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Medical Research Council Versus Arthritis Centre for Musculoskeletal Ageing Research

MRC Medical Research Council

VERSUS ARTHRITIS

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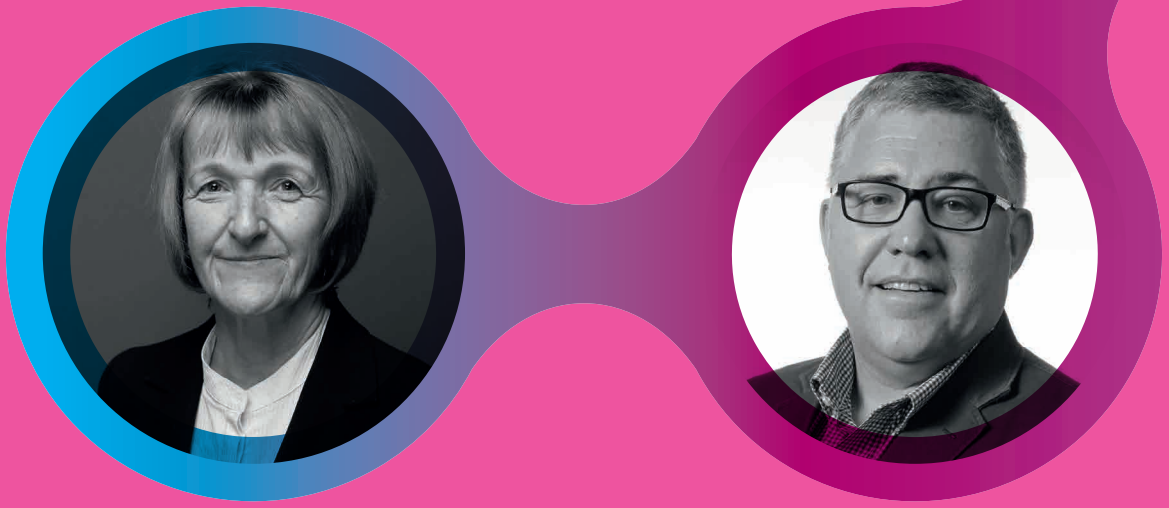

Message from the directors – Professor Janet Lord and Professor Paul Greenhaff

Multidisciplinary research, at scale, is required if we are to achieve meaningful impact on the decline in musculoskeletal function and increased risk of developing arthritis with age. The Medical Research Council Versus Arthritis Centre for Musculoskeletal Ageing Research is a partnership between the Universities of Birmingham and Nottingham, uniting the significant research strengths of both partners in musculoskeletal physiology, metabolism, neurophysiology, endocrinology, inflammation biology and motivational psychology. The Centre also harnesses our ability to deliver interventions in human populations, both healthy elders and those with musculoskeletal disease or frailty.

Why musculoskeletal ageing research?

The importance of musculoskeletal ageing research for medical advance.

Life expectancy in the UK is increasing at a rate of approximately two years per decade, with one-in-three children born today now expected to reach 100 years of age. This would be a cause for celebration if it were not for the fact that increases in health span, the years spent in good health, are not keeping pace with lifespan changes. Estimates from the World Health Organization show a ten-year difference between health span and lifespan in the UK.

20% of the population consults their GP about a musculoskeletal problem each year

The age-related decline in the musculoskeletal system, leading to frailty and diseases such as osteoarthritis and rheumatoid arthritis, can be considered 'ageing that matters', due to the impact on independence, quality of life and ability to remain in employment. This compromise to the functioning of the musculoskeletal system accounts for the largest proportion of years lived with disability in the UK and musculoskeletal health is the fourth largest draw on NHS finances. Moreover, ageing is not the only factor leading to musculoskeletal frailty and disability, with 16% of those disabled being victims of trauma. As the majority of trauma patients are aged 20–40, the economic impact extends over decades.

