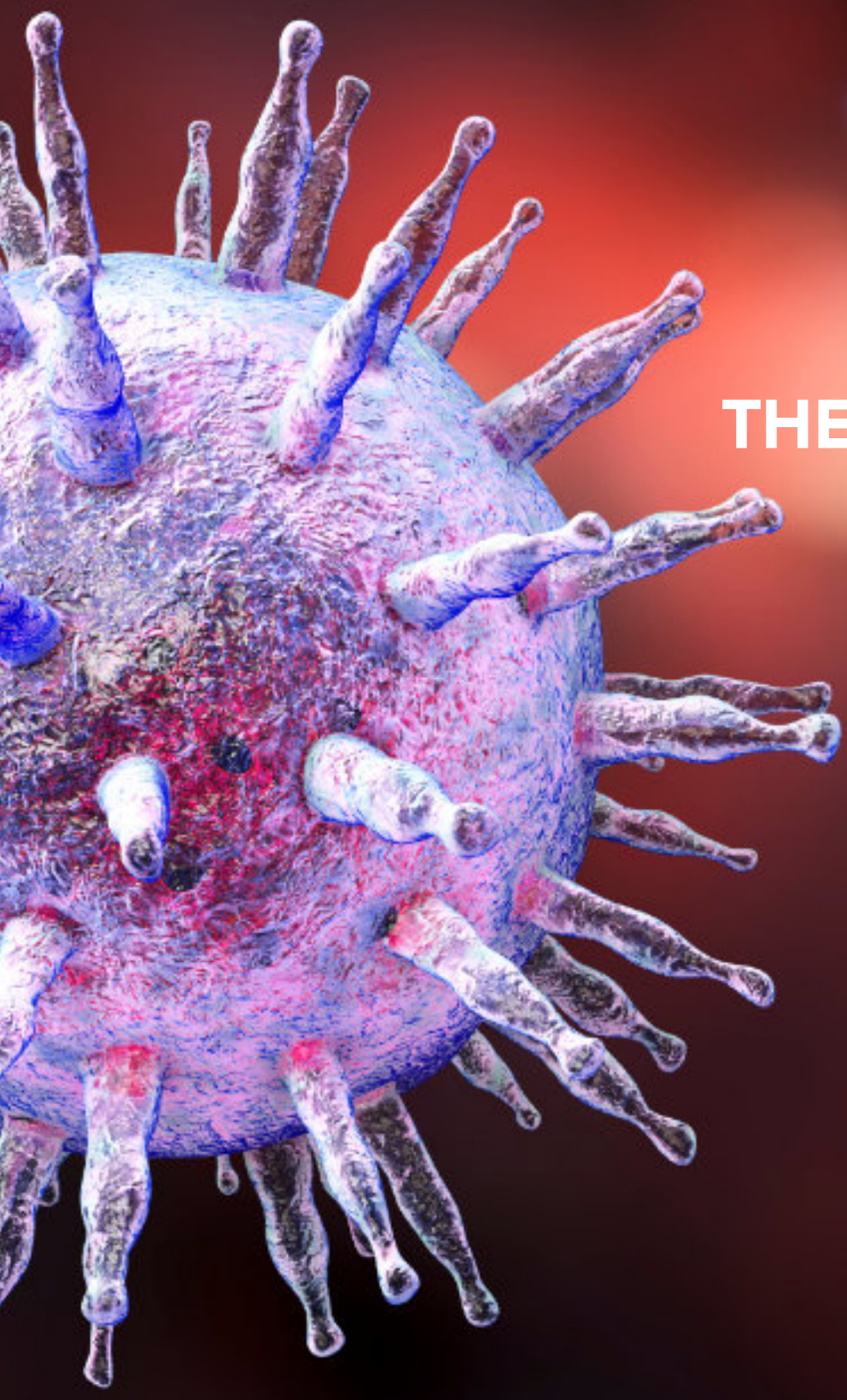
NEWS OF THE ME RESEARCH YOU ARE HELPING TO FUND

breakthrough



THE VIRUS ISSUE
(but not that one)

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ME RESEARCH UK

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Breakthrough magazine is published by ME Research UK, a Scottish Charitable Incorporated Organisation with the principal aim of commissioning and funding high-quality scientific (biomedical) investigation into the causes, consequences and treatment of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS). The charity also aims to energise ME research by identifying potentially important areas for future biomedical research, and producing high quality professional reviews and reports. *Breakthrough* is an open access publication and, apart from images and illustrations, the content may be reproduced free of charge, subject to the terms and conditions found at meres.uk/bt-terms.

