64th Annual Scientific Meeting
Exercise, Activity & Ageing Mechanisms

Liverpool John Moores University
Liverpool, United Kingdom

July 7th-9th 2014
Special Thanks to our Meeting Sponsors
<table>
<thead>
<tr>
<th>CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Welcome to the 2014 Annual Scientific Meeting</td>
</tr>
<tr>
<td>Local Organiser 2014 – Graeme Close</td>
</tr>
<tr>
<td>Meeting Schedule</td>
</tr>
<tr>
<td>List of Invited Speakers</td>
</tr>
<tr>
<td>Lord Cohen Medal Winner</td>
</tr>
<tr>
<td>Invited Speaker Biographies</td>
</tr>
<tr>
<td>Oral Presentation Abstracts</td>
</tr>
<tr>
<td>Poster Presentation Abstracts</td>
</tr>
</tbody>
</table>
On behalf of the British Society for Research on Ageing (BSRA) and Liverpool John Moores University (LJMU) I would like to welcome you all to the 64th Annual Meeting of the BSRA. I am delighted that LJMU are able to host this very special meeting, which we have called “Exercise, Activity & Ageing Mechanisms”. I know that you will participate in excellent presentations, highlighting the fundamental roles that exercise and activity can play in ameliorating many age-related conditions.

It is particularly poignant that a meeting focusing on exercise and ageing is held this year in Liverpool, because as an Institution we are celebrating 40 years of Sports Science at LJMU. Indeed, the building where the ‘Early Career Researcher Day’ is taking place is named the Tom Reilly Building after the late Tom Reilly, the first ever Professor of Sports Science in the UK. I am sure that Tom, a lifelong exerciser, who was still running marathons in his later years, would be delighted that LJMU is the host of such an important and exciting scientific meeting.

This year’s meeting has attracted excellent numbers with approximately 160 delegates attending. What I am particularly excited about is the mix of our regular attendees alongside new sport science-based researchers, which will, over the next 3 days, facilitate some exciting and fruitful new collaborations while consolidating existing ones. The programme boasts an excellent line up of world-class speakers alongside outstanding poster presentations. I would, encourage everyone to spend some time viewing the posters in order to discuss potential collaborations.

Members of the local organising team will be present throughout the conference and will be clearly visible in blue LJMU T-Shirts. If you need anything please ask these people for help, even if it is simply directions to the best local public house!

Finally, I sincerely hope you enjoy the friendly and relaxed atmosphere at this meeting and enjoy the spectacular conference dinner that we have planned for you. I hope that all of our new members stay with us at the BSRA and I look forward to seeing you not only at this meeting but also at future BSRA meetings. Please be aware that the 65th BSRA Annual Meeting will be held mid-July 2015, with the title ‘systems biology of the ageing immune system’ and organised by Sian Henson of UCL.

With very best wishes

Graeme and the local organising team

http://www.ljmu.ac.uk/
Dr Graeme L. Close, PhD
Local Organiser, BSRA Liverpool
2014

Graeme is a Reader in Applied Physiology and Sports Nutrition at Liverpool John Moores University (LJMU), UK where he is the programme lead for the MSc in Sports Nutrition. Having completed his PhD at LJMU in 2003 Graeme moved to The University of Liverpool, to develop his ageing research skills under the guidance of Professor’s Jackson and McArdle. In 2006 Graeme received a personal fellowship from Research into Ageing to investigate the role insulin resistance in age related muscle frailty. Following the completion of this fellowship Graeme returned to LJMU as a Senior Lecturer in Sports Science and developed his own research group. Graeme’s research group is focused upon the effects of vitamin D deficiencies in athletic performance, the role of antioxidants in the recovery of muscle function and the etiology of age-related loss of muscle mass.

From an applied perspective, Graeme is accredited with the UK Strength and conditioning Association (UKSCA), he is an accredited physiologist with the British Association of Sport and Exercise Sciences (BASES) and is on the Sport and exercise Nutrition register (SENr). Graeme is currently the head of Sports Nutrition at Munster Rugby and Salford Red Devils RLFC, he is the lead nutritionist for British Ski and Snowboard as well as working with professional jockeys and European Tour golfers and is a research consultant to Team GB rowing. Prior to his academic studies, Graeme was a former professional rugby league player and has represented his country at youth and student level.
## MEETING SCHEDULE

### Monday 7th July

<table>
<thead>
<tr>
<th>Time</th>
<th>Mechanisms of Ageing</th>
<th>Early Career Researcher Programme</th>
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<tbody>
<tr>
<td>12.30</td>
<td>Arrival</td>
<td>Tea, coffee, lunch</td>
</tr>
<tr>
<td>13.30</td>
<td>Graeme Close</td>
<td>Welcome &amp; purpose of ECR day</td>
</tr>
<tr>
<td>14.00</td>
<td>Laboratory Tours</td>
<td>4 * 30 minute laboratory visits</td>
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<tr>
<td><strong>16.00</strong></td>
<td></td>
<td><strong>Tea &amp; Coffee</strong></td>
</tr>
<tr>
<td>16.30</td>
<td>Claire Stewart</td>
<td>Chair</td>
</tr>
<tr>
<td>17.00</td>
<td>Breakout</td>
<td>Small group grant ideas session</td>
</tr>
<tr>
<td>17.45</td>
<td>Presentations</td>
<td>4 * 10 minute presentations by team</td>
</tr>
<tr>
<td></td>
<td>Graeme Close</td>
<td>Prize for best grant idea</td>
</tr>
<tr>
<td><strong>18.30</strong></td>
<td>Graeme Close</td>
<td>Chair</td>
</tr>
<tr>
<td></td>
<td>Stuart Phillips</td>
<td>At the intersection of nutrition and physical activity: active aging in the new millennium</td>
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<tr>
<td><strong>19.30</strong></td>
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<td>Welcome Reception</td>
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## Tuesday 8th July

### Mechanisms of Ageing

<table>
<thead>
<tr>
<th>Time</th>
<th>Speaker(s)</th>
<th>Topic</th>
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<tbody>
<tr>
<td>09.15</td>
<td>Anne McArdle</td>
<td>Chair</td>
</tr>
<tr>
<td>09.45</td>
<td>David Gems</td>
<td>Metabolism and ageing</td>
</tr>
<tr>
<td>09.45</td>
<td>Maria Abad</td>
<td>Reprogramming in vivo: The power of manipulating cell plasticity</td>
</tr>
<tr>
<td>10.15</td>
<td>Marco Narici</td>
<td>Sarcopenia &amp; loss of muscle quality</td>
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<tr>
<td>10.30</td>
<td>Alexandre Benedetto et al</td>
<td>Stress resistance in ageing worms</td>
</tr>
<tr>
<td>10.45</td>
<td>Zoe Glover et al</td>
<td>ACER, diet and ageing Drosophila</td>
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<tr>
<td>11.00</td>
<td></td>
<td>Posters, Tea and Coffee</td>
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### Protein Turnover

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<thead>
<tr>
<th>Time</th>
<th>Speaker(s)</th>
<th>Topic</th>
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<tbody>
<tr>
<td>11.20</td>
<td>Stuart Phillips</td>
<td>Chair</td>
</tr>
<tr>
<td>11.20</td>
<td>Brian Kennedy</td>
<td>Dissecting the TOR Pathway for Aging and Chronic Disease</td>
</tr>
<tr>
<td>11.50</td>
<td>Paul Greenhaff</td>
<td>Activity, exercise and Ageing Mechanisms</td>
</tr>
<tr>
<td>12.00</td>
<td>M. Brook et al</td>
<td>Protein Synthesis, resistance exercise training and ageing</td>
</tr>
<tr>
<td>12.35</td>
<td>Stephen Frenk &amp; J Houseley</td>
<td>Genome changes with ageing</td>
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<tr>
<td>12.50</td>
<td></td>
<td>Posters and Lunch</td>
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### From Molecules to Man

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<thead>
<tr>
<th>Time</th>
<th>Speaker(s)</th>
<th>Topic</th>
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<tbody>
<tr>
<td>14.00</td>
<td>Claire Stewart</td>
<td>Chair</td>
</tr>
<tr>
<td>14.00</td>
<td>Alan Morgan et al</td>
<td>HSPs involved in yeast ageing</td>
</tr>
<tr>
<td>14.15</td>
<td>S. Scullion et al</td>
<td>ROS and electrical stimulation</td>
</tr>
<tr>
<td>14.30</td>
<td>V. Pekovic –Vaughan et al</td>
<td>Chronobiology and ageing</td>
</tr>
<tr>
<td>14.45</td>
<td>S. Shepherd S et al</td>
<td>HIT and ageing</td>
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<tr>
<td>15.00</td>
<td>S.L. King et al</td>
<td>Stair descent, gait and ageing</td>
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<tr>
<td>15.15</td>
<td></td>
<td>Posters, Tea and Coffee</td>
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### BBSRC - Damage Accumulation, Adaptation and Frailty