Statistics concerning age-related compromise to the musculoskeletal system make it clear that doing nothing to improve the musculoskeletal health of our ageing population is an expensive choice and an untenable long-term position:

- 740,000 adults are admitted to Accident and Emergency each year after a fall, which resulted in 66,000 hip fractures in 2017
- 20% of the population consults their GP about a musculoskeletal problem each year
- The NHS spends more than £5 billion annually on musculoskeletal health
- Low muscle mass predicts all-cause mortality in older people
- Arthritis affects over 10 million people in the UK and there are more than 175,000 joint replacements annually as a result
- The indirect cost to the economy of arthritis, in terms of working time lost, is estimated at £14 billion

740,000 adults are admitted to Accident and Emergency each year after a fall, which resulted in **66,000** hip fractures in 2017

Ageing is a complex process that results in the reduced functioning of most of the body's organ systems, with the musculoskeletal system (muscle, bone, tendon and cartilage) significantly affected. The musculoskeletal system is compromised not only by loss of muscle, bone and cartilage with age, but also by the decline in function of the nervous system, which results in reduced control of movement and balance leading to frailty. Ageing is also often accompanied by weight gain, which puts further strain on joints and contributes to erosion of cartilage and bone, increasing the chances of developing osteoarthritis. Importantly, both ageing and obesity are associated with decreased physical activity levels, an increased level of systemic inflammation, an altered anabolic hormone milieu, muscle anabolic resistance to nutrition and exercise and insulin resistance, all of which affect the ability of the body to maintain a healthy musculoskeletal system and accelerate chronic disease progression.

Therefore, increased physical activity and interventions that are able to reduce inflammation, correct age- and obesity-related hormone and body composition changes, and sustain tissue metabolic health offer a way forward for delaying age-related changes in the musculoskeletal system and disease progression. Indeed, strong relationships exist between physical inactivity and chronic disease and all-cause and disease-specific mortality rates. The problem is we do not yet know the rate of change or mechanistic basis of these relationships.

Hippocrates in 400 BC said that "Walking is man's best medicine" – sadly it's a drug that too few of us take in old age, adding to our risk of physical frailty.

Professor Janet Lord

Mission and objectives

Our aim is to carry out research that will address major knowledge gaps in relation to age-related musculoskeletal decline and improve understanding of the progression to age-related musculoskeletal disease, notably osteoarthritis and rheumatoid arthritis.

We investigate the factors that impact upon this trajectory, including lifestyle factors such as sedentariness, physical activity, nutrition (including gut microbiota) and obesity. We also research sarcopenia secondary to chronic inflammatory diseases such as chronic obstructive pulmonary disease (COPD) and inflammatory bowel disease, which are associated with significant muscle wasting. More recently we have also embraced research into the consequences of major trauma, which is a leading cause of musculoskeletal compromise and disability in younger adults. We are developing and validating interventions to ameliorate musculoskeletal decline aiming to transform the quality of life for patients and broaden the social and economic impact of our research.

The Centre for Musculoskeletal Ageing Research strives to become an internationally recognised and globally networked research platform, capable of generating novel and clinically testable approaches to reduce musculoskeletal ageing and disease.

Through strategic collaborative working with other Centres of Excellence in the UK and overseas, the Centre for Musculoskeletal Ageing Research leverages the expertise, resources and facilities required to achieve a step change in mechanistic understanding and the testing and implementation of interventions, ensuring impact on musculoskeletal health at scale. Working with health service providers and policymakers we are ensuring that we can continue to operate in a range of delivery settings and accelerate adoption of our findings.

We are delivering our vision through five objectives...

Objective one

To increase understanding of the processes influencing the rate of ageing of the musculoskeletal system and how these increase susceptibility to musculoskeletal decline in acute (trauma and infection) and chronic musculoskeletal disease (Primary – osteoarthritis, rheumatoid arthritis, Secondary – chronic obstructive pulmonary disease, inflammatory bowel disease).