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The Gateway, North Methven Street,
Perth, PH1 5PP, UK
Tel: 01738 451234, Email: contact@meresearch.org.uk

In this issue

In the spotlight

What's happening in the world of ME research and funding

Editorial

Welcome to the new issue of *Breakthrough* magazine. Along with many other features, this issue focuses on two new ME Research UK-funded studies exploring the potential role of viral infections in ME/CFS.

This will be of particular interest to those who state that their illness was triggered by a viral infection, and highly relevant given current thinking over long COVID. Dr Nuno Sepulveda at the London School of Hygiene & Tropical Medicine is looking at Epstein-Barr virus, while Prof. Elisa Oltra is investigating the link between human endogenous retroviruses and ME/CFS. We are delighted to be supporting these two new pieces of research. You can read more about them on page 7.

We also have the latest article from Cort Johnson, on page 11, who takes a look at some of the large-scale research projects in ME/CFS being carried out at the moment, including DecodeME and the You + ME registry.

A new version of the NICE Clinical Guideline on ME/CFS is due to be published imminently. ME Research UK, along with other stakeholders, provided evidence and comment as the review progressed. We are heartened by the improvements to the guidance, and all signs are that this has the potential to making a real difference to those affected by ME/CFS.

Elsewhere in this issue, you can find a round-up of selected ME research from around the globe (page 14), and some of the ways our loyal supporters have continued to fundraise in what has been a challenging year for us all (page 16). See page 18 for some more ideas.

This issue comes with a flyer promoting our spring fundraising appeal. As you know, ME Research UK relies solely on the support of our fundraisers and donors. We are so grateful for this support because it allows us to commission and fund more critical biomedical research into ME/CFS. If you are able to help, please consider making a donation or setting up a standing order.

Thank you very much, and I hope you enjoy the spring 2021 issue of *Breakthrough*.

Jonathan Davies
Chair, Board of Trustees

Walk for ME

ME Research UK is grateful once more to be chosen as one of the featured charities for 2021's Walk for ME scheme.

COVID-19 restrictions permitting and adhering to all social distancing and health advice, the initiative is most popular around ME Awareness Week.

The scheme has encourages supporters to walk, run, swim and ride for two ME biomedical research-focused charities.

Luke Remnant explains more about the campaign on page 17.

If you would like to part, please visit our website for more details: meres.uk/walk4ME

DecodeME

Registrations continue for anyone who is interested in taking part in – or being kept informed about – the world's largest ever bio-medical study of ME/CFS – DecodeME.

DecodeME plans to look at DNA changes in people with ME/CFS by collecting saliva samples from 20,000 people with the illness.

The investigators hope to identify genetic differences that increase a person's risk of becoming ill with ME/CFS, and the findings may also provide insight into the underlying causes of the condition.

The involvement of people with ME/CFS across the UK will be essential to the study's success.

You can register at decodeME.org.uk, and participants need to be aged 16 years or over and living in the UK.

Updated NICE guideline

Draft indicates major improvements

A replacement for the much-criticised NICE Clinical Guideline on the diagnosis and management of ME/CFS is due to be published this year.

Its contents are taken into account by NHS health and social-care professionals in England and Wales, but it is also influential across the UK.

The guideline includes recommendations on assessment and care, safeguarding, access to care, and symptom management.

However, many across the ME world – from people with ME/CFS to patient organisations and charities – have long held serious concerns about the usefulness of the current version.

An update is therefore welcome news indeed, and a draft of the new version was published late last year. ME Research UK has been involved as a stakeholder in the review process, providing feedback, and co-funding a survey of the experiences of people with ME/CFS who received cognitive behavioural therapy (CBT) or graded exercise therapy (GET).