<table>
<thead>
<tr>
<th>Time</th>
<th>Speaker(s)</th>
<th>Topic</th>
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</thead>
<tbody>
<tr>
<td>15.45</td>
<td>Helen Griffiths</td>
<td>Chair</td>
</tr>
<tr>
<td>15.45</td>
<td>Russ Hepple</td>
<td>Mitochondrial dysfunction and sarcopenia</td>
</tr>
<tr>
<td>16.15</td>
<td>Maeve Rea</td>
<td>Systems and ageing in the oldest old</td>
</tr>
<tr>
<td>16.15</td>
<td></td>
<td>Can HIT reduce inflammatory and immune mediated morbidity and mortality with age</td>
</tr>
<tr>
<td>16.45</td>
<td>D. Bartlett et al</td>
<td>ShARM initiative</td>
</tr>
<tr>
<td>17.00</td>
<td>P. Potter</td>
<td></td>
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<tr>
<td>17.15</td>
<td></td>
<td>Break</td>
</tr>
<tr>
<td>17.30</td>
<td>Prof Malcolm Jackson</td>
<td>Cohen Medal Lecture</td>
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<tr>
<td>18.15</td>
<td></td>
<td>Close</td>
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<tr>
<td>19.30</td>
<td></td>
<td>Drinks Reception and Dinner at the Crypt Hall, Liverpool Metropolitan Cathedral.</td>
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</tbody>
</table>
### Mitigation and Metabolism - BBSRC

<table>
<thead>
<tr>
<th>Time</th>
<th>Speaker</th>
<th>Topic</th>
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</thead>
<tbody>
<tr>
<td>09.15</td>
<td>Richard Farragher</td>
<td>Chair</td>
</tr>
<tr>
<td></td>
<td>Donald Ingram</td>
<td>Calorie Restriction Mimetics: State of the Art</td>
</tr>
<tr>
<td>09.45</td>
<td>Olly Witard</td>
<td>Muscle protein metabolism in older adults</td>
</tr>
<tr>
<td>10.15</td>
<td>P Potter et al</td>
<td>The Harwell ageing mutant screen</td>
</tr>
</tbody>
</table>

**10.30** Posters, Tea and Coffee

### Regenerative Medicine

<table>
<thead>
<tr>
<th>Time</th>
<th>Speaker</th>
<th>Topic</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.00</td>
<td>Marco Narici</td>
<td>Chair</td>
</tr>
<tr>
<td></td>
<td>Costis Maganaris</td>
<td>Tendon structure and function; in-vivo and adaptations in ageing</td>
</tr>
<tr>
<td>11.30</td>
<td>Liz Laird</td>
<td>Regenerating old joints - collagenous tissue engineering</td>
</tr>
<tr>
<td>12.00</td>
<td>J Bass et al</td>
<td>The VDR in skeletal muscle cells</td>
</tr>
<tr>
<td>12.15</td>
<td>K Goljanek-Whysall et al</td>
<td>miRNAs and age related muscle wasting</td>
</tr>
<tr>
<td>12.30</td>
<td>Claire Stewart</td>
<td>Skeletal muscle stem cells models of atrophy, fusion and repair</td>
</tr>
</tbody>
</table>

**13.00** Vote of thanks and close: Helen Griffiths & Graeme Close
LIST OF INVITED SPEAKERS

Malcolm Jackson  University of Liverpool, UK
Claire Stewart  Liverpool John Moores University, UK
Stuart Phillips  McMaster University, CA
Maria Abad  Spanish National Cancer Research Centre, ES
David Gems  University College London, UK
Paul Greenhaff  University of Nottingham, UK
Russle Hepple  McGill University, CA
Donald Ingram  Louisiana State University, US
Brian Kennedy  Buck Institute, US
Liz Laird  University of Liverpool, UK
Costis Maganaris  Liverpool John Moores University, UK
Maeve Rea  Queens University Belfast, NI
Oliver Witard  University of Stirling, UK
LORD COHEN MEDAL
Awarded to Professor Malcolm Jackson

Lord Cohen Medal

Lord Henry was a British Physician, Doctor and Lecturer. He was elected to the chair of medicine at the University of Liverpool in 1934. Knighted in 1949, he was President of the British Medical Association from 1951. After a coronary thrombosis in the following year, Cohen decided to devote his life to the greater work of teaching. He was raised to the peerage as Baron Cohen of Birkenhead, of Birkenhead in the County Palatine of Chester, on 16 June 1956 and was elected President of the General Medical Council in 1961. In 1964, he became President of the Royal Society of Medicine, receiving the society's gold medal in 1971. Lord Cohen of Birkenhead died in August 1977, aged 77.

In his name, the Lord Cohen Medal is awarded to individuals that have made a considerable contribution to ageing research, either through original discoveries or in the promotion of the subject of gerontology in its broadest aspect. It is the highest award for services to gerontology in the United Kingdom and is awarded on a sporadic basis by the British Society for Research on Ageing.

Recipient of the Lord Cohen Medal – Professor Malcolm Jackson

The BSRA is delighted to award Professor Malcolm Jackson with the Lord Cohen Medal. Professor Jacksons contribution to research and public outreach in ageing research is truly remarkable and thoroughly worthy of this prestigious award. Professor Jackson, who is Director of the MRC-Arthritis Research UK Centre for Integrated Research into Musculoskeletal Ageing (CIMA) will be delighted to receive the award given the historical connection to Liverpool and indeed the University of Liverpool.
Malcolm has published 173 original articles, 97 invited chapters or review articles and edited 2 books. His total research income over last 5 years is ~£5M from MRC, BBSRC, US NIA, Arthritis Research UK and previously from Wellcome Trust and Research on Ageing. Malcolm's research focus is on the sources and functions of reactive oxygen and nitrogen species in skeletal muscle with a particular emphasis on aging and the causes of age-related loss of skeletal muscle mass and function. Supervised 22 successful PhD students. Currently serves on MRC Population and Systems Medicine Board, BBSRC Ageing Working Group and DRINC steering group and Joint Research Councils Lifelong Health and Wellbeing Advisory Board.

**Academic Background**

BSc Hons Biochemistry, University of Surrey 1974; PhD University College London, 1980; DSc 1994; FRCPath 1996.

**Posts held:** 1974-1982 NHS Biochemist, University College Hospital, London; 1982 1984 Lecturer, Department of Medicine, UCL; 1984 – 1990 Senior Lecturer, Department of Medicine, University of Liverpool; 1990 1994 Reader, University of Liverpool. 1994 Professor of Cellular Pathophysiology (personal chair), University of Liverpool.