Objective three

To increase national and international networking to create a significant musculoskeletal ageing research, training and dissemination platform, exploiting synergies with other Centres of Excellence (including our sister centre, the MRC Versus Arthritis Centre for Integrated research into Musculoskeletal Ageing).

To develop and test interventions to improve musculoskeletal health using highly innovative cross-cutting platforms established in the Centre.

Objective five

To work with key policy and health practice influencers, industry and Patient and Public Involvement (PPI) groups to determine routes to translation of our research findings.

Objective four

To increase use of existing cohorts and databases to support our mission.

Our research vision and strategy, which is encompassed in these five major objectives, will be delivered via three integrated research themes and strategic partnership working.

Research themes

Theme One

Mechanisms of musculoskeletal ageing – aiming to increase understanding of the mechanistic basis of age-related musculoskeletal decline and the factors modulating this trajectory, including cell senescence, inflammation, metabolism, physical inactivity and sedentariness, obesity, nutrition and the gut microbiome.

The mechanisms underlying anabolic resistance with age are a major interest in the Centre.

- Professor Phil Atherton and Professor Ken Smith use stable isotope tracers and deuterated water to quantify protein and substrate turnover in acute and chronic intervention studies in older people to understand better the aetiology and drivers of anabolic resistance, including a focus on insulin resistance;
- Use of tracer approaches combined with metabolomics (with Professor Rick Dunn at Birmingham and Dr Dan Wilkinson at Nottingham) to generate non-invasive biomarkers of muscle protein synthesis and breakdown in humans, which can then be used in large-scale intervention studies in Theme 3;
- Professors Ian MacDonald and Nate Szewczyk use their access to spaceflight research facilities to study the effects of immobilisation on insulin resistance and muscle anabolic responses;
- Dr Tim Constantin-Teodosiu determines alterations in skeletal muscle intermediary metabolism and associated molecular regulation of anabolic responses;
- Professor Martin Hewison researches the impact of Vitamin D bioavailability on muscle anabolic responses and bone biology;
- Professor Greenhaff and Dr Leigh Breen are examining the impact of sedentary behaviour and obesity on muscle metabolic quality and the mechanistic determinants;
- Professor Gareth Lavery is investigating the role of declining NAD+ supply in muscle mitochondrial function with age in humans as supplementation with nicotinamide riboside has been shown to restore NAD+ levels and reduce functional senescence in muscle cells in mice;
- Professor Janet Lord is determining the processes driving accumulation of senescent cells with age, specifically involvement of reduced NK cell cytotoxicity towards senescent cells;
- Professor Chris Miall researches the impact of behavioural training on neural control of movement with age;
- Dr Ned Jenkinson researches the impact of age and disease on motor control and movement learning;
- Dr Raymond Reynolds studies the central mechanisms involved in compensation for age-related vestibular loss and the variability that increases fall risk;
- Dr Matt Piasecki researches the impact of age on neuromuscular junction function.

*This theme is led by **Professor Philip Atherton** (University of Nottingham) and **Professor Martin Hewison** (University of Birmingham)*

> As we age skeletal muscle becomes less sensitive to the anabolic effects of exercise and protein, understanding why will allow us to develop adjunct therapies to be used with exercise to improve muscle strength.
>
> Professor Phil Atherton

Theme Two

Ageing and the progression to disease and frailty – aiming to identify the processes driving the progression of musculoskeletal decline with age towards clinical frailty, rheumatoid arthritis and osteoarthritis. This theme will also identify drivers of musculoskeletal decline in diseases where sarcopenia and weakness prevail (COPD, inflammatory bowel disease, trauma, infection).

Professor Greenhaff has a longstanding interest in COPD-associated sarcopenia through his involvement in the Medical Research Council/ABPI Chronic Obstructive Pulmonary Disease consortium and Professor Buckley is a theme lead in the Versus Arthritis Rheumatoid Arthritis Pathogenesis Centre of Excellence, which ensures good links to the Centre for Musculoskeletal Ageing Research.