Although we must wait until April for the final version, most observers (including us) were delighted to report that the contents of the draft indicate great improvements from the previous version. Here are some of the main points:

- The draft guideline acknowledges that people with ME/CFS may have experienced prejudice and disbelief.
- Clinicians are instructed to suspect ME/CFS if a person has had persistent symptoms for at least 6 weeks in adults

or 4 weeks in children. A diagnosis can be confirmed after 3 months of symptoms.

- The draft states that "there is no current treatment or cure for ME/CFS".
- Controversies about CBT and GET are acknowledged, and healthcare professionals are told not to offer CBT as a treatment or cure for ME/CFS, nor any programme based on fixed incremental increases in physical activity or exercise (e.g. GET).
- In addition, therapies derived from osteopathy, life-coaching and neurolinguistics (e.g. the Lightning Process) are not to be prescribed.
- The draft guideline acknowledges that energy management is not curative, but personalised advice about symptom management should be given to people with ME/CFS.

Dialogues for a Neglected Illness

New videos available

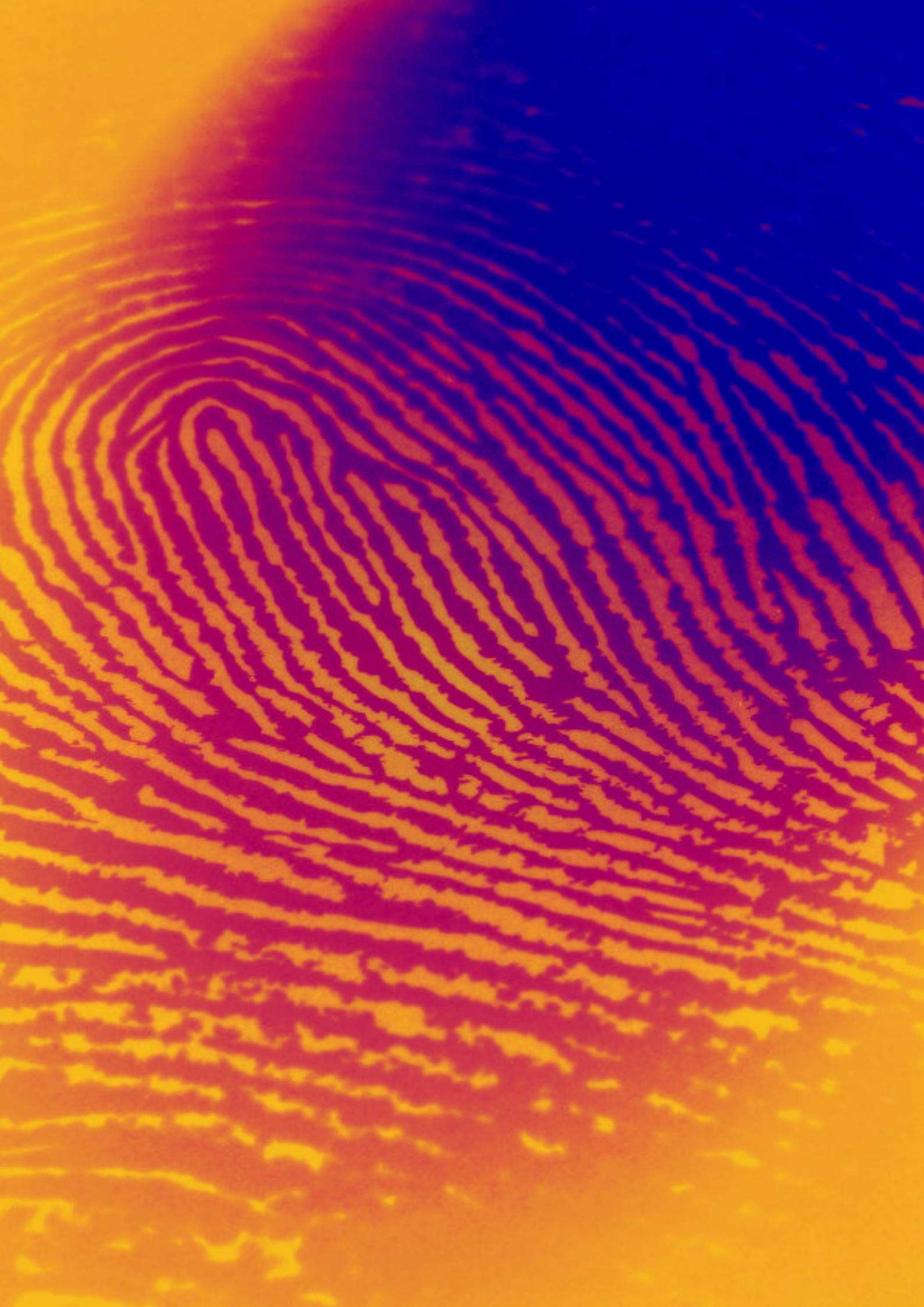
In the last issue of *Breakthrough* we highlighted a valuable new resource being developed by filmmakers Natalie Boulton and Josh Biggs, with the help of an award from the Wellcome Public Engagement Fund.