**In addition:**

<table>
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<tr>
<th>Year</th>
<th>Position</th>
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<tr>
<td>1997–2001</td>
<td>Head, Department of Medicine, University of Liverpool</td>
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<tr>
<td>2000-2001</td>
<td>Deputy Dean, Faculty of Medicine, University of Liverpool</td>
</tr>
<tr>
<td>2001-2002</td>
<td>Interim Dean, Faculty of Medicine, University of Liverpool</td>
</tr>
<tr>
<td>2004-2008</td>
<td>Head, Division of Metabolic and Cellular Medicine, School of Clinical Sciences, University of Liverpool.</td>
</tr>
<tr>
<td>2004-2010</td>
<td>Deputy Head &amp; Interim Head, School of Clinical Sciences, University of Liverpool.</td>
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<tr>
<td>2005-2009</td>
<td>Associate Dean for Research, Faculty of Medicine, University of Liverpool.</td>
</tr>
<tr>
<td>2007-2013</td>
<td>Adjunct Professor, Department of Cell and Structural Biology, University of Texas at San Antonio, USA.</td>
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</table>
Claire Stewart graduated with a B.Sc. Honours in Developmental Biology from the University of Glasgow. Following one year in Industry at Amersham International, she returned to academia undertaking a PhD investigating the roles of the insulin-like growth factors (IGFs) in regulating muscle mass. Her PhD was sponsored by Ciba Geigy and undertaken at the Babraham Institute, Cambridge. Wishing to add cell and molecular biology to her biochemistry and physiology background, she moved to Washington University Medical School to complete a postdoctoral fellowship under the guidance of Peter Rotwein. It was here she made the seminal discovery of a role for the IGFs in promoting not only skeletal muscle cell growth and differentiation, but also survival. In 1996 she returned to the UK, to the University of Bristol where she developed the first adult human skeletal muscle stem cell cultures derived from patients with cancer. This was followed by muscle and adipose tissue stem cell isolations from children, thus providing models for studying the impact of age and disease on cellular adaptation. In 2004 Claire moved from Bristol to to MMU and the Institute for biomedical research into human movement and health, where her research focused on investigating the impact of age, disease, damage and nutrition on human muscle adaptation, both in vitro and in vivo. She was made a Professor of cell and molecular biology in 2006. In late 2012, Claire was recruited to LJMU as a Professor of stem cell biology where she is now planning to link her expertise surrounding muscle adaptation to age, injury and disease to the field of healthy ageing. Her research focus throughout has therefore been on the interaction of growth factors and cytokines on cellular responses, specifically with age, injury and disease. Claire has published extensively in her field, has been invited to present and chair at a number of National and International conferences and is on the boards of both ageing and stem cell societies. Claire is highly motivated by her research questions, but thrives on the opportunity to support and to mentor students and early career researchers as they progress through their careers.
Stuart Phillips graduated with a B.Sc. in biochemistry and an M.Sc. in Human Nutritional Biochemistry from McMaster University in 1989 and 1991, respectively. He obtained his Ph.D. from the University of Waterloo in Physiology in 1995. He went on to work in Dr. Robert Wolfe’s laboratory at the University of Texas Medical Branch in Galveston, Texas. He returned to McMaster University in 1999 as an Assistant Professor in Kinesiology and Medicine. He was subsequently promoted to Associate Professor in 2003. His research is focused on the impact of nutrition and exercise on human protein turnover, specifically in skeletal muscle in athletes, during weight loss, and in older persons. He is a consultant to several private sector companies, several professional ice hockey and football teams. His research is funded by the CIHR and NSERC, the USDA, and the Canadian Foundation for Innovation. Dr. Phillips is a New Investigator award recipient from the Canadian Institutes for Health Research and also a recipient of the Ontario Premier’s Research Excellence Award. An enthusiastic and energetic group of graduate students are the true heart of Dr. Phillips’ more than 180 publications, 100 public presentations and continuing enthusiasm for research.
Maria studied Biology in the Autónoma University in Madrid, following which she undertook her PhD in the Institute for Biomedical Research, Madrid, under the supervision of Ignacio Palmero, in the field of tumour suppression and cellular senescence. In 2009 Maria joined Manuel Serrano's lab at the Centro Nacional de Investigaciones Oncológicas (CNIO). Maria’s research interests are rooted in Stem Cell Biology and Cellular Reprogramming.
David Gems was a postdoc at the University of Missouri-Columbia USA with Don Riddle before moving to UCL with a Royal Society fellowship in 1997. Much of his work uses the nematode C. elegans to understand the genes and mechanisms that control aging. He has also contributed to studies of aging in Drosophila, the mouse and the nematode Strongyloides ratti, and penned articles on the ethics of aging research. He is a founder member and a Director of the UCL Institute of Healthy Ageing, and has contributed to some 90 research papers, review articles and book chapters. Web link: http://www.ucl.ac.uk/iha/

Academic background

2012   Professor of Biogerontology, Institute of Healthy Ageing, UCL.
2005   Reader in the Biology of Ageing, Dept. of Genetics, Evolution and Environment, UCL.
1997-2004 Royal Society Research Fellow, Department of Biology, University College London.
1993-96   Postdoctoral fellow, University of Missouri-Columbia, USA. Genetics of aging in C. elegans.
1991-93   Postdoc, Imperial College London. Biology of nematode parasite Toxocara canis.
1987-90   Ph.D., Institute of Genetics, University of Glasgow. Aspergillus nidulans genetics.
1984-86   Various work in Costa Rica, Nicaragua (Sandinista regime), Mexico, USA.
1980-83   School of Biological Sciences, University of Sussex. B.Sc. (Hons.) Biochemistry.
Paul Greenhaff is Professor of Muscle Metabolism and head of the Metabolic and Molecular Physiology research group in the School of Life Sciences at the University of Nottingham. He is also deputy director of the Medical Research Council/Arthritis Research UK Centre for Musculoskeletal Ageing Research. The research group’s strength lies in the experimental application of integrative physiology. Colleagues within the group cover the range of expertise and techniques necessary to perform integrated metabolic investigations in healthy human volunteers and patients, and to dovetail these with relevant animal, cell and molecular biological approaches, enabling truly translational research. Current research in his laboratory is focussed on the control and integration of muscle fuel utilisation in ageing, exercise and surgical trauma, and the molecular regulation of muscle mass in ageing, immobilisation, exercise training, inflammation (obesity, COPD, endotoxaemia) and statin myopathy. Recent and current research projects are funded by Arthritis Research UK, the Biotechnology and Biological Sciences Research Council, the Dunhill Medical Trust, industry and the Medical Research Council.
Prof. Russle Hepple, PhD

Director, McGill Research Centre for Physical Activity & Health
FRQS Chercheur Boursiers ~ Senior
Associate Professor
Department of Kinesiology
Department of Critical Care Medicine
McGill University Health Center
Meakins Christie Laboratories
Department of Medicine
McGill Centre for Studies in Aging
McGill University
Tel: 514 934-1934, x 35509
E-Mail: russell.hepple@mcgill.ca

Dr. Russ Hepple is an Associate Professor at McGill University with a primary appointment in the Department of Kinesiology and a research appointment in the Research Institute of the McGill University Health Centre. He is also a member of the Department of Medicine and Meakins Christie Laboratories at McGill University. Russ received his PhD from the Department of Physiology at the University of Toronto in 1996 where he had examined the effects of resistance versus aerobic training in adaptations of the oxygen transport system in healthy older men. He subsequently did a 3-year postdoc in the Division of Physiology at the University of California San Diego with Drs. Peter Wagner and Odile Mathieu-Costello examining structural determinants of muscle aerobic capacity. In the fall of 1999 he moved to the University of Calgary to start his own laboratory in the Faculty of Kinesiology and Faculty of Medicine. He remained in Calgary for 11 years during which time he created a laboratory with a focus on the mechanisms of declining skeletal muscle mass and function with aging. He moved to McGill University in 2011 where his current primary research focus involves examining the mechanisms of mitochondrial involvement in aging muscle and the mechanisms by which exercise training can protect the aging motor unit. He is also interested in mitochondrial involvement in long-term consequences of chemotherapy in skeletal muscle of cancer survivors, and how aging processes may exacerbate the consequences of non-muscle primary diseases for skeletal muscle. Russ has held continuous funding through CIHR since 2001 and currently holds 2 CIHR operating grants as PI. Throughout his career he has held several research awards including New Investigator Awards from the Heart & Stroke Foundation of Canada and CIHR, a Senior Investigator Award from the Alberta Heritage Foundation for Medical Research, and most recently a Chercheur Boursiers Senior award from the Fond de Recherche Quebec Sante. He serves on two grant peer review panels with CIHR and the Skeletal Muscle and Exercise Physiology study section of the NIH. He has published 65 research articles in highly respected journals during his career.
Dr. Ingram holds an academic appointment as Professor and Chief of the Nutritional Neuroscience and Aging Laboratory at the world-renown Pennington Biomedical Research Center (PBRC) in Baton Rouge, Louisiana, USA, which is a component of the Louisiana State University (LSU). Prior to this position, Dr. Ingram served as Chief of the Laboratory of Experimental Gerontology at the National Institute on Aging, National Institutes of Health, in Baltimore, Maryland. He received his B.A. in psychology from Louisiana State University in 1970 and his doctorate in psychology and gerontology from the University of Georgia (UGA) in 1978 followed in 1979 by a Postdoctoral Fellowship at the Jackson Laboratory, Maine, before joining the National Institute on Aging in 1980. In 2012, Dr. Ingram was also appointed as Professor (part-time) within the Geriatrics Section, Department of Internal Medicine, LSU Health Science Center, New Orleans. He also serves at the Associate Director of the Animal Phenotyping Core for the Nutrition Obesity Research Center at PBRC.

With over 350 scientific publications to his credit, Dr. Ingram has conducted pioneering research focused on nutritional and pharmacological interventions designed to attenuate aging, age-related disease, and functional decline. As a major new research area, his lab is investigating the development of calorie restriction mimetics. The objective is to identify compounds that mimic effects of calorie restriction by targeting metabolic and stress response pathways affected, but without actually restricting caloric intake. Other major lab activities involve developing and conducting behavioral assays of aging in rodents with focus on motor and memory performance. The objective is to identify mechanisms of age-related decline in motor and memory performance. As a primary objective of this research, investigations are directed toward preclinical development of pharmacological, hormonal, genetic, and nutritional interventions that improve behavioral function. His research has produced patented drugs for treating Alzheimer’s disease. Most recently, he has begun extensive studies on the health benefits of whole foods, particularly berry fruits. In this regard, he is involved in several clinical studies investigating whole foods and food supplements on physical and cognitive health.