- The theme integrates Principal Investigators researching various aspects of musculoskeletal disease pathogenesis. This includes how the microbiome influences systemic inflammation and disease pathogenesis led by Professor Karim Raza and Dr Niharika Duggal. The human intestine contains a diverse array of bacteria that contribute to health but when dysregulated can also promote disease. Recent studies in inflammatory arthritis suggest alterations in the intestinal microbiota and its interaction with the immune system may underlie disease. However, whether these changes are causal or correlative and their mechanism of action remain to be established.
- Dr Simon Wyn Jones investigates epigenetic mechanisms in pathogenesis, studying the role of long non-coding RNAs in driving the increased risk of osteoarthritis with obesity and assessing their potential as therapeutic targets;
- Tissue resident stromal cells play a role in determining the switch to persistence in rheumatoid arthritis and Professor Buckley researches how ageing processes in fibroblasts affect this switch and offer a new therapeutic target;
- Dr Rowan Hardy investigates the interaction between inflammation and glucocorticoid metabolism (11BHSD1 activity) as a driver of muscle and bone degradation with ageing and in rheumatoid arthritis, working with very early arthritis samples as well as animal models of rheumatoid arthritis on an 11BHSD1-/- background;
- Professors Atherton and Greenhaff (with Professor Dileep Lobo, Versus Arthritis Pain Centre, and Versus Arthritis Centre for Sport, Exercise and Osteoarthritis, and Professor Mick Steiner, Leicester Respiratory Biomedical Research Centre theme) are determining the contribution of physical inactivity to muscle dysfunction in osteoarthritis and COPD, and the mechanistic basis of trauma and infection-related sarcopenia and metabolic dysregulation;
- Dr Liz Sapey and Dr Daisy Wilson work on the role of innate immunity and systemic inflammation in muscle wasting in COPD;
- Professor Janet Lord researches the processes driving sarcopenia in rheumatoid arthritis, chronic liver disease and inflammatory bowel disease using his extensive clinical cohorts and using support from the Birmingham Inflammation Biomedical Research Centre;
- Professor Andy Clark is assessing dysregulation of anti-inflammatory mechanisms in ageing and rheumatoid arthritis pathogenesis, looking at the regulation of the master inflammatory gene regulator tristetraprolin by DUSP phosphatases;
- Dr Helen McGettrick is assessing a novel anti-inflammatory adipokine signalling mechanism.

*The theme will be led by **Professor Paul Greenhaff** (University of Nottingham) and **Professor Chris Buckley** (University of Birmingham).*

Theme Three

The **interventions to improve musculoskeletal health and function** theme involves assessment mainly of lifestyle, but also pharmacological interventions in healthy, frail and disease populations to improve musculoskeletal health and function, including approaches to increase adoption of lifestyle change.

The theme involves Principal Investigators and their teams and benefits from access to clinical research facilities and trials units at both The University of Nottingham and the University of Birmingham.

Physical activity and nutritional interventions form the largest element of this theme.

- Dr Carolyn Greig combines nutrition (the leucine metabolite HMB) with resistance exercise to increase muscle function in frail elders in a community setting. She is also part of a consortium investigation into Vitamin D and protein supplementation to improve muscle function;
- Dr Leigh Breen is working with industry to test a range of nutrients, including fish oils and phosphatidic acid to improve muscle quality;
- Dr Kostas Tsintzas is evaluating the efficacy of diet and exercise interventions on metabolism, including the timing of exercise in relation to nutrient intake;
- Dr Beth Phillips is using high-intensity interval training (HIIT) in a pre-habilitation setting, testing its ability to build up musculoskeletal reserve in older patients undergoing elective surgery;
- Larger scale and community-based evaluations are carried out by several researchers in the Centre. Professors John Gladman, Pip Logan and Tahir Masud all evaluate physical activity enhancement and falls prevention programmes in the community;
- Professor Janet Lord and Professor Wiebke Arlt are testing anabolic agents (DHEA) for their ability to overcome trauma-related (hip fracture as well as major trauma) sarcopenia and re-set the HPA axis;
- Professor Dagmar Scheel-Toellner has identified a novel B cell population, FcRL4 expressing, that accumulates with age and in rheumatoid arthritis and are major autoimmune effectors. She is working with industry via a Medical Research Council DPFS grant to develop antibodies to delete these cells as a treatment for rheumatoid arthritis;
- Professors Liam Grover and Duncan Shepherd are developing delivery methods for cell therapy to regenerate bone, cartilage and tendons;
- Dr Ned Jenkinson is using non-invasive brain stimulation to improve motor control;
- This theme is also developing approaches to motivate people to make lifestyle changes with Dr Sally Fenton applying self-determination theory to increase physical activity and reduce pain and fatigue in patients with rheumatoid arthritis.

