NEWS OF THE ME RESEARCH YOU ARE HELPING TO FUND

breakthrough

The Gene Issue

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ME RESEARCH UK

Welcome

Breakthrough magazine is published by ME Research UK, a Scottish Charitable Incorporated Organisation that funds research into Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (also known as ME/CFS). The charity has an international remit, and its principal aim is to commission and fund high-quality scientific (biomedical) investigation into the causes, consequences and treatment of ME/CFS. It also aims to energise ME research by identifying potentially important areas for future biomedical research, producing high quality professional reviews and reports, and presenting research at meetings and conferences. *Breakthrough* is an open access publication and, with the exception of images and illustrations, the content may be reproduced free of charge, subject to the terms and conditions found at:

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

This issue

In the spotlight

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

Prof. Nancy Klimas (left) from the Institute for Neuro Immune Medicine in Florida

Thinking globally

Setting up a genetic database for ME/CFS

Prof. Nancy Klimas is Director of the Institute for Neuro Immune Medicine at Nova Southeastern University, and an old friend of ME Research UK. Nancy now leads a large programme of research into ME/CFS and other neuro-immune disorders, and has just started recruiting for a one-of-a-kind study – creating a database of genetic data from ME/CFS patients and healthy controls across the world.

Taking part is simple. Volunteers will need a computer with internet access and an e-mail account, and agree to have their genes mapped using genetic testing websites. The raw genetic data will then be fed into the ME/CFS Genetic Database, and participants will be asked to complete regular online surveys.

All communications are by secure e-mail server, and no travel is necessary. Further information can be found on the Institute's website: nova.edu/nim/research/mecfs-genes.

More and more people across the world (not just ME/CFS patients) are having genetic testing done, and a large number of publicly available testing sites now offer this service (for a fee, of course). The insight of Nancy and her team is that the individual results from ME/CFS patients can be collected together into one database so that the information contained in thousands of results can ultimately be analysed and compared with other diseases.

London Marathon

Will you run for us?

Virgin Money London Marathon is the largest annual fundraising event on the planet, and ME Research UK is offering one lucky supporter the opportunity to take part.

We've been allocated a guaranteed place for the race on 23rd April 2017, but it needs to go to the person best placed to raise both awareness and funds. If you wish to take part, you will need to complete and return an application form (from our website). If you prefer, call us and we'll e-mail you a copy.

The successful applicant will be asked for a £100 registration fee – to offset part of the cost of the place we've secured – and to aim to raise £1,500. Guaranteed places are highly prized, so please get your application in early if you want to take up this great opportunity to raise money and awareness – and have some fun too!

Focus on funding
Free fundraising

Are there really ways to help fund our research that don't cost anything? Not a single penny? Nothing? Well, we've found two.

ME Research UK has teamed up with **Amazon** and **easyfundraising** to allow our friends to support us as they shop – very useful to know, particularly as Christmas is not far away.

If you connect to Amazon via the link on our website, Amazon will make a donation to ME Research UK, at no extra cost to you. The amount the charity receives will depend on what you spend and the product purchased. So the next time you order a book, DVD or one of a myriad of goods, please remember to click through to Amazon from **meresearch.org.uk**.

Easyfundraising is a convenient way to access a virtual shopping mall filled with the UK's largest and best online outlets. There are over 2,700 top retailers available, including John Lewis, M&S, Tesco Direct and Sainsbury's. Major insurance companies, travel agents and mobile phone companies have signed up too. The site also offers amazing and exclusive deals. In fact, most of your online shopping could be done through easyfundraising. Just register online at **easyfundraising.co.uk**, choose ME Research UK as your good cause, and start shopping as usual.

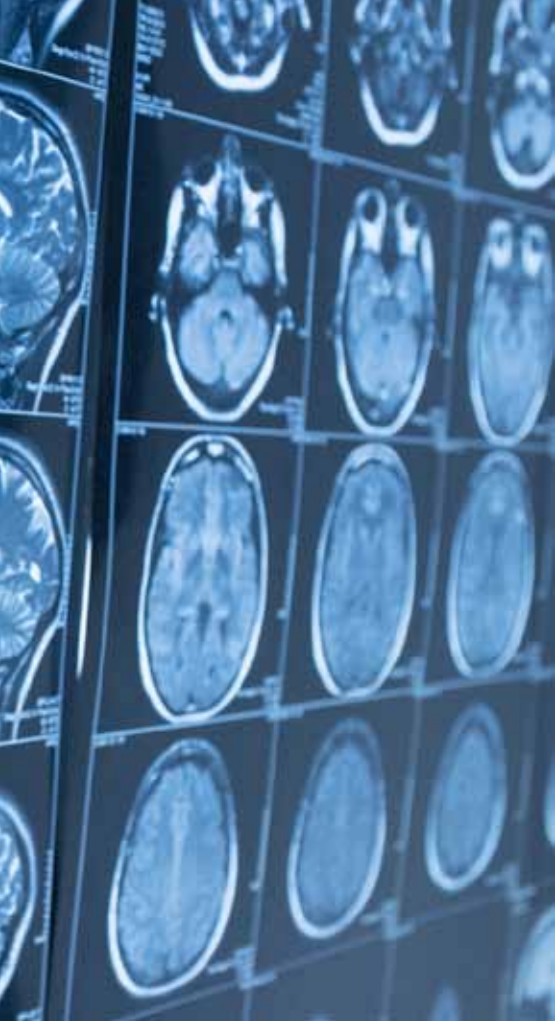
As time goes by
Changes in brain white matter over 6 years

Most research studies are cross-sectional, a snap-shot at a particular time. These studies have their uses, but they don't tell us about long-term changes, which can be considerable if there is continuing disease.

One of the very few longitudinal studies in ME/CFS was recently reported by researchers at Griffith University, Australia. The patients had originally taken part in a study in 2011 which found a reduction in white matter in the midbrain. After approximately 6 years, 15 of the original ME/CFS patients and 10 healthy controls agreed to participate in a repeat evaluation, using the same MRI scanner to measure any brain changes.