Dr. Ingram serves on editorial boards of several biomedical journals, including the Journals of Gerontology, is the past editor of Gerontology, currently Editor-in-Chief of the Journal of the American Aging Association. He is a Past President of the American Aging Association (1999) and the Gerontological Society of America (2011). He also serves as a scientific advisor to several nutritional and pharmaceutical companies, including GeroScience, Inc.; Proctor & Gamble; Welch’s, Inc.; QR Pharma, Inc.; Juvenon, Inc., and CanCog, Inc. Dr. Ingram has received several honors including the 1978 Zimmer Award from the Department of Psychology, UGA; a 1996 Merit Award from the National Institutes of Health; the 2002 Harman Research Award from the American Aging Association, and the 2013 Distinguished Graduate Alumni Award from UGA.
Dr. Brian Kennedy is internationally recognized for his research in the basic biology of aging and as a visionary committed to translating research discoveries into new ways of detecting, preventing and treating age-related conditions. These include Alzheimer’s and Parkinson’s diseases, cancer, stroke, diabetes and heart disease among others. He leads a team of 20 principal investigators at the Buck Institute - all of whom are involved in interdisciplinary research aimed at extending the healthy years of life.

Kennedy earned his PhD at the Massachusetts Institute of Technology. His pioneering work as a graduate student led to the discovery that Sirtuins (SIR2) - enzymes that coordinate cell stress and metabolism - are key factors in the aging process. His current work involves nutrient signaling pathways linked to dietary restriction with an emphasis of the TOR pathway. Scientists in the Kennedy lab study aging in several model organisms, including yeast, nematode worms, mice, and humans. His research involves an intensive focus that is unusual in the field - his work seeks to move discoveries from simple organisms into mammalian animal models as quickly as possible in order to develop new approaches to alleviate age-associated diseases in humans.

Kennedy has published more than 100 manuscripts in prestigious journals including Science, Nature, Cell and the Proceedings of the National Academy of Sciences. He served on the National Institutes of Health Cellular Mechanisms of Aging and Development study section from 2006 to 2012, as well as on the grant review committee for the American Federation for Aging Research. He is co-Editor-in Chief of Aging Cell, and an Associate Editor for multiple journals. He is co-founder of Delos Pharmaceuticals, is a co-author on aging research patents and serves as a consultant for Biotech and Pharmaceutical companies.

He is actively involved in aging research in the Pacific Rim, which features the largest elderly population in the world. He is a visiting professor at the Aging Research Institute at Guangdong Medical College in China. He is also an Affiliate Professor in the Department of Biochemistry at the University of Washington, Seattle.
Liz completed a BSc in Biochemistry and Biological Chemistry at the University of Nottingham and went on to carry out an Arthritis Research UK-funded PhD at the University of Manchester, investigating the biochemical basis of an inherited skeletal dysplasia caused by mutations in cartilage oligomeric matrix protein (COMP). Postdoctoral research carried out within the Wellcome Trust Centre for Cell-Matrix Research examined how the assembly and turnover of extracellular matrix is regulated by genetic factors, proteolytic enzymes and protein trafficking. This research included the identification of an actin-based cellular mechanism (fibripositors) mediating collagen fibril alignment in developing tendon (Canty et al., J. Cell. Biol. 2004, 165;553-63 and J. Biol. Chem. 2006, 281;38592-8) and the award of the Rupert Timpl prize from the International Society for Matrix Biology in 2006. Liz was appointed to a Lectureship at the University of Liverpool in 2010 and was successful in applying for an MRC New Investigator Research Grant. Liz is currently a Senior Lecturer in the Institute of Ageing and Chronic Disease and is affiliated with the MRC-Arthritis Research UK Centre for Integrated research into Musculoskeletal Ageing (CIMA). Current research interests include understanding the dynamics of collagen synthesis and turnover, the role of stem cells in musculoskeletal homeostasis and the role of glucose in musculoskeletal ageing. Tissues of interest are primarily tendon and ligament but include cartilage, bone, cornea and intervertebral disc, as well as fibrotic tissue.
Costis Maganaris gained his PhD in 1999 and became a Professor of Musculoskeletal Biomechanics in 2005. In 2012 he moved to Liverpool John Moores University to lead the Biomechanics group at the Research Institute for Exercise and Sport Sciences. His research interests are focused on musculoskeletal structure and function, the plasticity that muscles, tendons and joints exhibit in response to ageing, exercise, disease and disuse, and the implications for locomotion, especially stair negotiation. He has authored and co-authored more than 100 SCI papers and received international awards of excellence and external funding from medical charities and research councils.
Maeve was educated at Queens University Belfast and did postgraduate research in immunogenetics at Stanford University, USA. She is a Fellow of Higher Education Academy, a Harvard Macy Scholar and teaches and co-ordinates the undergraduate Module in Ageing and Health at Queens.

As a Consultant Physician she provides clinical care to Elderly people with a special clinical and research interest in those over 90 years of age. She set up and co-ordinates a longitudinal study of octo/nonagenarians, Belfast Elderly Longitudinal Free-living Ageing STudy (BELFAST), contributing understanding to the genetic, immunological, cardiovascular and nutritional factors relating to longevity. She is principal investigator in the FP 6 EU Integrated Project-Genetics of Healthy Ageing (GEHA)-which recently identified genes related to longevity in 3500 European nonagenarian sibling pairs. As a co-ordinator in the ACUME2 Socrates Thematic Network, she has linked GeHA science with the narrative of GeHA participants giving their insights into their longevity in an authored book called ‘Super Vivere: Reflections on Living Long and Ageing Well’. She is a current Trustee of AgeNI, a former Chair of British Geriatrics Society Northern Ireland, Member of the Policy Committee British Geriatrics Society in London and previously a visiting lecturer to the British Geriatrics Society Teaching Programme for Geriatric Fellows in Taiwan.
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Oliver Witard is a lecturer in the School of Sport at the University of Stirling in Scotland. Previously, he was a post-doctoral research fellow (2008-10) and doctoral researcher (2005-08) in the School of Sport and Exercise Sciences at The University of Birmingham in England. Both his doctoral and postdoctoral work was under the supervision of Professor Kevin Tipton.

The focus of his research is the adaptive response of human skeletal muscle to exercise and nutrition, in particular protein feeding. His primary interest is optimising nutritional strategies to support the gain of muscle mass in athletes and the elderly. Other interests include the role of nutrition for maintaining performance and immune function during intensified periods of endurance training (‘overreaching’).

He has given both oral and poster presentations at international conferences showcasing findings from his work. In 2010, he received the Young Investigator Award at the European College of Sports Sciences Congress for his work investigating the effect of increased protein intake on tolerance to endurance training.

Outside of work, Oliver likes to think of himself as a football player and a middle / long-distance runner.
Oral Presentations
Book of Abstracts

In Presentation Running Order
Demographic trends tell us that aging is not a secular, but a global concern. The incidence of almost every single chronic disease increases with aging and yet the most prevalent of these have a substantial modifiable lifestyle component. The WHO defines ‘active aging’ as the process of optimizing opportunities for health, participation and security in order to enhance quality of life as people age. While there is no one prescription for active aging the thesis proposed here is that utilization and promotion of physical activity in a preventive and curative fashion in aging would be highly efficacious in facilitating more older persons to age ‘actively’. In addition, while ‘good nutrition’ is a contentious topic it seems that some basic nutritional tenets, if followed, could substantially reduce chronic disease risk. What is underappreciated is at the junction of physical activity and nutrition there is a likelihood of synergistic benefit for health in aging. Moreover, the ‘side effects’ of implementation of the strategies presented are likely to spread well beyond the direct benefits known to exist to areas including alleviation of risk for dementia and cognitive decline. Evidence for the benefits of nutritional, with a focus on protein, and physical activity will be presented and the ramifications of nutritional and physical activity strategies discussed.
Why do humans live longer than other higher primates? Why do women live longer than men? What is the significance of the menopause? Answers to these questions may be sought by reference to the mechanisms by which human aging might have evolved. Here, an evolutionary hypothesis is presented that could answer all three questions, based on the following suppositions. First, that the evolution of increased human longevity was driven by increased late life reproduction by men in polygynous primordial societies. Second, that the lack of a corresponding increase in female reproductive lifespan reflects evolutionary constraint on late-life oocyte production. Third, that antagonistic pleiotropy acting on androgen-generated secondary sexual characteristics in men increased reproductive success earlier in life, but shortened lifespan. That the gender gap in aging is attributable to androgens appears more likely given a recent report of exceptional longevity in eunuchs. Yet androgen depletion therapy, now used to treat prostatic hyperplasia, appears to accelerate other aspects of aging (e.g. cardiovascular disease). One possibility is that low levels of androgens throughout life reduces aging rate, but late-life androgen depletion does not.
Reprogramming in vivo: The power of manipulating cell plasticity

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The ability to reprogram differentiated cells into induced pluripotent stem cells (iPS cells) has considerably improved our current understanding of cellular plasticity and has also helped to paving the way towards regenerative medicine. However, little was known about whether or not in vivo reprogramming is feasible and if so, what type of cells are generated in vivo and what are their implications in the organism. We have generated a “reprogrammable” transgenic mouse strain that ubiquitously express the so-called Yamanaka factors upon treatment with doxycycline. We have shown that transitory induction of the four Yamanaka factors in mice, for just one week, is able to induce dedifferentiation and pluripotency in a variety of tissues and to various degrees. Mice that had activated the reprogramming factors developed multiple teratomas, which is indicative of complete reprogramming events in vivo. Indeed, reprogrammable mice present circulating iPS cells in the blood and, at the transcriptomic level, these in vivo generated iPS cells are closer to embryonic stem cells (ES cells) than standard in vitro generated iPS cells. Moreover, in vivo iPS cells efficiently contribute to the trophectoderm lineage and generate embryo-like structures that express embryonic and extraembryonic markers, suggesting that they achieve a more plastic or primitive state than ES cells. Our results could be relevant for the development of future applications of reprogramming in regenerative medicine.
Sarcopenia and loss of muscle quality: are we barking up the wrong tree?