*This theme is led by **Dr Carolyn Greig** (University of Birmingham) and **Professor Ian Macdonald** (University of Nottingham).*

Technology platforms and resources

To facilitate musculoskeletal research in humans within the Centre, but also nationally, we have invested built or expanded a range of facilities and resources. These include state of the art technologies for analysing tissue turnover, imaging and metabolomics as well as well phentoyped cohorts.

Underpinning all these themes are ready access to cohorts, eg, the lifelong exercisers cohort (125 master cyclists aged 55–79 at inception in 2012) in collaboration with King's College, London; the Physical Activity and Healthy Ageing cohort (200 healthy elders not meeting exercise guidelines, inception 2011 at the University of Birmingham); Medical Research Council Chronic Obstructive Pulmonary Disease MAP cohorts (more than 200 muscle wasted and non-wasted patients); the BEACON cohort of very early arthritis patients; the SIRS and SIFTI longitudinal cohorts of major trauma victims (250 patients).

These cohorts are unique in that they have been extensively phenotyped, many with several tissues stored (including muscle, serum, urine and blood cells), whereas existing UK cohorts rarely store tissue or analyse physiology in-depth. One exception is the UK Biobank, which has extensive physiological, biomarker and lifestyle data on 500,000 adults and we intend to use this resource and other pre-existing datasets to identify factors affecting the trajectory to physical frailty and musculoskeletal disease in themes one and two.

Analysis of cohort members using our advanced magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS) facilities in the Sir Peter Mansfield Imaging Centre provides deep phenotyping capability to the Centre members and 'omics analysis is supported by the Phenome Centre Birmingham, while isotope tracer methods to study tissue and protein turnover is fully supported with an extensive facility at The University of Nottingham. Combining these advanced methodologies and detailed in vivo human biology, we aim to discover fundamental parameters that govern musculoskeletal decline and develop interventions to maintain musculoskeletal health, achieving a step change in musculoskeletal ageing research.

Public engagement activity

The Centre for Musculoskeletal Ageing Research is very active in communicating its research to the general public through the web, social media and national press, as well as an ongoing programme of interactive activities which we encourage all our Principal Investigators and students to participate in. This includes running regular large-scale public engagement (PE) events on healthy ageing targeting older adults, including our annual 'Agewell' event, which attracts around 150 attendees, with enhanced dissemination via the Centre website and regular newsletters.

We proactively contribute to major national events such as the British Science Festival as well as local university and hospital open days; local talks and interactive discussion activities by individual researchers such as Pint of Science, Café Scientifique, University of the Third Age and interviews on local radio. We are active in communication via print media with general articles written with

science or health journalists (Innovage, Saga and Yours magazines) as well as regular press releases and articles in the national press eg, *the Guardian, The Sunday Telegraph, The Times* and the *Daily Mail*. Our universities were founding partners in *The Conversation UK*, and we have embraced this opportunity through a number of articles.