Overall, there were no significant differences between the patients and the controls in the total volume of brain grey matter (which contains the bodies of nerve cells that help process information) or white matter (mainly nerve fibres). It was when the researchers looked at two specific areas that they noticed pronounced changes over time. In ME/CFS patients, but not in the controls, there was a decrease in the volume of white matter in the left inferior fronto-occipital fasciculus (IFOF) and/or the arcuate fasciculus. There were also corresponding changes in grey and white matter volumes in neighbouring brain regions, and the brain volume changes correlated with patients' symptom scores.

The IFOF is a bundle of nerve fibres that passes backwards from the frontal lobe of the brain, its fibres radiating out in a fan-like pattern. It represents one of the many 'long association fibres' that unite different parts of the same hemisphere of the brain. It's thought that the IFOF connects attention, language processing and working memory networks, so its shrinkage over time may be associated with the memory, concentration or attention problems and visual deficits known to occur in ME/CFS. Sim-



"Abnormal connections among brain regions and reductions in white matter that continue as the illness progresses"

ilarly, the arcuate fasciculus connects two areas that are important for language, and abnormalities in this structure were reported recently in ME/CFS patients by US researchers at Stanford University.

The Australian researchers concluded that ME/CFS is a chronic illness with abnormal connections among brain regions and reductions in white matter that continue as the illness progresses. This is in line with the findings of a recent review suggesting that structural changes in the brain and alterations in connectivity are a feature of the disease.

Conference season

Autumn 2016 will see two biomedical conferences: the UK ME/CFS Research Collaborative (CMRC) Conference 28–29 September in Newcastle, and the IACFS/ME Research and Clinical Conference in Florida in October.

As usual ME Research UK will be at the UK conference. The full programme is still being put together, but the confirmed speakers – who have all received funding from ME Research UK in the past – include Dr David Patrick (University of British Columbia, Canada), Dr Sarah Knight (Murdoch Childrens Research Institute, Australia) and Prof. David Jones (Newcastle University).

The full conference is primarily for researchers, but ME patients, their families, or members of the general public are welcome to become associate members of the CMRC to attend the Associate Member session which brings together researchers and patients. We hope to see you there.

What remains unknown is why the abnormalities in brain white matter are occuring. It may be, as the authors suggest, that a gradual and chronic reduction of blood flow (hypoperfusion) to the brain contributes to continuing shrinkage of white matter, with a corresponding increase in regional grey matter as the brain tries to compensate for the loss. However, white matter is thought to be highly susceptible to inflammation, and its loss could well be the result of chronic oxidative stress (see page 15) or an ongoing infectious process.

One step at a time

Walking and coordination problems in ME/CFS

Lots of ME/CFS patients have difficulties standing, but they can also have problems walking. In fact, one of our previously funded investigations at Glasgow Caledonian University found that the energy demands of walking were greater than normal for people with the illness.

For some years, researchers at Antwerp University Hospital have been taking an in-depth look at the physical capabilities of people with ME/CFS. Two of their most recent findings are that patients' upper limb muscles recover more slowly from exercise, and that they have weaker muscles in the trunk and arms.

Continuing their programme of work, the Belgian researchers have now examined 'automaticity' in women with ME/CFS. Automaticity involves being able do things automatically, without the mind being occupied with more basic tasks. A good example is the ability to walk and speak at the same time; famously, Julius Caesar was able to ride a horse, hold a conversation and read a book at the same time. Automaticity while walking (gait automaticity) is particularly important, though it is no easy task. A variety of factors can interfere with it, including central nervous system damage and vision problems, and that's why gait automaticity is used to indicate frailty and is a good predictor of falls among the frail elderly.

The Belgian researchers' findings were very revealing. When starting to walk, only 3% of non-disabled controls looked down at the ground first, compared with 24% of patients. After closing their eyes and being asked a question, 56% of the patients stopped walking compared with only 5% of controls. The researchers also observed deterioration in walking during the test, whether slowing down or extending the arms to keep balance, losing direction or changing pace dramatically. While walking with closed eyes, 38% of patients had either a severe deterioration in their gait or had stopped walking. The fact that ME/CFS patients find it a challenge to multi-task when walking chimes with findings in patients with other chronic illnesses such as stroke or Parkinson's disease.

Many people with ME/CFS will not be surprised by these results – after all, they have lived for many years with the cognitive impairment and neurological dysfunction that underlie problems with automaticity. And, in fact, expert clinicians have long recognised these symptoms in their patients; as the Canadian Consensus Document said in 2003: "Ataxia, muscle weakness and fasciculations [twitches], loss of balance and clumsiness commonly occur". Yet, these impairments in basic day-to-day functioning in people with ME/CFS remain unknown to scientists, GPs and other healthcare professionals. They may, however, have clinical or diagnostic value, and should not be ignored.

Regular gifts

The research we report in *Breakthrough* is made possible by donations large and small. Regular giving allows us to plan for the future because we know, day in and day out, that there is a steady stream of income upon which we can rely.

The easiest way to give regularly is by standing order. It's simple to set up, and your donations are collected automatically from your bank. Please consider completing the standing order form at the back of *Breakthrough* (or via our website) to begin donating quickly, easily and safely.

You can make a difference this month and every month. Your regular gift will allow us to fund more vital research and continue providing information on ME/CFS to patients and professionals in the years to come.

Join me for tea

Eleanor Whitby, our new Marketing Director, invites you to host a tea party in ME Awareness Week

As the newest member of the ME Research UK team, I thought I'd introduce myself to all our friends and supporters. My role is to energise the fundraising and event side of the charity's activities, and over the months to come I'll be unveiling a range of initiatives. In fact, I'd love to hear from you with your own ideas, so please do contact me at any time.

ME Awareness Week is the time when we all try to do something to raise awareness of ME to our family and friends and the wider community – it's the time when we fight back. In 2007, it runs from the 11th to the 17th of May, and I'm recruiting a buzzing group of people to join me in our Cup of Tea for ME campaign. The idea is to hold a tea party any time in that week, drink a cup of tea (or coffee), have a chat, eat some cake and ask your friends, family and work colleagues to donate a small amount to our research fund. Afterwards, you can send us some photos which we'll publish on Facebook or in *Breakthrough* magazine.