Dialogues for a Neglected Illness is a series of videos addressing different aspects of ME/CFS, including its diagnosis, management, treatment and patient experiences.

The project has continued to grow rapidly since last year, with several new videos added.

These have included patients' own accounts of their symptoms such as post-exertional malaise, cognitive impairment, pain and hypersensitivity. There are also new videos covering the management of severe ME/CFS, and the use of pacing as part of activity management.

The series is available to watch at dialogues-mecfs.co.uk, and is highly recommended as a valuable source of information for people with ME/CFS, carers, clinicians and anyone with an interest in the illness.



Finger prints

Two new studies are investigating potential **biomarkers for ME/CFS based on viral infections**

The emergence of so-called 'long COVID' has highlighted the potential long-term consequences of viral infection, with symptoms such as fatigue, muscle pain and brain fog lasting for months.

Of course, this is a familiar scenario to people with ME/CFS, many of whom identify a viral infection as the trigger for their illness.

So it is no surprise that significant research into ME/CFS has focused on the role of viral infections in the illness, including Epstein-Barr virus (EBV) and human endogenous retroviruses (HERVs). And these specific viruses form the basis of two new studies recently awarded funding by ME Research UK.

Epstein-Barr virus

First we'll look at the project from Dr Nuno Sepulveda at the London School of Hygiene & Tropical Medicine, who, in collaboration with Prof. Carmen Scheibenbogen at Charité Universitätmedizin Berlin, is investigating responses to EBV as a possible biomarker for ME/CFS.

Nearly all people are infected with EBV at some time in their lives. In most cases, the immune system takes care of the virus, leaving the individual with adaptive immunity – antibodies that can recognise and eliminate future EBV infections.

However, EBV can cause glandular fever in children and young adults, and has been asso-

"biomarkers able to discriminate people with ME/CFS would be a huge step forward"


Dr Nuno Sepúlveda

ciated with the development of autoimmune conditions such as rheumatoid arthritis and multiple sclerosis (i.e. diseases caused by an abnormal immune response).

EBV has also long been suggested as a trigger for ME/CFS, and Dr Sepulveda highlights the four main reasons for this:

1. Most humans are chronically infected with EBV.
2. The virus is already known to cause several diseases, including autoimmune conditions.
3. It produces proteins similar to ones that are found in the body.
4. People with ME/CFS are often found to have active EBV infections or antibody reactivity against EBV.

In previous experiments, Prof. Scheibenbogen and her team found that antibody responses against two EBV-derived proteins (antigens) in particular were increased in people with ME/CFS compared with healthy control subjects. These two antigens are similar to the human proteins, lactoperoxidase and thyroid peroxidase.

Potential biomarkers

Dr Sepulveda's group then took that data and analysed it further to identify fifteen to twenty antigens that were increased or decreased in ME/CFS patients compared with control subjects.

The results were used to develop a statistical model that could predict a diagnosis of ME/CFS based on the characteristic 'fingerprint' of antibody responses to those antigens. The model was particularly sensitive in identifying patients with an infectious trigger for their illness.

