a wide range of mostly chronic medical problems.


# Dr Julian Blanco

**Leader of the Irsi Caixa Research Institute's Cell Virology and Immunology Research Group, Barcelona, Spain**

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

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

**#IIMEC9 Abstract: External View of ME Research Strategy**

When ME/CFS knocked the door of biomedical research, most teams were already working in other life threatening diseases, and little attention was paid to this disease. Reversing this situation to take advantage of the massive work and exceptional advances that biomedical research has made in the last decade, should be a major goal. The advances in the clinical definition of ME, the undeniable data on the prevalence of the disease are major players contributing to push ME towards the frontline of biomedical research.
What will ME/CFS find in the current research landscape? Most of diseases can now be approached from a completely different scientific perspective that could be approached ten years ago. New technologies and new analysis tools generating and managing million of data are now available. This information will inform us on the genetic basis of the disease and the implication of intestinal microbiota or the immune system in its pathophysiology. However all this powerful arsenal of technology will be useless in the absence of a proper choice of patients. Clinical efforts in diagnosis and in the definition of clinical trials will be therefore determinant to achieve the final goal.

# The Invest in ME/UCL Rituximab Clinical Trial

## An International Event

When Invest in ME announced in June 2013 that we were planning a UK trial of rituximab for ME there was a great deal of interest raised.

The rituximab trial follows the exciting work which has been, and is being performed in Norway by the Haukeland University hospital researchers Professor Olav Mella and Dr Oystein Fluge.

The response from around the world emphasises how great the need is for high-quality biomedical research into ME. This has been sorely lacking for a generation with funding mostly being squandered on psychological interventions which have no hope of finding cause or making available effective long term or permanent treatments.

The research work in Norway was backed up by impressive and dedicated patient advocacy by the **Norwegian ME Forening** which has raised the profile of ME in Norway and throughout the world. Their tireless work encouraged IiME as did the more recent success of the fantastic Norwegian ***ME and You*** campaign to raise funds for the Norwegian research.

These efforts have created a real sense of hope amongst patients.

Our wonderful supporters have risen to the occasion and their efforts have validated the decision to initiate the UK trial with UCL.


The imaginative Let's Do It For ME campaign has continued to produce ideas to raise funds and awareness and **The MATRIX** is an example of a unique method of achieving both.

We have had donations from around the world, ranging from £1 to £3,000.

A very generous foundation has donated £25,000 already and pledged £200,000 toward the clinical trial. This was in memory of the late Roger Heindry who sadly passed away in March 2013. We are very grateful for this extraordinarily generous offer from the donating foundation. It was an amazing gesture from compassionate and caring people who want to make a difference.

It allows the hopes of many patients to become a reality – allows a vision to be maintained that there is a future for ME patients and that we, patients and families and supporters, can make a difference.

A few good people can change things. One event can change everything.

As such, IiME and our supporters have managed to initiate and organise something which many thought was not possible.

This is an international event and is followed and funded by many around the world.

Our objective is to ensure that a clinical trial of rituximab is allowed to be performed by the best researchers possible and to ensure that this trial makes a valuable contribution to the collective ME research pool. We have stated before that we believe in achieving results by the most direct method, where possible.

For IiME the issue of making rapid progress in ME research is important, it is personal. The need is here - the need is now.

We continue our efforts to raise the remaining funds. We thank all those who are supporting this trial and we will continue to provide information on the status of the trial as we progress.

Please contact IiME directly if you or your organisation would like to assist or contribute. If anyone would like to ask any questions about the UK rituximab trial then please use the Contact form on the rituximab web site. With this trial we can take a huge leap forward in ME research.

Let's Do Research! Let's Do It For ME!

# 9th Invest in ME International ME Conference 2014
# 30th May 2014, London
# Conference Agenda

| Start | Presenter | Presentation |
|---|---|---|
| 07.45 | *Registration* | |
| 08.55 | Welcome to IIMEC9 | Dr Ian Gibson |
| 09:05 | Professor Jonathan Edwards | Lessons for ME Research from Rheumatoid Arthritis Research |
| 09:35 | Professor Angela Vincent | Finding Antibodies in Neorological Diseases |
| 10:10 | Professor Jonas Blomberg | Infection-induced autoimmunity in ME |
| 10.40 | *Break* | |
| 11:00 | Professor Mady Hornig | Pathogen Discovery in ME |
| 11:40 | Professor Carmen Scheibenbogen | EBV and ME/CFS |
| 12:10 | Professor Simon Carding | Gut Microbiota and ME/CFS |
| 12.35 | *Lunch* | |
| 13:25 | Professor Sonya Marshall-Gradisnik | Current Knowledge of Immunological Biomarkers in ME |
| 14:05 | Professor James Baraniuk | A framework for future fMRI characterizations in ME Patients |
| 14:45 | Professor Julia Newton | ANS and ME |
| *15.15* | *Coffee/tea Break* | |
| 15:35 | Prof Maureen Hanson | Markers of Post-Exertional Malaise |
| 16:10 | Dr Amolak Bansal | Diagnosis/Treatments for ME within NHS |
| 16:25 | Dr Andreas Kogelnik | Diagnosis/Treatments for ME in USA |
| 16:40 | Dr Andreas Kogelnik<br>Dr Amolak Bansal<br>Dr Saul Berkowitz | Panel Discussion |
| 17.00 | Dr Julian Blanco | External View of ME Research Strategy |
| 17:20 | Dr Ian Gibson | Plenary Session |
| *17.30* | ***Adjourn*** *(Note that the agenda, format and times are subject to change)* | |



# Raising money & awareness for ME sufferers, Invest In ME & the Rituximab Trial

## www.92in92.blogspot.co.uk


## Visiting 92 English Football League Grounds in 92 hours. Starts April 16th 2014

JustGiving www.justgiving.com/teams/strobl or text IIME92 £1 £2 £5 to 70070

# One Event Can Change Everything

# A rituximab clinical trial for ME

## Let's Do Research

**www.ukrituximabtrial.org**

Myalgic Encephalomyelitis (ME) is a serious, chronic neurological disease.
A UK trial of rituximab for ME is being initiated and organised by UK charity Invest in ME Research and University College London.
The charity wishes to establish a Centre of Excellence for ME in the UK.
Please support us and help us to help people with ME.
Let's Do It For ME. Let's Do Research.

**Invest in ME Research**
*(formerly Invest in ME )* UK charity nr. 1153730

www.investinme.org email: info@investinme.org ldifme.org

Small Charity BIG Cause
Support ME Awareness Invest in ME
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