We have a special Cup of Tea for ME page in the fundraising section of our website with lots of ideas about how you can have a successful day – from where to hold it (home or office), things you'll need (teapots, cake-stand, etc.), and a few simple home-bake recipes brought together by our Founding Ambassador Betty McRae. We've also created some simple tickets and posters that you can personalise and print out. And we can send you leaflets and back issues of Breakthrough magazines to help raise awareness.

I hope you'll join me in hosting an event, and to register your Cup of Tea for ME event please contact me at the number or email below.

Eleanor Whitby, Marketing Director
meruk.marketing@pkavs.org.uk
07921 311 743
www.meresearch.org.uk/fundraising/tea-for-me/

mixed msesgaes

Micro RNAs involved in immunity may have a role as biomarkers in ME/CFS, according to a study from the University of London

All living cells contain ribonucleic acid (RNA) which controls manufacture of the proteins needed for all essential functions of life, from hormones to immunological signalling molecules. It comes in different forms, and the best known is messenger RNA which passes information from our DNA to the sites where proteins are actually made. In recent years, however, another fascinating form has been identified: micro RNA or miRNA. While other types of RNA have a positive role in the creation of proteins, miRNAs tend to prevent things happening – they 'silence' messenger RNA molecules by cleaving them, destabilising them, or interfering with their work.

A lot of effort has gone into discovering whether miRNAs are involved in human disease, and many different miRNA molecules have been linked with different diseases in the past few years. We now know that they are involved in regulating blood cell formation and dampening down immunological responses, and that they also have a role in constraining or subduing the workings of many, if not most, biochemical pathways in the body.

Dr Robert Petty and Prof. Jonathan Kerr (Queen Mary University of London, and St George's University of London & Universidad del Rosario, Colombia) recently published a report in the journal *PlosOne* on the role of miRNAs in ME/CFS. The work was part of a programme of research funded over many years by ME Research UK and the now closed CFS Research Foundation, focussing on developing a genetic 'signature' for the illness (see the box on page 11).

miRNA expression

The team examined miRNA expression in mononuclear white blood cells (T-cells, B-cells, natural killer cells and monocytes involved in defence and im-

munity), and there were three stages to the experimental work. The first step was to determine whether miRNA expression (i.e. its activity) was different between one set of 15 ME/CFS patients and 30 healthy people.

Next, the researchers undertook a replication stage, attempting to repeat their findings in another independent set of 20 ME/CFS patients and 20 controls, and to identify the particular types of mononuclear cells involved. The final step involved a separate experiment to see if the ME/CFS-associated miRNAs could be linked with particular genes by 'transfecting' them into primary natural killer cells and observing which genes were activated.

Potential biomarkers

In essence, the analysis identified 'differential expression' or activation of 34 miRNAs, all of which were up-regulated. Using quantitative PCR to validate the findings, expression changes were confirmed in four of these miRNAs which, in addition, were found to be suitable for further investigation as potential biomarkers for ME/CFS. The two miRNAs which showed the greatest over-expression were hsa-miR-99b and hsa-miR-330-3p; both are know to be important in other illnesses. For instance, hsa-miR-99b has a distinctive pattern of miRNA expression in primary muscular disorders, while hsa-miR-330 miRNA signatures are associated with certain blood cell tumours.

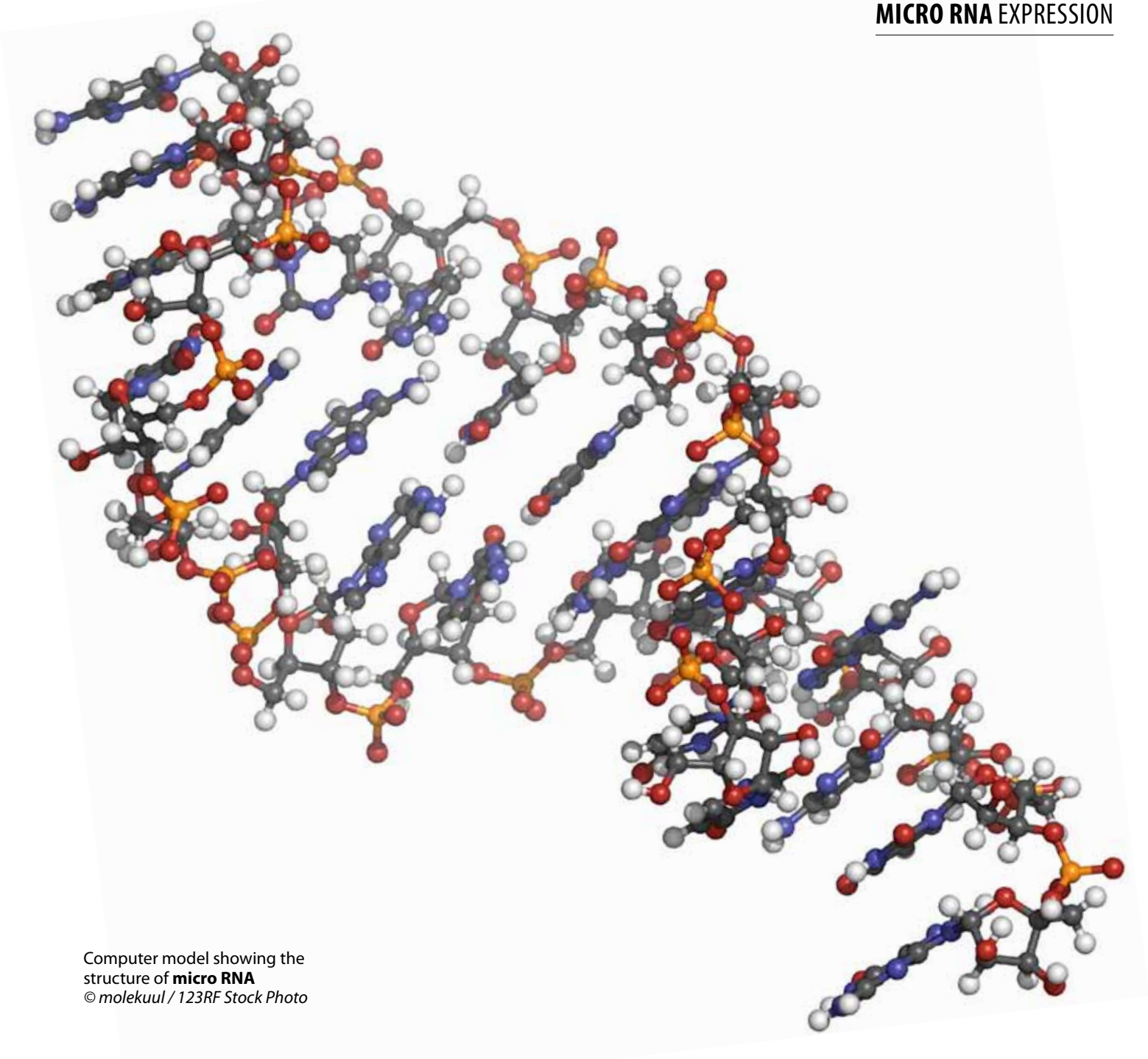
At the replication analysis, changes in miRNA expression were found in the four types of white blood cells, with the most significant abnormalities occurring in natural killer cells. There were also changes in the expression of genes involved in the activation of cellular processes and immunity. The researchers concluded that the natural killer cells were 'activated' but with reduced functioning, consistent with what we know already about the low activity of these cells in ME/CFS.