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Sarcopenia, the age-related loss of muscle mass, affects >50% of the population aged 75 yr and over and is a main cause of impaired physical performance and reduced mobility. Amongst the several factors contributing to sarcopenia neuroendocrine changes are regarded as primary drivers of this condition (1) and responsible for δ-motoneurons and neuromuscular junction (NMJ) degeneration, for muscle fibre denervation which, also fuelled by mitochondrial dysfunction and oxidative damage, leads to loss of motor units and muscle weakness. One of the major functional characteristics of sarcopenia is the disproportionate loss of muscle strength: at the age of 80 yrs, the loss of muscle strength is about 4-fold greater than that of muscle size. This intrinsic muscle weakness, also known as a deterioration in ‘muscle quality’ has traditionally been reconducted to a decrease in fibre specific tension, reduced excitation-contraction coupling and reduced neural drive. However, new evidence suggests that this disproportionate loss of force also arises from changes in the extracellular matrix (ECM) and of associated proteins, leading to a decrease in lateral force transmission (2), which in young muscle normally contributes to >50% of muscle force output. Hence, the muscle weakness associated with sarcopenia may not only take origin from muscular changes but also in the ECM tissue connecting sarcomeres to the tendon.

References
Acute stress resistance in ageing worms: Older does not mean frailer.

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In various species, long-lived mutants tend to be stress resistant and vice versa. It suggests that the same mechanisms that protect against stress also promote longevity, or that stress is contributing to lifespan shortening. One would then expect older animals to be more sensitive to stress. To investigate this, we developed a new technique to perform stress assays at a higher throughput. Worm populations are aged over one day to two weeks, and oxidative, thermal or osmotic acute stresses are performed in 384-well plates. Exploiting the fact that dying worms fluoresce in blue (Coburn et al. PLoS Biology 2013), worm survival over time is inferred from the time-lapse recording of blue fluorescence with a plate-reader. From the blue fluorescence curves, we determine the average time of death following stress, providing a quantitative measure of stress sensitivity. We screened lifespan variants and found that depending on the stress, the correlation between age and stress sensitivity can be opposite. Although heat stress resistance negatively correlates with age, oxidative stress resistance positively correlates with age, which argues against the oxidative damage theory of ageing. We started uncovering the underlying mechanisms.
To investigate the role of ACE-like enzymes in dietary effects on ageing-related and circadian health, function and metabolism we are studying Acer (angiotensin-1-converting enzyme related), a homolog of human ACE, in the fruit fly Drosophila melanogaster. Human angiotensin-1-converting enzyme (ACE) is believed to have a role in blood homeostasis including the regulation of blood pressure, specifically by raising blood pressure when needed. In Drosophila, it has been previously been shown that Acer null flies show a phenotype of disrupted night-time sleep but not day-time sleep (Carhan et al, 2010). Fecundity is determined by dietary yeast (Skorupa et al, 2008), however Acer nulls do not show the expected increase in fecundity with increasing dietary yeast and our preliminary data suggest that Acer is also involved in the regulation of lifespan and energy storage in response to nutrient intake. Acer is thus a novel gene involved in ageing and nutrient responses. The major aim of this project is to investigate how Acer modulates lifespan, sleep and physiological responses to nutrient intake. Here we show that null mutants of Acer have extended lifespan, and different sleep patterns under different dietary levels of sugar and yeast. Future experiments will measure storage of sugars (glucose and trehalose), feeding behaviour, and establish possible links to nutrient sensing pathways in response to these dietary changes.
There is a growing sense that a holistic understanding of aging biology may be achievable. This would represent a tremendous advance in our collective biological understanding and afford opportunities for novel interventions to enhance human health. The TOR pathway is one point of convergence and a clinically approved drug targeting the TOR kinase, rapamycin, extends murine lifespan and healthspan. Many more small molecules will be added to the list of anti-aging compounds, but here rapamycin and TOR will be used to conceptualize how agents extending healthspan might be developed to improve human health. I describe studies testing mechanisms by which reduced TOR signaling impacts aging, including (1) assessment of downstream substrates of the TORC1 complex, (2) identification of tissues where this pathway impacts aging and (3) determination of the potential therapeutic value of targeting this pathway for effective prevention and/or therapy in chronic diseases of aging. In addition, we are actively trying to create modified versions of rapamycin that have efficacy with reduced side effects. Progress on these efforts will be reported.
Activity, exercise and ageing mechanisms

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In the UK, the percentage of people aged 65 years and over increased from 15 – 17% (1.7 million) between 1985 and 2010. Furthermore, it is projected that by 2035 people aged >65 years will make up 23% of the UK population, with those aged >85 years accounting for 5% of the total population (1). Increased life expectancy does not necessarily increase health expenditure, but ill-health in the final part of life certainly does. It is imperative therefore that research on the “normal” ageing process that will inform on strategies for improving health span and well-being is prioritised, thereby reducing pressure on the health and social care systems and improving quality-of-life. With this in mind, this lecture will focus on the striking paucity of data on the role of physical inactivity in the development of many of the features associated with poor health and well-being in older age. It is our contention that many of the biological features attributed to “ageing” per se may in fact be a consequence of previous and/or current levels of physical inactivity. Indeed, many of the purported negative effects of ageing e.g., anabolic resistance of muscle to exercise and nutrition, muscle insulin resistance and lipid accumulation and accelerated muscle strength loss can be manifested in young people simply by exposure to inactivity. Research examining interactions between ageing and physical activity needs to be prioritised.

References
Chronic deficits in muscle protein synthesis (MPS) may underlie blunted skeletal muscle hypertrophy in response to resistance exercise training (RET) in old versus younger men

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Resistance-exercise-training (RET) increases muscle mass/function and remains the most effective countermeasure for sarcopenia. We previously showed that muscle protein synthesis (MPS) and hypertrophy are blunted in older vs. younger individuals exposed to allied RET paradigms (1,3). Here, we hypothesized deficits in longer-term MPS (quantified using D2O) would reflect blunted hypertrophy in older (O) vs. younger (Y) men. We recruited 8 Y (23±1) and 7 O (70±1) men who undertook 6-wks progressive unilateral RET (6×8 reps, 75%-1RM/3-wk); MVC and 1-RM were assessed throughout, as was DXA (0/6-wk) and muscle ultrasound (0/3/6-wk). After baseline bi-lateral muscle biopsies, subjects consumed 150ml-D2O (70-Atom%) then 50ml.wk-1 with bi-lateral biopsies at 3/6-wk to quantify MPS using GC-Pyrolysis-IRMS, as: MPS=(%d-1)=-Ln((1-[APE Ala/APEP])/t))×100. Firstly, Y men possessed greater leg-muscle mass and strength at baseline (P<0.05). After 6-wks RET, 1-RM increased in Y (31±5%; P<0.01) and O (24±3%; P<0.01) men, while MVC increased in Y but not O men at all joint angles e.g. 60° Y: 31±6% (P<0.01), O: 15±13% (P=0.4). After 6-wks RET, quadriiceps mass [by DXA] increased significantly only in Y men (Y: 4±1%; P<0.05 vs. O: 1±0.3%; P=0.2), as did muscle-thickness (Y: 13±2%; P<0.05 vs. O: 4.2±2%; P=0.08). Basal rates of MPS were not affected by age or RET. Instead, reflecting muscle hypertrophy, MPS was increased only in Y men and only over the first 3-wks RET: (Y: 22±9%; P<0.05; O: 11±4; P=0.09). We conclude RET-muscle adaptations occur rapidly, are blunted in healthy O men (2,3) and that chronic deficit’s in MPS could underpin this.