The investigators believe these findings are a very promising stage in the search for biomarkers for ME/CFS, so it is very important to test whether they can be confirmed in other groups of patients.

The aim of their new study is therefore to do just that – to evaluate the top fifteen EBV-derived antibody responses in samples from 100 people with ME/CFS, 50 healthy control subjects and 50 patients with multiple sclerosis, all obtained from the UK ME/CFS Biobank.

If the initial findings are confirmed, and these responses can be used as disease-specific biomarkers able to discriminate people with ME/CFS, that would be a huge and much-needed step forward in the diagnosis of this illness.

Prof. Elisa Oltra (left) and her team at the Catholic University of Valencia

Epigenetics

Our second new study involves epigenetics, which has become a promising field in ME research.

One tantalising prospect is that epigenetics may be involved in the link between HERVs and ME/CFS, and this is the area being investigated in the newly funded study by Prof. Elisa Oltra, Karen Gimenez-Orenga and their team at the Catholic University of Valencia in Spain.

Genetics is how a person's characteristics (including susceptibility to illnesses) are passed on from one generation to another via their genes. However, we now know that the genes we are born with simply provide a template for what is to come.

Epigenetics refers to the ways by which our body can turn genes on or off in a cell (their expression) and affect the cell's function. If we encounter a toxin, our cells can respond by changing which genes are expressed.

How might this be relevant to the possible link between HERVs and ME/CFS?

HERVs are a family of viruses contained within the human genome – that is, their DNA has become part of our DNA and is passed on from generation to generation. Despite making up 8% of our genome, most are generally thought to be dormant.

However, there is evidence that some HERVs may have a role in the development of diseases such as multiple sclerosis and diabetes. And HERVs have also been proposed as potential triggers of ME/CFS.

HERV activation

Prof. Oltra's hypothesis is that epigenetic changes can cause activation of HERVs present in our body, leading to an immune response and the resulting symptoms that are characteristic of ME/CFS.

She and Karen Gimenez-Orenga plan to identify HERVs that are over-expressed in 12 women with severe ME/CFS compared with a group of women with fibromyalgia.

The team will also look at the effects of activation of these ME-associated HERVs on nerve and muscle cells in laboratory conditions, to understand their potential impact on ME/CFS symptoms.

The results will then be validated in an extended group of 50 women with ME/CFS, 25 with fibromyalgia, and 25 healthy control subjects.

Prof. Oltra's hope is that these HERV 'fingerprints' could be used in the diagnosis of ME/CFS, or for patient subtyping. But their findings will also help to establish whether activation of HERVs could be at the root of the disease.

Furthermore, the cell model being developed could be a valuable tool in the future for assessing the effectiveness of potential treatments for ME/CFS.

Postcards from Nevada

In his latest postcard, **Cort Johnson** looks at some of the larger ME/CFS studies currently being conducted around the world

Size matters in research. All things considered, bigger is better – a lot better.

Studies can never analyse all people with a particular illness, of course. Including all 250,000 people with ME in the UK would produce really accurate results, but it would be uber-expensive and time-consuming.

It is far better, and more realistic, to study a representative sample and extrapolate those findings to the rest of the group. The problem is getting that representative sample.

Small studies are susceptible to something called 'sampling error' – where a sample inadvertently includes unrepresentative patients and then produces misleading results.

The rituximab saga presents a good, if painful, example of that. Three early rituximab studies (including a placebo-controlled and double-blinded study) produced excellent results. However, a large phase-3 trial subsequently failed to show any benefit. Despite the study authors warning that this outcome was possible, it was nevertheless a bitter disappointment.

Fibromyalgia recently suffered a similar setback when an updated version of pregabalin (which affects the transmission of pain) blasted through earlier trials, but then failed miserably during a 3,600-person worldwide clinical trial.

The rituximab and pregabalin sagas taught the ME


Cort Johnson

and fibromyalgia communities that size truly does matter in medical research.

The remedy is to have large, rigorously constructed studies. Funding woes have constrained the size of many ME studies, but the times they are changing.

DecodeME

The 20,000-person, £3.2-million DecodeME genome-wide association study (GWAS) dwarfs any other genetic study – indeed any other study – attempted in ME thus far.