Immune abnormalities

Overall, the researchers found that four miRNAs expressed in mononuclear white blood cells had potential as biomarkers in ME/CFS, particularly hsa-miR-99b and hsa-miR-330-3p which may also be involved in the natural killer cell dysfunction characteristic of the illness. As the authors point out, the results are particularly interesting since the messenger RNAs regulated by hsa-miR-99b and hsa-miR-330-3p have a large degree of overlap with the messenger RNAs found to be upregulated in previous work at St George's, supporting the view that abnormalities in the innate immune system are involved in the development of ME/CFS.

"Four micro RNAs expressed in mononuclear white blood cells had potential as biomarkers in ME/CFS"

Because miRNAs are 'protected' and stable in a number of body fluids and tissues, there is now an enormous quantity of literature on their use as possible biomarkers, mainly in cancer but also in other diseases such as epilepsy, malarial infection and multiple sclerosis. In all of these illnesses, there is a need for non-invasive, easily detected, sensitive biomarkers, and ME/CFS is no different. For that reason, these interesting findings deserve to be taken much further in larger validation studies, as well as investigations to clarify the particular role played by immune system abnormalities in the illness. ●



Computer model showing the structure of **micro RNA**
© molekuul / 123RF Stock Photo

Gene research at St George's University of London

Prof. Jonathan Kerr's group at St George's University of London was one of the most active in defining the molecular basis of ME/CFS.

Its research programme got underway in 2003, focussing on gene expression and immune system impairments. Other studies targeted protein biomarkers (the backbone of any diagnostic test), and gene regulation abnormalities in Gulf War illness and ME/CFS.

In 2008, the group announced its identification of a putative gene 'signature' for ME/CFS, consisting of 88 human genes. A subsequent blinded study showed the 'signature' to be less robust across populations, though it was able to successfully classify roughly two-thirds of both ME/CFS and healthy samples.

Other investigations focussed on single nucleotide polymorphisms (SNPs) – small genetic changes in DNA that vary between individuals and which may be useful for diagnosis. The group found 21 SNPs that vary in frequency between ME/CFS patients, people with depression and healthy individuals.

Although the group is no longer active at St George's University of London, its members are still publishing the results of their work, and Prof. Kerr is now based at the Del Rosario University in Bogota, Colombia.

lighting up your genes

Research in Canada using cutting-edge technology to investigate **genetic changes during exercise** in ME/CFS patients

One of the hallmarks of ME/CFS is that the symptoms are made worse by (even quite mild) exercise, up to 48 hours afterwards. In fact, the 2007 NICE Clinical Guideline requires 'post-exertional' symptoms (delayed, with slow recovery over several days) for a diagnosis. This is why various research groups have tried to measure physiological changes after exercise, finding differences in immune characteristics and increased oxidative stress in ME/CFS patients compared with healthy people.

Exercise involves an increase in gene activity to produce many of the substances needed for movement. This process is called 'gene expression', and measuring gene expression can be a sensitive way of assessing the body's global response to the demands of exercise. To date, there have been a number of these investigations in ME/CFS patients, with some evidence of post-exercise increases in immune cell gene expression (specifically in interleukin-10 and Toll-like receptor genes). However, these studies have tended to focus on pathways relevant to the immune system, and none have used the more comprehensive high-throughput RNA sequencing approaches developed recently. Also, very few have followed measurements through from the flare-up of symptoms to the recovery phase.

Next generation gene sequencing

Dr David Patrick and colleagues at the University of British Columbia in Vancouver, Canada are studying post-exercise fatigue and malaise in ME/CFS patients using newly available gene sequencing technologies along with standardized exercise testing, which allows objective categorisation of patients according to their response to exercise.

"RNA sequencing allows a much deeper probe of gene expression than previously possible"

Dr David Patrick of the University of British Columbia, Vancouver, Canada

Their use of next generation sequencing, including RNA sequencing (see below), allows a much deeper probe of gene expression (especially as it relates to immune signalling after exercise) than has previously been possible. They hope to identify specific patterns or responses that might explain the prolonged and debilitating symptoms of fatigue.

Exercise tests

The study will involve 15 women with ME/CFS and 15 healthy controls. Each person will undergo two maximal cardiopulmonary exercise tests 24 hours apart, with ECG monitoring and pulse oximetry. Questionnaires on fatigue, symptoms and time to recovery will be administered before and immediately following each test, and again 3 and 7 days later. Blood samples will also be collected, from which total RNA will be extracted to identify genes that are expressed differently before and after exercise. These genes will then be validated by real-time polymerase chain reaction analyses.