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Cellular ageing is characterised by a progressive deterioration of physiological function. The ageing process in humans is associated with an increased risk of cancer, diabetes, heart disease and neurodegeneration as we get older. Numerous theories have been proposed to explain the origins of ageing. Some postulate that cells progressively deteriorate merely as a consequence of environmental “wear and tear”, whilst others hypothesise that ageing performs an integral role in the management of resources by killing off previous generations. In contrast to these theories, we propose that ageing may have evolved as a positive trait rather than a negative one, allowing a subpopulation of individuals to rapidly adapt to environmental change. We show that aged yeast cells undergo an epigenetic shift that gives them a fitness advantage over younger cells upon a sudden change in nutrient availability. Therefore, ageing may offer individuals a different life strategy whereby relative fitness in times of plenty is sacrificed in order to provide a significant competitive advantage in the event of sudden environmental change.
Genome-wide analysis of small heat shock proteins involved in yeast ageing

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Genes involved in basic cellular processes such as metabolic regulation, stress resistance and genomic stability determine longevity in organisms as divergent as yeast, worms, flies and mammals. This suggests that there may be conserved universal mechanisms involved in ageing. Evidence to support this idea comes from the observation that lifespan can be increased in all these model organisms by reducing the amount of nutrients consumed – a phenomenon known as dietary restriction (DR). In Saccharomyces cerevisiae, replicative lifespan can be increased by reducing the concentration of glucose from the standard 2% down to 0.5% or below. However, the precise mechanisms by which dietary restriction increases yeast lifespan remain unclear and controversial. We have found that Hsp12 and Hsp26 are greatly upregulated by DR and by various manipulations known to retard ageing. Furthermore, lifespan extension by DR was abolished in an hsp12Δ/hsp26Δ double mutant strain, indicating that these small heat shock proteins are essential for the longevity effect of dietary restriction. To shed light on the mechanisms by which Hsp12 and Hsp26 affect longevity, we performed Synthetic Genetic Array (SGA) and Quantitative Fitness Analysis (QFA) screens to identify genetic interactions of HSP12/26 on a genome-wide scale. This involved the generation of thousands of double mutant strains and analysis of their growth under various conditions, including DR. Results from these genome-wide screens, which will be presented here, have revealed novel genetic interactions that may provide insight into the cellular functions of Hsp12 and Hsp26 and how this impacts on DR-induced lifespan extension.
Ageing is associated with the accumulation of reactive oxygen species (ROS) and there is growing interest in the role of these species in health and disease. Electron paramagnetic resonance (EPR) is a technique which can detect ROS in tissues. The aim of this study was to examine the generation of ROS in both the sciatic nerve and tibialis anterior (TA) muscle of old (25-27 month) and young (6-8 month) WT mice at various time points following electrically stimulated muscle contractions. Both old and young WT mice were anaesthetised and subject to 15 mins of electrically stimulated contractions. Mice received an infusion of the spin probe, 1-Hydroxy-3-carboxy-2,2,5,5-tetramethylpyrrolidine (CPH), via a tail vein over 2 hrs commencing 15 min or 24 h following contractions. The EPR spectra of sciatic nerve and TA were recorded at liquid nitrogen temperature using a Bruker benchtop e-scan spectrophotometer. In young mice, following 15 min of isometric contractions and immediate CPH infusion, both sciatic nerve and TA muscle showed an increased level of oxidised CPH probe compared with control mice that did not undergo contractions. In old mice this increase post contractions was not seen. In young mice, at 24 h post isometric contractions, the levels of oxidised spin probe were similar those of control mice but in old mice at 24 h post contractions there were significant increases in ROS compared with the control non-contracted mice and mice at 15 min post contractions. Findings also indicate that the oxidation of CPH was higher in old mice at rest compared to young mice at rest. This research was financially supported by the BBSRC.

EPR analysis indicates that an increase in the formation of reactive oxygen species occurs in the sciatic nerve and tibialis anterior muscle following electrically stimulated contractions

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Virtually all aspects of mammalian physiology are governed by circadian clocks and exhibit daily ~24h rhythms, such as activity/rest cycles, hormonal release and body temperature. Circadian clocks are an evolutionarily conserved timing mechanisms which anticipate external daily changes to optimally match the bodily functions to surrounding environment. The rhythms in peripheral organs are entrained by a master pacemaker residing in suprachiasmatic nuclei (SCN) of the brain’s hypothalamus, which is itself synchronised by daily light-dark cycles and strengthened by a scheduled exercise. Emerging research has shown that disruptions of circadian rhythms (as a result of genetic variation, ageing, 24h lifestyle) lead to many age-related chronic pathologies. In this study, we investigated behavioral and molecular rhythms of SCN neurons and peripheral tissues from young (<4m) and aged (>24m) transgenic clock-reporter mice in response to voluntary exercise (wheel-running). Using locomotor activity tracking and real-time bioluminescence recordings of molecular rhythms, we reveal significant periodicity changes in activity rhythms of aged mice in response to voluntary exercise. Moreover, the molecular rhythms of SCN pacemaker neurons displayed a striking feature of lower amplitude and advanced phase timing suggesting a profound temporal misalignment with the rhythms in peripheral tissues. Furthermore, genome-wide transcriptome profiling of aged SCN showed significant alterations in the pathways linked to synaptic plasticity, epigenetic regulation and inflammation. All together, these findings reveal for the first time the molecular basis for age-related changes in the circadian clockwork and suggest potential chrono-therapeutic targets for ameliorating disrupted circadian physiology during exercise and ageing.
Improvements in exercise capacity and cardio-metabolic risk following group-based high intensity interval training (HIT) are similar in young and older individuals

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Introduction: HIT is accepted as a novel, time-efficient exercise strategy to improve fitness and health in young individuals. Here we compare improvements in exercise capacity and cardio-metabolic risk following 10 weeks of HIT in two age groups.

Methods: 46 sedentary volunteers, separated into young (32±1 y, 8M, 14F, 26.6±0.9 kg.m-2) and old age groups (52±1 y, 7M, 17F, 28.7±1.1 kg.m-2; P<0.05 age difference), undertook instructor-led group-based HIT classes (≤25 min per session, 3x.wk-1) in a real life gym setting. Improvements in exercise capacity (VO2max), body composition (bioimpedance), insulin sensitivity (oral glucose tolerance test) and blood lipid profiles were measured as the relative change from baseline. Results: Adherence to the HIT intervention was not different (young 83±3%, old 87±3% sessions attended). Training improved VO2max (young 9±2%, old 10±2%; P<0.05) and induced small decreases in weight (young 1±1%, old 1±1%; P<0.05) and relative fat mass (young 2±2%, old 3±2%; P<0.05). Fasting insulin concentrations tended to decrease (young 9±5%, old 9±4%; P=0.07) whereas insulin sensitivity (Matsuda) improved post-training (young 18±6%, old 24±9%; P<0.05). Fasting serum concentrations of triglyceride (young 7±4%, old 7±3%; P<0.05), total cholesterol (young 6±3%, old 5±3%; P<0.05) and LDL cholesterol (young 8±5%, old 10±5%; P<0.05) were reduced after training. No significant differences between groups were detected in effect size for the variables reported.

Conclusions: The results provide evidence that instructor-led, group-based HIT can be implemented with a high adherence and is successful in increasing aerobic exercise capacity and reducing cardio-metabolic risk factors in individuals over a large age range.
Introduction:
Age-associated alterations in balance mechanisms and deteriorations in muscle strength may necessitate alternate stair descent strategies to ensure safe negotiation. The aim of the study was to compare the influence of increased step rise and stair negotiation strategies, specifically step-over-step (SoS) and step-by-step (SbS), on gait patterns in the elderly.

Methods:
Eleven elderly participants descended a four-step custom-built instrumented staircase at a self-selected speed. Participants descended using a SoS or SbS strategy on two step configurations: a standard rise of 170mm (STD) and an increased rise of 255mm (INC). A 3D motion analysis system synchronised with force platforms embedded into the staircase, was used to capture whole body centre of mass (CoM) velocity, acceleration and kinetic data of the leading limb.

Results:
Compared to SoS, SbS in the STD configuration reduced the CoM vertical (0.48m/s vs -0.09m/s) and A/P velocity (0.50m/s vs 0.21m/s) during late stance and swing transition, with similar reductions in vertical and A/P velocity in SoS vs SbS (-0.67m/s vs -0.11m/s and 0.49m/s vs 0.23m/s) in the INC configuration. SoS in the INC configuration resulted in increased plantarflexor (1.10Nm/kg vs 1.45Nm/kg) and hip extensor moment (-0.08Nm/kg vs 0.43Nm/kg) compared to SoS in the STD configuration, with no differences in the SbS strategy.