Studies of this size are not just robust, they have legitimising and multiplying effects as well. The fact that a field can get its act together enough to produce such a large study says something important about it.

DecodeME is expected to identify dozens if not hundreds of genes that increase a person's risk of getting ME. Those genes will then provide clues about the molecules and cellular pathways at play in this illness.

Just what those are is anyone's guess at this point. Past GWASs have sometimes produced completely unexpected insights – novel genes that are so off the beaten path that one wonders how they would ever have been uncovered otherwise.

A GWAS in Crohn's disease, for instance, identified two mysterious gene variants which pointed to a process called autophagy that no one had suspected played a role. A recent review lauded the promise that autophagy drugs have for Crohn's Disease.

Researchers moved quickly with large-scale GWASs to identify risk factors for pneumonia and severe disease in COVID-19. One study identified thirteen genes that constituted 'druggable targets' – and over fifty drugs and compounds which might help.

We don't know what DecodeME will find. What we do know is that large-scale studies like this are foundational – they are a critical part of any disease field's infrastructure. Every disease needs one – and now we have one.

You + ME registry

Patient registries are another foundational element. They are complex and take a lot of work, and again say something about the maturity of a field. Solve ME's You + ME patient registry took years to develop.

There's something about big data that makes researchers' toes tingle with anticipation – and large patient registries provide a ton of data. They also provide the kind of data this disease really needs.

"Bigger is better in medical research"

Pharmaceutical companies love them because they tell them about the nitty gritty of a disease. Solve ME's Sadie Whittaker – the force behind the You + ME registry – knows that well. She saw first-hand how large patient registries transformed drug development in cancer.

If the ME community embraces it, the You + ME patient registry will be able to do the 'deep phenotyping' that provides the accurate descriptions of this disease that drug companies hunger for.

The You + ME registry already has a UK partner in DecodeME, and will be going global soon.

Small but comprehensive

Small but very comprehensive exploratory studies present another way in which size is making a difference. In this scenario, small groups of patients are put through incredibly comprehensive testing regimens in the hope that they will provide leads for future research.

These studies are so expensive and so time-consuming that the results must count, meaning that researchers put a premium on getting as representative a sample of patients as possible. For instance, more than one thousand tests were done per patient in the Open Medicine Foundation's small but incredibly comprehensive Severe ME/CFS study at the Stanford Research Center.

Avindra Nath noted that his NIH-funded, 100-person, two-week plus, $5-million, intensive in-hospital study was the most comprehensive assessment of any disease he'd ever seen. Nath was so concerned about getting the right patients that he performed a study within a study. Not only did he set up a separate doctor's panel to assess the potential participants, but he had each patient go through a week of testing before they were admitted to the full study.

These small but large studies are precious because they cover so much ground, will likely lead to new insights, and come from trusted researchers.

The future

Strap your boots on, though – we haven't have seen anything yet. A tsunami of funding – over a billion dollars' worth – is about to hit the long COVID field.

You want big monitoring studies? One Duke University study hopes to follow 100,000 COVID-19 patients over time, while another study took a supercomputer to its limit for a week to study samples from 17,000 COVID-19 patients.

These studies – which dwarf anything that's been done in ME/CFS – began before the billion-dollar-plus award for long COVID funding was announced in the USA.

Given that long COVID appears at this point to be a kissing cousin of ME, expect ME patients to show up in some nice, big, complex studies – which brings us back to the You + ME patient registry. Long COVID researchers are going to need people with ME to be in their studies, and finding patients is what patient registries do best. Enrolling in the You + ME registry when it goes global is one easy way to help move the science further.

Bigger is better in medical research – and bigger is coming in a big way for ME and long COVID. The future has never looked brighter.

Research bites

Our round-up of recent research from around the world

MicroRNA – the factory foreman

Nepotchatykh et al., Scientific Reports, 2020

While DNA contains the instructions that tell our cells how to make proteins, it's RNA that does all the actual hard work. RNA is essentially a single-stranded copy of DNA, and its three main forms act as the blueprint, factory and labour for protein manufacture within the cell. However, there are several other kinds of RNA. These include microRNA, which has a regulatory role and can therefore control the production of proteins. Abnormalities in microRNAs are known to be involved in the development of cancer and other diseases, and researchers in Canada have been investigating whether microRNA may also play a role in the development of ME/CFS.