Dr Patrick obtained funding from the National Institutes of Health in the USA for most of the work in this investigation, involving RNA sequencing of samples collected before exercise on the first and second days. In addition, ME Research UK has awarded funding to allow him to undertake further measurements of mRNA expression before and after exercise on days 3 and 7, to understand better what happens to ME/CFS patients during the flare up in symptoms following exertion. ●

In more depth
What is RNA sequencing?

Ribonucleic acid (RNA) molecules are found in all living cells, where they have a crucial role in transmitting genetic information and manufacturing the many proteins needed to keep the body functioning.

RNA sequencing is a very new technique that uses 'next-generation sequencing' to estimate the amount of RNA in a biological sample at any particular time. It allows researchers to count the number of RNAs made in each cell (which can be billions) and it can be used to analyse RNA activity dynamically, even while change is occurring.

Clinically, its major use is in identifying the different types of RNA molecules in a sample, and telling whether these have been modified – both are important indicators of how cells are functioning.

At present, researchers in the USA are using RNA sequencing to find new and low-frequency RNAs associated with disease processes such as oral cancer or Alzheimer's disease. The technique is even being used to identify genes actively expressed in complex bacterial communities such as those in the human gut.

stress relief

More new research exploring **oxidative stress and the role of Nrf2**

Over the past decade, ME Research UK-funded researchers at the University of Dundee have uncovered a range of biological abnormalities in ME/CFS, including high levels of apoptotic (dying) white blood cells and increased arterial stiffness. Their main finding has been that people with ME/CFS have abnormally high levels of oxidative stress, which can harm blood vessels and muscles, and increase the risk of cardiovascular disease.

It is important to discover the origin of the free radical molecules causing the oxidative stress, so that ways of counteracting them can be developed. For this reason, ME Research UK has given further funding to Dr Faisel Khan's research team in Dundee to investigate the role of nuclear factor erythroid-derived 2 (Nrf2). This is an extremely important regulatory protein in the body, and is now believed to be a master activator of the body's natural defence against oxidative stress. When free radicals are produced, Nrf2 is activated and stimulates the body's antioxidant pathways providing a buffer against oxidative stress.

Low Nrf2 activity?

The researchers' aims are to test whether Nrf2 activity is low (in quantity and in gene expression) in blood samples from ME/CFS patients, and whether Nrf2 levels are related to levels of oxidative stress. Importantly, the team will also examine whether the Nrf2 antioxidant system of ME/CFS patients can be activated by certain foodstuffs and by some therapeutic drugs. At present, several drugs that stimulate the Nrf2 pathway are being assessed as treatments for other diseases, including multiple sclerosis in which oxidative stress is involved, but this is the first time ME/CFS patients have been studied.

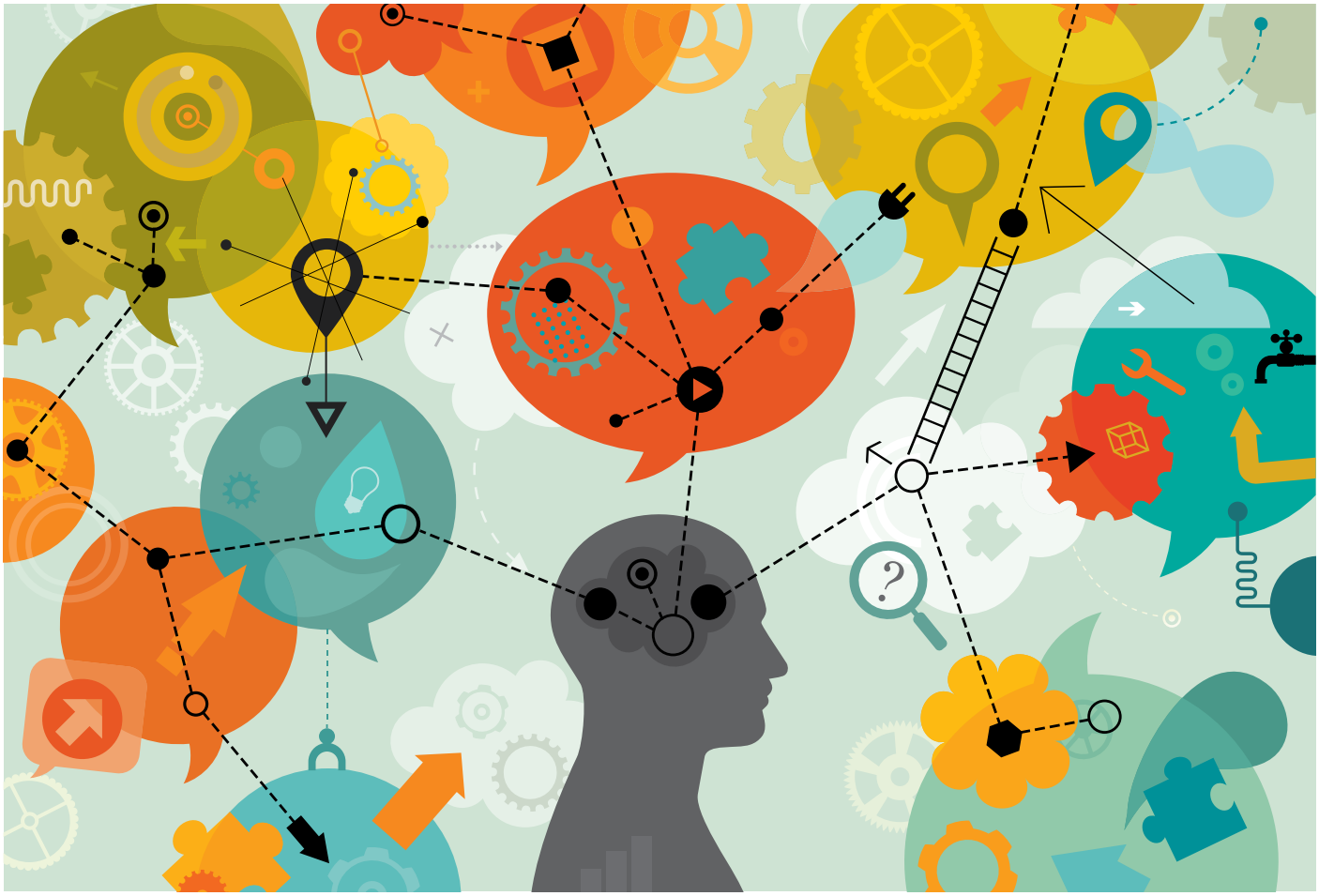
Dr Faisel Khan from the University of Dundee