Discussion:
An alternate stair descent strategy offers greater CoM control in the potentially dangerous transition between stance and swing. Concurrently, the tandem double stance period negates the need for increased muscle moments in late stance required to eccentrically control the lowering of body mass in the traditional SoS strategy. SbS could offer increased CoM control and stability during stair descent.
Mitochondria play multiple roles involved in maintaining homeostasis in skeletal muscle and their dysfunction is frequently postulated as a mechanism for deterioration of aging muscle. Notwithstanding this point, aging muscle at more advanced and thus clinically relevant ages is characterized by a marked accumulation of severely atrophied denervated muscle fibers. Since denervation itself can recruit mitochondrial-mediated pathways of atrophy, understanding the degree to which mitochondrial alterations in aging muscle represent a primary organelle defect versus being secondary to denervation is essential to inform therapeutic strategies for aging muscle. To this end, my talk will address the progression of mitochondrial functional impact with advancing age and the contribution of denervation to recruitment of mitochondrial-mediated pathways of atrophy, with discussion of the therapeutic implications of these findings.
Understanding how to age better is important to people, to populations and for government policy. Dr Rea will discuss some of the immunological, genetic, nutritional and cardiovascular risk factors which her research group has found in her BELFAST cohort of octo/nonagenarians who appear to have aged well, not only with long ‘lifespan’ but also with ‘healthspan’. She will also discuss recently published findings on genes related to longevity in 3500 European nonagenarian sibling pairs in EU Genetics of Healthy Ageing (GEHA) and her findings and insights about longevity from the GeHA nonagenarian siblings themselves.
Can high intensity interval training reduce the risk of inflammatory and immune mediated morbidity and mortality with age?


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Background: Ageing is accompanied by reduced immune function and increased systemic inflammation (inflamm-ageing), both of which contribute to morbidity in older adults. Exercise has known health benefits mediated in part by improving these functions but with age there is a sharp decline in exercise participation. High-intensity interval training (HIIT) offers a paradigm shift by utilising short periods of exercise and mimicking physiological improvements seen in endurance type training (ET). However, little is known about the effects of HIIT on inflammation and immune function per se and in particular in older adults.

Method: To address this issue 90 sedentary healthy participants (20-60yrs) were randomly assigned to either 10-weeks of spin-ergometer HIIT or ET and comprehensively assessed for inflammatory and immune modifications. HIIT consisted of repeated sprints (15-60secs) and recovery periods (<25mins/session, 3sessions/week). ET consisted of continuous cycling (~65% VO2max, 30-45mins/session and 3-5sessions/week). Adherence to HIIT was greater than ET (p<.001).

Results: Both HIIT and ET reduced inflammation (CRP, IL-6, IL-8, MCP-1), improved endocrine biomarkers of ageing (leptin:adiponectin, cortisol:DHEAs) and improved immune function (neutrophil & monocyte). Following stratification for age [<40yrs (Young); >40yrs (Middle-Aged)] HIIT showed reduced IL-8 for Young (p=.002) and Middle-Aged (p=.049), reduced leptin:adiponectin [Young (p=.002) & Middle-Aged (p=.039)] and reduced cortisol:DHEAs [Young (p=.017) & Middle-Aged (p<.001)]. HIIT improved monocyte bactericidal activity (p<.05) and neutrophil phagocytosis (p=.017) in Middle-Aged but not Young HIIT participants.

Conclusion: In conclusion, HIIT reduces inflammation and improves immune function similar to ET in older adults and offers the potential to improve health in elderly adults.
In order to manage the rise in life expectancy and the concomitant increased occurrence of age related diseases, research into ageing has become a strategic priority. Mouse models are commonly utilised as they share high homology with humans and show many similar signs and diseases of ageing. However, the time and cost needed to rear aged cohorts can limit research opportunities. Sharing of resources can provide an ethically and economically superior framework to overcome some of these issues but requires dedicated infrastructure. ShARM (Shared Ageing Research Models) (www.ShARMUK.org) is a new, not-for-profit organisation funded by Wellcome Trust, open to all investigators. It collects, stores and distributes flash frozen tissues from aged murine models through its biorepository and provides a database of live ageing mouse colonies available in the UK and abroad. It also has an online environment (MICEspace) for collation and analysis of data from communal models and discussion boards on subjects such as the welfare of ageing animals and common endpoints for intervention studies. Since launching in July 2012, thanks to the generosity of researchers in UK and Europe, ShARM has collected more than 2,000 tissues and has in excess of 2,000 mice registered in live ageing colonies. By providing the appropriate support ShARM has been able to bring together the knowledge and experience of investigators in the UK and Europe to maximise research outputs with little additional cost and minimising animal use in order to facilitate progress in ageing research.
Reactive oxygen species and muscle ageing: Active participants or by-standers?

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Reactive oxygen and nitrogen species have been implicated in the processes of ageing for a considerable period of time, although recent data indicate that they are not the fundamental determinant of lifespan in several experimental models. Older hypotheses focused on the potential role of ROS in inducing oxidative damage as the mechanism by which they might influence longevity, but it has become apparent in recent years that in normal physiology ROS play fundamental roles in regulating multiple redox-regulated signalling pathways in all tissues. Skeletal muscle generates superoxide and nitric oxide as part of normal activity and the activities of these species and secondary species derived from them are increased during contractile activity. The functions of contraction-induced ROS appear multiple and are the subject of considerable current investigations and our group has focussed on the role of ROS as mediators of the generation of some acute stress responses following contractions. Ageing is associated with a chronic activation of these stress responses at rest and an attenuation of the responses to contractions. In muscle, interventions to overcome this attenuation were found to lead to a preservation of muscle function in transgenic models. Aberrant ROS activities in muscle from aged mice and humans appear to contribute to the defective responses to contractile activity during ageing and a major question now being addressed is whether the age-related changes in ROS generation originate in the muscle or are secondary to age-related changes in other tissues.

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By reducing dietary intake by 20-50% in a wide variety of species, many health benefits have been reported, including reduced incidence and retarded onset of chronic diseases, enhanced stress protection, and maintenance of youthful function in conjunction with increased lifespan. Calorie restriction (CR) has proven to be the most robust means to retard aging, but its application to human aging represents a challenge. Reports of persons who practice CR and from controlled clinical studies also indicate such regimens can positively impact indices of health and risk factors for disease. Nonetheless, despite evidence that CR produces beneficial effects in humans, therapeutic application would be problematic due to difficulties of compliance and other quality of life issues. To address this challenge, the concept of CR "mimetics" (CRM) has been introduced as a method to obtain "anti-aging" and health-promoting benefits of CR without requiring reduced food intake. Several candidate CRM compounds have been proposed with different strategies involving upstream to downstream targeting. These include inhibitors of glucose metabolism (acarbose, glucosamine, 2-deoxyglucose, mannoheptulose), insulin sensitizers (metformin), sirtuin activators (resveratrol, nicotinamide, oxaloacetic acid), and mTOR inhibitors (rapamycin, spermidine). The field of CRM has evolved to commercial applications and is generating new candidates to evaluate, but there remains uncertainty about what targets will be most effective and what proof will be required to demonstrate efficacy of candidate CRM.
Ageing is associated with a gradual decline in skeletal muscle mass, strength and performance. However, muscle loss is not an inevitable consequence of advancing age. Although the aetiology of age-related muscle loss is clearly multifactorial, mechanistically, a key contributor to age-related muscle loss is anabolic resistance: the reduced sensitivity of older muscle to the key stimuli (i.e., nutrients, and physical activity) that regulate muscle mass. Theoretically, two viable approaches exist for overcoming anabolic resistance: (1) increase the potency of anabolic stimuli and (2) increase the sensitivity of muscle to anabolic stimuli. The general aim of this presentation focuses on how physical activity patterns of older adults can be targeted to overcome age-related anabolic resistance. Specifically, the importance of factors such as exercise intensity, volume and modality for stimulating gains in myofibrillar protein mass will be addressed. From a practical standpoint, this presentation makes the recommendation that older adults should combine high volume (rather than high-intensity) resistance exercise and endurance exercise into their everyday activities of daily living.
Diseases associated with ageing pose an increasing social and financial burden on society and represent a vital imperative for research in the biomedical sciences. We are undertaking the first large-scale project to investigate the interaction between genetic variation and the pleiotropic effects of ageing. We are employing mutagenesis and phenotyping to specifically generate new models of late onset or age-related disease. The emphasis will be on the exploration of the phenotype space in ageing mouse mutant populations providing us with the opportunity to: identify genes and pathways involved in age related disease, scrutinise these models for biomarkers of age related disease, and provide better platforms for pre-clinical assessment of new therapies for such diseases. Pedigrees are being aged to 18 months and undergo comprehensive phenotyping across a wide range of disease areas at several time points throughout the life of the mice. To date we have identified lines with age-related hearing loss, cardiovascular disease, retinal degeneration, neurodegeneration, obesity, and bone disease which are being mapped and characterised in detail. We have also identified three separate lines that appear to be resistant to obesity and may represent beneficial mutations; remaining lean as the mice age with normal lean mass but greatly reduced fat mass. The age challenged mice are an important resource for many research groups, identifying novel genes and pathways resulting in age-related phenotypes. In addition disease phenotypes we are now beginning to screen for advantageous or healthy ageing phenotypes.
By virtue of their anatomical location, tendons act as force transmitters between the muscle and the skeleton and enable joint movement to occur. However, the tendons do not act as rigid links, but exhibit viscoelastic properties. Due to the poor blood supply and metabolic activity of tendons relative to other organs it has long been thought that the viscoelastic properties of human tendons exhibit little plasticity. Advancements in imaging applications has made it possible to obtain tendon mechanical properties in vivo and showed that human tendons exhibit plasticity in response to maturation, ageing and conditions of altered mechanical loading. The presentation will review the current state of knowledge on the adaptability of human tendons to ageing, disuse and exercise and implications for muscle-tendon function and assessment.
Collagen fibrils provide an architectural framework and mechanical integrity to many skeletal and non-skeletal tissues and type I collagen is the major fibrillar collagen in vertebrates. Collagen fibril synthesis, organisation and maturation is a complex multi-step process involving both cells and physical environmental factors. In earlier work studying embryonic tendon development it was found that linear collagen fibril organisation is dependent on actin-based plasma membrane protrusions (fibripositors). Fibripositors are also present in developing cornea, skin and periosteum, however the cellular mechanisms coordinating tissue-specific three-dimensional arrangements of collagen fibrils are not well understood. Tissue repair often involves the formation of a scar tissue that does not recapitulate the original arrangement of collagen fibrils and can integrate poorly with the surrounding uninjured tissue, eventually leading to tissue degeneration or fibrosis. We are currently studying the production of normal and abnormal collagen (I) in stem cells and in both normal and fibrotic tissue, with the aim of understanding the role of stem cells in repair versus regeneration of collagenous tissues. We have found that differentiation of mesenchymal stem cells is associated with changes in collagen (I) gene expression and an altered ratio of collagen (I) mRNAs, indicative of altered collagen (I) production in stem cells.
Skeletal muscle cell autonomous role of the vitamin D receptor