The study involved measuring circulating microRNA expression in blood samples from people with severe ME/CFS, both before and after they were asked to undergo a stress challenge (involving compression of the arm) to induce post-exertional malaise (PEM). After this challenge, the investigators found changes in the expression of eleven microRNAs, most of which are known to be involved in the regulation of immunity. Furthermore, these changes could be used to distinguish ME/CFS patients from control subjects with a high accuracy. However, this technique's value as a diagnostic test may be limited by the willingness of patients to undergo a test that induces PEM.

ME/CFS following COVID-19

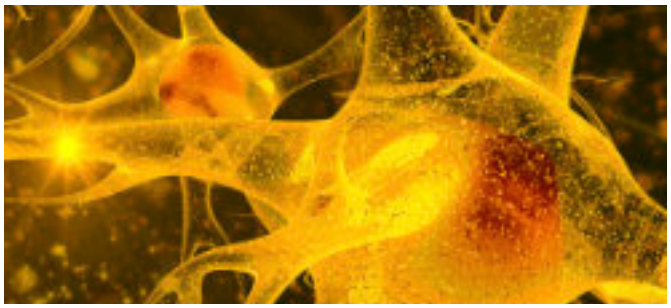
Kedor et al., medRxiv, 2021

In line with our feature on the role of viral infection in ME/CFS, one hot topic in recent months is whether infection with the SARS-CoV-2 virus is associated with an increased risk of developing ME/CFS. Published for now as a non-reviewed, preprint manuscript, researchers in Berlin have reported on 42 patients with COVID-19 who had persistent, moderate-to-severe fatigue six months after their acute illness. Significantly, almost half of these individuals fulfilled the 2003 Canadian Consensus Criteria for a diagnosis of ME/CFS.

Papillomavirus vaccine

Hviid et al., BMJ, 2020

The human papillomavirus (HPV) vaccine is offered to children worldwide for the prevention of cancers caused by the virus. However, media-fuelled concerns suggest that the vaccine might cause autonomic-dysfunction conditions such as ME/CFS, CRPS and POTS. There is actually no evidence of such a link, and researchers in Denmark confirmed this recently by following up nearly 1.4 million females, in whom the risk of developing an autonomic-dysfunction condition was not raised in the year following HPV vaccination.



Tarlov cysts

Hulens et al., Pain Medicine, 2020

Tarlov cysts are fluid-filled sacs formed on nerves at the base of the spine, which can press on the nerves and cause debilitating pain and abnormal sensation. Patients with these cysts are often initially diagnosed with ME/CFS or fibromyalgia, and researchers in Belgium report that the prevalence of Tarlov cysts is three times higher in these patient groups than in the general population. This raises the possibility of a link between the presence of Tarlov cysts and these conditions, perhaps relating to an increase in cerebrospinal-fluid pressure causing irritation to the nerves.

Who benefits from Ampligen?

Strayer et al., PLOS ONE, 2020

Rintatolimod (better known as Ampligen) has been around for decades as a potential treatment for ME/CFS, but a lack of evidence means it has never been granted FDA approval. While some patients improve on Ampligen, many do not. Researchers in the USA (who, it should be noted, work for the pharmaceutical company in question) recently reported disease duration as a possible factor influencing the efficacy of this drug. Those with ME/CFS for less than eight years were more likely to show improvements on an exercise treadmill tolerance test after Ampligen treatment.

Friends united

Recent fundraising activities by our supporters. To support ME Research UK and raise funds for ME research, please visit our website for ideas.

Thank you!

Although the pandemic has severely limited the fundraising that people can do for their favourite charity, our supporters are still finding ways to help. We are so grateful to every one of you. For some more ideas of how to raise funds in the current climate, see over the page.