During the 18-month investigation, blood samples will be taken from 40 ME/CFS patients attending the unit headed by Prof. Julia Newton and Prof. Fai Ng in Newcastle, and from age and sex-matched control subjects recruited from the general population. The samples will be transported to the Vascular and Inflammatory Diseases Research Unit at the University of Dundee where a range of biochemical assays will be performed to measure oxidative stress and Nrf2 protein levels, as well as the activity of genes regulated by Nrf2. An important part of the experiment is to examine whether Nrf2-regulated genes can be activated in white blood cells by foodstuffs and/or therapeutic drugs, and whether oxidative stress is affected. So the researchers will treat white blood cells from patients and controls with various doses of dietary compounds that activate Nrf2, and with some medications.

If low Nrf2 levels are found to play a central role in the increased oxidative stress found in ME/CFS patients, stimulation of Nrf2 could become the target of further research. The findings may also have broader implications for studies of Nrf2-targeted treatments in other conditions characterised by elevated oxidative stress, such as cancer, diabetes and liver disease. ●

Research bites

Our round-up of recent research from around the world



Mapping the brain

Boissoneault et al., Magnetic Resonance Imaging, 2016

Very sensitive methods are needed to measure the activity of the living brain, and one of these is called arterial spin labelling (ASL). This technique uses magnetic resonance imaging to measure blood flow and map functional connectivity, which refers to the relative patterns of activation in different regions of the brain at any particular time.

Problems with memory, attention span and reaction time are common in ME/CFS, so researchers in Florida were awarded funding from the National Institutes of Health in the USA to explore brain functional connectivity in the illness using ASL. The team found differences between ME/CFS patients and healthy control subjects in activation patterns in different regions of the brain. The patients had greater functional connectivity than did the controls in 5 of 21 regions (including the anterior cingulate cortex), but less connectivity in 4 of 21 regions (including the left parahippocampal gyrus). The researchers point out that brain regions, such as the parahippocampal gyrus, where activity is decreased are those involved in memory retrieval and storage. They suggest that, overall, ME/CFS patients have abnormal connectivity patterns linked to neurocognitive problems and to mood or cognitive disturbances.

Research on functional connectivity is still in its infancy, of course, so it is not yet possible to compare these results with findings in other diseases, but it seems that brain network integrity declines with age, and that the decline can be faster in chronic conditions.

Human placental extract

Park et al., Biological and Pharmaceutical Bulletin, 2016

In traditional Chinese medicine, human placental extract (HPE) derived from full-term placentas is used to treat various illnesses. In an investigation from Korea, 40 ME/CFS patients and 38 people with chronic fatigue alone were given commercially available HPE manufactured by GCJBP Corporation of Korea (which funded the study). HPE or normal saline was injected under the skin three times a week for 6 weeks. Overall, fatigue was reduced to a greater extent (albeit modestly, by around 10%) after HPE than after saline in the ME/CFS group but not in the chronic fatigue group. Placental products are classed as unusual alternative therapies in the West, of course, and none are licensed by regulatory authorities.

Recovery from biotoxin exposure

Gunn et al., American Journal of Care Reports, 2016

In February 2014, a 25-year-old man in Texas was diagnosed with chronic ulcerative colitis. Over the next 6 months, his health deteriorated and he developed the multisystem symptoms of ME/CFS, including post-exertional malaise and pain. However, a urine test for mycotoxin was positive, and examination of air filters from his water-damaged house identified *Stachybotrys chartarum*, a toxic 'black mold'. Testing eventually revealed that he was genetically susceptible to chronic immune disturbance, and he recovered after moving house and starting immune treatment. Today, he is off medication and back to work, and his case shows how easy it is to mistake ME/CFS for another treatable disease unless additional testing is done.

Mitochondrial DNA mutations

Billing-Ross et al., Journal of Translational Medicine, 2016

Mitochondria produce energy, and mutations in their DNA (mtDNA) can have very serious consequences. As some symptoms of ME/CFS could be due to mitochondrial abnormalities, investigators at Cornell University examined mtDNA from 193 ME/CFS patients and 196 control subjects stored in the CFI Biobank. Fascinatingly, disease-causing mtDNA mutations were found in none of the ME/CFS patients, though one mutation was found in the controls. Also, the incidence of heteroplasmy (more than one type of mtDNA), which can also have detrimental effects, was low. While these findings will be welcome news to many patients, mitochondrial genes may still play a part in affecting particular symptoms and their severity.

Accessing healthcare services

Hansen & Lain, BMJ Open, 2016

How do people with ME/CFS feel about the healthcare they receive? Oddly enough, very few people had ever asked them until a group from The Arctic University of Norway surveyed 431 women members of The Norwegian ME Association. Most of the women (62%) had lived with ME/CFS for 10 years or more, 92% had visited a GP in the previous year, and 10% rated their illness as severe. Overall, quality care by GPs was described as poor by 33% of the women and very poor by 27%, and the equivalent figures for specialist care were 27% and 21%. In the Norwegian population as a whole, 76% of all patients rate their care as good or excellent, so these findings are a cause for concern and a wake-up call for healthcare in Norway.

Depending on others

Williams et al., Journal of Health Psychology, 2016

Chronic illness and physical limitations are a fact of life for people with ME/CFS, but how do they feel about being dependent on others? To answer this, researchers from the University of the West of England collected the experiences of patients physically dependent on others for help day-to-day. Six themes came up again and again.

Loss of independence was a major factor, often associated with a sense of guilt for being a burden to other people. The invisibility of the illness was another issue, particularly trying to explain the illness to others and make them understand why help was needed. Also, anxieties about the present and future were a problem, particularly about being able to access help when needed and whether it would come from people able to "understand and handle the task in an appropriate manner".