Public involvement activities

As well as communicating our research, we attempt to fully involve patients and the public in our work, following the INVOLVE principles around distinct support for participation, engagement and involvement. For our work on physiological musculoskeletal ageing, we work with the Birmingham 1000 Elders, several of whom are centenarians. The Elders group is managed by Professor Lord and they are involved at every level of our work, from acting as a focus group helping design research studies or associated information sheets, to being active researchers and disseminators, as well as research participants. For example, members of the Elders were involved as commissioners on the production of the Birmingham Policy Commission Report *Healthy Ageing in the 21st Century: the best is yet to come*, which launched at The House of Lords and Birmingham City Council. The Elders even changed the research question from 'the Challenge of Ageing' to 'Healthy Ageing', taking a more positive stance. The Elders are also involved in public engagement activity, one good example being the exercise DVD and associated book that we produced for chair-based exercises for older adults in collaboration with a local company Move It or Lose It. The Elders themselves were featured in the DVD, demonstrating the exercises in their own homes, and it was their suggestion to make a book, as they pointed out that they did not always want to watch a DVD but would benefit from a book they could work through at their leisure.

Finally, the Elders are of course research participants and we currently have more than 20 studies running that would not be possible without them. For our arthritis work, we also have a very active patient and public involvement (PPI) group, R2P2 (Rheumatology Research Patient Partnership), who assess all studies involving patients before they go for grant funding and/or ethical approval. We provide training for our PPI members so that they are confident working with researchers.

Collaborations

We have partnerships working to aid translation of research into practice at scale involving engaging with policy influencing units (eg, such as Versus Arthritis and Medical Research Council), local health policymakers (directors of public health, Academic Health Science Networks) and sustained multidisciplinary, international and cross-sector working at scale.

The Centre has translational and outward-facing activity through establishing links with industry including big pharma and instrumentation companies (GlaxoSmithKline, Novartis, Abbott Nutrition, Smith and Nephew, Thermo Fisher, Nestle), small- to medium-sized enterprises (Zymo, Biomet, HUR) and community-based lifestyle companies (Move it or Lose It); collaborating with major European and US research groups working in musculoskeletal ageing, and expanding links to Brazil and China.

Increased global networking is a key component of our vision that will help delivery in each of our research themes and examples of our activity to achieve this are:

- Visits and Centre-funded PhD studentships to facilitate working with leading musculoskeletal centres in the UK, Denmark and the USA (University of California San Diego, University of California, Berkeley; University of Illinois at Urbana-Champaign, the Universities of Florida and Houston), as well as with industry partners;
- We make pump-priming funds available to catalyse new cross-site, national and international collaborations.

Careers and training

With the continued growth in the older population, we see a growing need for research and training in musculoskeletal ageing and health.

> **There is a shortage of researchers trained in multidisciplinary musculoskeletal ageing. Our Centre is addressing this issue through our Doctoral Training Programme with 22 PhD students.**
>
> Dr Simon Wyn Jones

Training underpins our aims of building further capacity in musculoskeletal ageing research and extending our focus to cover the role of ageing processes in disease pathogenesis to ensure we can translate laboratory science to patient benefit. We offer a multi-layered approach to our training, with a strong Doctoral Training Programme for non-clinicians, additional postgraduate and CPD-level activity for clinicians, advanced workshops and links to other doctoral training programmes.

To ensure students gain an outstanding training experience a period spent in another world-leading laboratory is important. Centre-funded Students have the opportunity to spend up to one year in a collaborating institute or selected centres of musculoskeletal ageing research excellence and industry in the UK or overseas. We also enhance the training environment by offering reciprocal exchange visits to our collaborating institutions, for their doctoral students.

The Centre is a key supporter of identified priority national skills needs, particularly around interdisciplinary skills but also quantitative skills. The latter focuses on the technologies available in the Centre, including human stable isotope tracer methods, metabolomics, health informatics, magnetic resonance imaging and spectroscopy as applied to human musculoskeletal ageing and disease.

The Centres unique facilities and expertise in these areas will help to meet recognised methodological skills gaps in human ageing research in the UK. We also run courses jointly with our sister Centre to integrate our training capability, eg, systems biology, animal models of musculoskeletal ageing and disease, inflammation in ageing and epigenetics.

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