To the Western Wall

The Western Wall in the Old City of Jerusalem is one of the most-recognised religious sites in the world, and will make a splendid destination for Miriam Simmonds, her husband Mendy and their dog as they complete a 25-kilometre trek in aid of ME Research UK. Miriam and family are making the trip on 21 May 2021, with the hope that their campaign will raise funds for ME research as well as "much needed awareness of ME/CFS that affects so many people". You can donate via Miriam's JustGiving page at bit.ly/39QASH3.
חוטב לויט דל היהיש

Blue Sunday

Anna Redshaw started the Blue Sunday tea party for ME as a way of celebrating her birthday as she was too unwell due to ME. Family and friends joined in a virtual party with tea and cake, and the idea has now become an ME community event, with friends and family gathering together online and in real life to connect with loved ones, and to raise money and spread awareness. Thank you, Anna. You can donate via bit.ly/3p17br9.

01

02

03

01 Fiona and Raymond Williams warm up for their 100-km workout

02 Blue Sunday tea party organiser **Anna Redshaw**

03 Anyone can join in the **Walk for ME**

Not the John Muir Way

Last year, Fiona and Raymond Williams had planned to walk the 100 kilometres of the John Muir Way in memory of their youngest son, Andrew, who was severely affected with ME and sadly died in 2019. However, COVID-19 put paid to that and they had to think again. So Fiona and Raymond decided to complete the distance at home by doing four five-kilometre YouTube workouts every day for five days. "Lots of our friends and family joined in at home at various times to support us," says Fiona. "We were pleased that most commented there was no way they could have done more than one or two a day, and certainly not for five days!" The new plan meant that many people shared their page and videos, and awareness of ME was spread further than they could have hoped. Many thanks to Fiona and Raymond. What a great achievement, and a marvellous sum raised for ME Research UK.

Walk for ME

Luke Remnant explains more about the campaign: "We started Walk for ME in 2013 hoping that family and friends of people with ME could do sponsored walks on their behalf, and to raise awareness of ME. We have been overwhelmed with the response, and these events have raised more than £160,000. We support ME Research UK every year as they are such a fantastic charity with a proven track record of investing into the causes of ME."

FUNDRAISING
IDEAS FOR LOCKDOWN

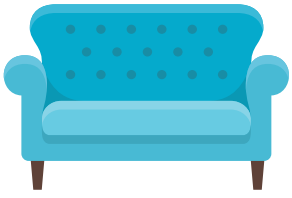
Sell something you've made to your friends

Hold a birthday fundraiser on Facebook

Organise a quiz for your friends on Zoom

Give up something you love for a month

Throw a virtual tea party for friends & family



Do a sponsored event from your own home

Standing Order Form

To support our work, please consider setting up a standing order by completing this form and sending it to: **ME Research UK, The Gateway, North Methven Street, Perth, PH1 5PP**

☐ Please tick this box to indicate you are happy for us to collect and store your personal information, in accordance with our Privacy Policy at meresearch.org.uk.

Name of account holder(s)

Instruction to your Bank or Building Society

To the manager, Please arrange to debit my/our account with the amount detailed below, once every month until further notice.

Account number

Branch sort code

Address and postcode

Debit amount (£)

Payment date each month

Telephone number

Date of first payment

Name of Bank or Building Society

Pay to: Virgin Money, 158/162 High St, Perth, PH1 5PQ, UK, Account: ME Research UK, a/c no: 50419466, Branch code: 82-67-09

Branch address and postcode

☐ **Tick** if you would like us to treat this, any future donations to ME Research UK (SC036942), and all payments in the previous 4 years, as Gift Aid donations, meaning your donation can increase in value by a quarter at no extra cost to you. You confirm that you are a UK taxpayer and understand that if you pay less Income Tax and/or Capital Gains Tax than the amount of Gift Aid claimed on all your donations in that tax year it is your responsibility to pay any difference. Please notify us if you wish to cancel this declaration, change your name or home address, or no longer pay sufficient tax on your income and/or capital gains. If you pay Income Tax at the higher or additional rate and want to receive the additional tax relief due to you, you must include all your Gift Aid donations on your Self-Assessment tax return or ask HM Revenue and Customs to adjust your tax code.

Signature

Date