The three remaining themes were 'catch-22', where asking for help was almost as exhausting as completing the task; feeling angry and frustrated at having to rely so heavily on other people; and issues around accepting the condition. Some people found acceptance difficult, as they longed for the healthy life which was gone, but others found themselves starting to accept the "the reality of their life and limitations", with improvements in quality of life and emotional distress.

Different EEG patterns

Wu et al., Neuropsychiatric Disease and Treatment, 2016

An objective biomarker for ME/CFS is the diagnostic holy grail, so all avenues need to be explored. Researchers at the Chinese Medical Hospital in Shandong compared waking brain EEG patterns in 24 patients and 23 healthy people using novel technology to unravel the 'deterministic chaos' of brain activity. They found that brain electrical activities were significantly reduced in the patients, particularly in the right frontal and left occipital regions which are associated with memory, vision and judgment. We don't know why this should be – levels or uptake of chemical messengers in the brain may be reduced – but this is the second study to show EEG anomalies in ME/CFS patients, and the technique is worth investigating further.

Muscle abnormalities

Rutherford et al., Journal of Aging Research, 2016

Reviews of biomedical aspects of ME/CFS are rare, so the latest from Newcastle University is a welcome addition to the scientific literature. It brings together the evidence for biochemical abnormalities in skeletal muscles, the site of symptoms in many patients. While there are indications that the problem lies centrally – an abnormal increase in the firing of nerve cells far away in the brain and the spinal cord – other experiments have identified more local abnormalities, including problems with the generation and clearance of acid from muscle during exercise or abnormally raised levels of oxidative stress. As the authors point out, why focus on psychological explanations when there's so much evidence that biomedical problems exist?

"Loss of independence was a major factor… a sense of guilt for being a burden"

Intestinal bacteria and exercise

Shukla et al., PLoS ONE, 2016

The microbiome is the hidden world of microbes living mainly in the gut, and it can dramatically influence health. Researchers in Wisconsin wondered whether the movement of bacteria or their products from the intestine into the bloodstream during exercise could be causing some of the symptoms of ME/CFS. To test this, they collected blood and stool samples from ME/CFS patients and controls before and up to 72 hours after an exercise challenge. Overall, there were increases in specific bacterial clusters (*Firmicutes*/*Bacilli*) and a delay in the clearance of bacteria from the blood in patients compared with the controls. If the microbiome really is involved in post-exercise symptoms, increased intestinal permeability could be a key factor.

The perils of definitions

Jason et al., Diagnostics, 2015

Last year, the Institute of Medicine in the USA proposed a new case definition and a new name for ME/CFS – Systemic Exertion Intolerance Disease, or SEID. Since then, Prof. Leonard Jason in Chicago has been actively highlighting the problems this might cause. One of the most important is that the SEID case definition does not specify the many illnesses that need to be excluded by clinical assessment before making a diagnosis. Using four sets of data from ME/CFS patients, he shows that a diagnosis of SEID can easily be applied to people with other illnesses, including major depressive disorder. Misdiagnosis is already a problem in ME/CFS, and broadening the definition by adopting SEID could well make the situation even worse.

The Everest Challenge team celebrate their ascent

Friends united

Some of the many activities undertaken by our supporters to raise funds for ME Research UK.

Mount Everest Challenge

Earlier this year, a team of climbers scaled the equivalent of the height of Everest (8,850 metres) in a single day to raise money for ME Research UK. The unique climbing wall, hand sculpted to capture the curvature and complexities of natural rock, was at Watford Leisure Centre, and over 700 individual climbs, roughly one climb every 5 minutes for 9 hours, were needed to simulate Hillary & Tenzing's ascent in 1953. Our thanks go to team members Edward Cornes, Harry Smith, Monika Czarnowska, Luke Spencer, Tom Roberts and Aaron Huckle, among others.

Colourful fundraising

The Color Run – billed as the happiest 5k on the planet – is a unique paint race that celebrates healthiness and happiness. It is now the single largest event series in the world, hosting 225 events in 35 countries with 5 million runners doused from head to toe in different colours at each kilometre. One of them, our supporter Alan Morell, found out why it gets its name when he took part in the Birmingham event recently – happy but also messy.

Bonsai with love

In June this year at Failand Village Hall, there was a treat for anyone interested in the art of Bonsai. This event featured an exhibition of some of the UK's best bonsai, with many bonsai traders in attendance. Our thanks go to organiser Dan Barton whose granddaughter Jenny has had ME for 8

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01 Alan Morell is messy but happy after his Color Run

02 Jenny Barton with her Bonsai artwork

03 Susan Hymers enjoys her new hair colour

04 A Cup of Tea for ME with **Ann Jones** and friends

years, and to all the people who gifted magnificent trees for the auction and prizes for the tombola. Dan's wonderful bonsais can be seen at his website: danbartonbonsaipots.wordpress.com.

Cup of tea for ME

Lots of things happened in ME Awareness Week, and one was Ann Jones' coffee/tea morning. One of the organisers was recently diagnosed with ME and was struggling with symptoms and an unsympathetic GP, so that drove Ann on to make the event a success. As she says, "Organising it was fun and made me aware of the kindness and generosity of neighbours and friends, a great thing in itself." Teas for ME are becoming a feature of our fundraising (details on our website).

Snowdonia snowman

Congratulations (and thanks!) to Dave Thawley for competing in the Snowdonia Snowman Triathlon to raise funds. It's incredible to think that Dave completed the course – a 1,000-m open water swim, 70-km bike ride over a 4,000-ft assent followed by a fell run – in a little over 4 h 55 min. Dave's wife has ME, and he chose this event because it was beyond his capabilities and allowed him to experience something of the symptoms ME patients suffer every day.

Blue hair

"I can't run a marathon or climb a mountain so I dyed my hair blue for ME Awareness Month," said Susan Hymers – and that's exactly what she did with the help of Julia at 'Sisters in Leisure', Blaydon. Before Susan developed ME 17 years ago, she had a good career and an independent life, but now she relies on her husband Ian. As she explains, "I'm one of the lucky ones, I've got someone to care for me, but many haven't, and I honestly don't know how they cope."

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05 Rhiannon McAleer and **Mike Connor** with the proceeds of Hambrook Lodge's fundraising

06 Making their escape are **Lara Gibson** and **Rupert Swallow**

07 Jenny Chittick relaxes in bed as part of her online Screw ME Day to raise awareness of the illness

08 Exhausted but happy, **Samantha Ward** and **Bex De la Haye** celebrate completing their Mud Monsters Run

Masterful fundraising

Many thanks to the Bretheren of Hambrook Lodge (in the Province of Gloucestershire) for their fundraising activities over recent months. And thanks also to Mike Conner who, during his Mastership of the Lodge, nominated ME Research UK to be its chosen charity. Past Master Mike's daughter collected a cheque on our behalf from her dad. Rhiannon's university education (she has recently gained her PhD) was completed with the help of a carer as she continued her fight against ME.

Mud monsters!

Samantha Ward and her team mate Bex De la Haye took part in the Mud Monsters Run at East Grinstead this Spring. Sam completed the 5-km course in an amazing 105 min. Sam told us, "Five years ago my life changed completely when I developed ME. I was fortunate to be diagnosed quickly, but still had to use a mobility scooter, couldn't work and barely felt like I had a life. My recovery is amazing." Our thanks to Samantha who ended the day, "very sore and exhausted but so happy I did the mud run".

Partners in crime

Lara Gibson and fellow 'escapee' Rupert Swallow found a novel way to spend 36 hours and raise funds for ME research. They took part in DUCK Charities' Jailbreak event, seeing how far they could travel from Durham Students' Union in 36 hours. Participants were not allowed to pay for assistance and had to rely upon their own ingenuity and good luck, as well as the generosity of people they met. Just in the nick of time, they made it all the way to Brussels where freedom beckoned!

Standing Order Form

To allow us to press ahead with our mission to Energise ME Research globally, 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**.

Name of account holder(s)

Address

Postcode

Telephone number

Name of Bank or Building Society

Branch address

Branch postcode

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

Debit amount (£)

Payment date each month

Date of first payment

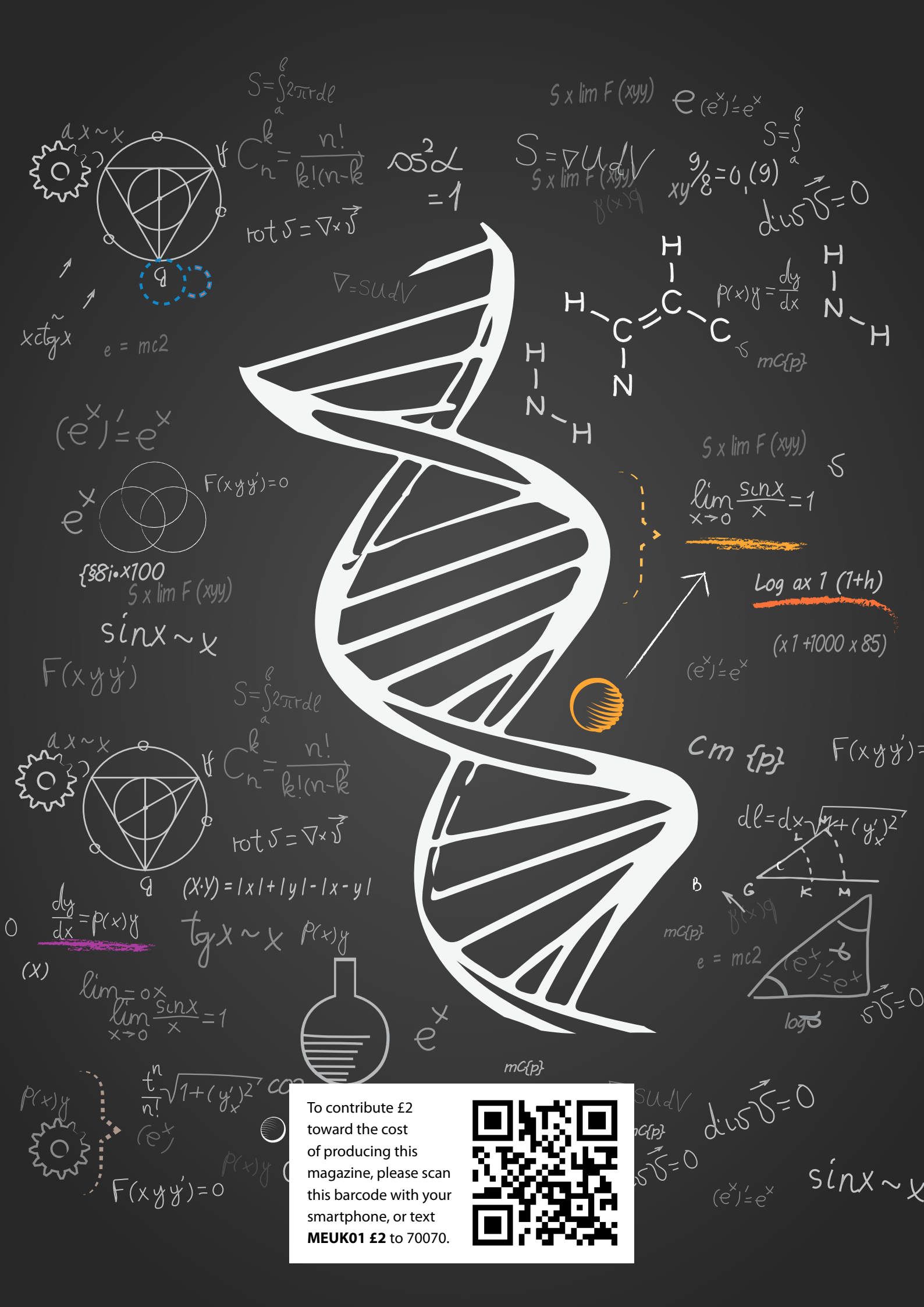
Pay to: Clydesdale Bank, 158/162 High Street, Perth PH1 5PQ, UK, Account: ME Research UK, Account no: 50419466, Branch code: 82-67-09

☐ ***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

Thank you for your support



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