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Epidemiological studies have linked Vitamin D deficiency to age-related declines in skeletal muscle function with an associated reduction in muscle expression of the Vitamin D receptor (VDR) (1). However, the role and function of the VDR in muscle remains poorly defined, with confirmation of bona fide expression in skeletal muscle cells only being recently substantiated (2). In order to enable study of the muscle cell autonomous role of VDR, we generated C2C12 muscle cells harboring shRNA lentiviral-mediated knock-down of the VDR. Knockdown (KD) of VDR was confirmed such that VDR-KD cells exhibited <85% of VDR expression vs. scrambled sequence shRNA (SCR) transfected cells. In terms of myogenesis, VDR-KD cells proliferated at a slower rate compared to SCR control cells (-27%±6%, P<0.01) as well as displaying a reduction in DNA synthesis (assessed via BRDU incorporation) (-31%±7%, P<0.05). Furthermore, altered cell-cycle activities, as assayed using flow cytometry approaches, were also evident in VDR-KD cells, with a greater proportion of the cell population being G0/G1 phase (+12±6%, P<0.05). VDR-KD cells also demonstrated altered differentiation characteristics, producing myotubes with a significantly greater diameter compared to SCR controls (+47±4% P<0.01) along with greater myonuclei number (i.e. SCR 10±0.3 nuclei/myotube vs. VDR 25±1, P<0.05). Finally, incubation of myotubes with IGF-1 increased protein synthesis in SCR (+16±0.4%, P<0.01), but not VDR-KD myotubes (-5±2%, N.S). The VDR appears to have pleiotropic effects in muscle cells playing a role both in myogenesis and the control of protein metabolism

References
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As the ageing population increases, it is essential to determine the mechanisms involved in ageing of the musculoskeletal system. A common characteristic of ageing is loss of skeletal muscle (sarcopenia) leading to a decreased life quality. There is currently little data available examining the involvement of epigenetic mechanisms in musculoskeletal ageing although such mechanisms are undoubtedly involved (Liu et al, Cell Rep. 2013). microRNAs are novel regulators of gene expression. microRNAs control myogenesis, regeneration and ageing (Goljanek-Whysall et al, PNAS 2011, Pincus et al, PloS Genetics 2011, Drummond et al, Amer J Physio 2008). To determine their role during ageing, we identified changes in microRNA and transcript expression in muscle in adult and old mice. Based on GO term analysis, we chose 2 microRNAs and their putative targets for further studies of their role in sarcopenia development. Our data show differential expression of miRNAs during muscle ageing, atrophy and regeneration. We validated miRNA targets related to acetylation and metabolism and characterised novel miRNA:target interactions in vitro. We are currently validating these interactions in vivo. This could lead to design of novel therapeutics for individuals affected by sarcopenia, effectively improving their lifestyle. The authors would like to thank University of Liverpool, Wellcome Trust, MRC-Arthritis Research-UK CIMA for funding.
Skeletal muscle comprises ~ 45% of the healthy human body mass. It is critical for development, growth, metabolism, posture, locomotion, thermoregulation and the provision of energy. Ageing, muscular dystrophies and cachexia are associated with muscle wasting and weakness, however, the mechanisms underpinning these losses may differ. Muscles hypertrophy (increase in size through an increase in the cross sectional area of individual fibres) when protein synthesis exceeds protein degradation, in response to e.g. loading, which ultimately leads to an increase in maximal force generating capacity. Conversely, muscles atrophy (decline in fibre size and cross sectional area) following disuse, unloading or disease, which culminates in a decline in peak force generating capacity - when protein degradation dominates. The adaptability of skeletal muscle, given its terminally differentiated state, is thought to be achieved via activation of resident muscle stem cells. The regulators of synthesis, degradation and ultimately muscle mass are therefore likely to involve complex cellular, biochemical and genetic controllers. Our research focuses on using and developing stem cell cultures to model the interactions of skeletal muscle cells with anabolic (insulin-like growth factors) and catabolic (tumour necrosis factor-alpha, interleukin-6) agents. Models span age, disease and injury and provide us with a means to understand the regulators (e.g. IGFBPs, PI3 kinase, MAP kinase, Adra1d, caspases and sirtuins), which influence survival, differentiation, migration or death of these cells. Key human studies complement our work (age, nutrition and exercise) and are critical, since severe loss of functional muscle mass contributes to increased morbidity and early mortality. This presentation will provide information on the use of our model systems and some insight into the regulators of muscle adaptation.
Poster Presentations

Book of Abstracts

Poster numbers can be found in the top right corner of each abstract page. This number refers to the location of the poster in the viewing area.
Stair descent is difficult and dangerous with reports that 10% of all fatal falls occur on staircases. Current regulations constrain step dimensions, but non-conforming staircases exist in older buildings. Staircases with higher rise or shorter going make additional demands on individuals. This study aimed to determine if the demands of non-conforming staircases produced biomechanical changes in older versus younger individuals.

Eighteen participants (7 older, 11 younger) performed stair descent on three staircase configurations; standard (ST, 175x275mm [rise x going]), short-going (SG, 175x175mm) and high-rise (HR, 325x275mm). Joint moments and centre of mass (CoM) accelerations were derived from movement analysis data and force platforms built into the steps of an adjustable staircase.

Lower CoM accelerations in the anterior-posterior and vertical directions occurred in older versus younger individuals when descending the ST (1.40m/s² vs 1.52m/s² (p=0.020) and 1.82m/s² vs 2.99m/s² (p=0.004) respectively) and SG staircases (0.80 m/s² vs 1.68 m/s² (p=0.016) and 1.43 m/s² vs 9.02 m/s² (p<0.001) respectively). Older, versus younger individuals exhibited lower sagittal-plane joint moments at the knee and ankle (84.48Nm vs 119.91Nm (p=0.036) and 86.42 vs 130.39Nm (p=0.039) respectively) on the HR staircase.

Lower moments at the knee and ankle on the HR staircase could suggest that older individuals may lack surplus muscle strength to support the body for a controlled descent. Lower CoM accelerations suggest that the older group perform the task tentatively to ensure a safe descent. The former result highlights an inherent difference between younger and older individuals and the latter suggests that the older group are aware of functional limitations and take measures to limit fall risks.

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Dementia is a global epidemic, 800,000 people were diagnosed in the UK (2013) and numbers are expected to triple by 2050. People with dementia (PwD) often find it difficult to adhere to medication regimens due to individual complexities. The repercussions of non-adherence may result in unfavourable outcomes such as hospital admissions. As a result we propose to develop an assistive technology (AT) to support medication adherence. A pre-selected song choice will be associated with medication and as such become an external reminder. Existing and ongoing research indicates the power of music for PwD. This research will contribute further to the field with an investigation as to how music can assist in medication adherence through classical conditioning. We are proposing to use person-centred approaches by involving PwD in participatory design sessions. This contrasts with other studies who in the main have only involved caregivers; as designers have assumed that PwD are not capable of informing design. PwD will be involved in collaborative sessions to enable the design of a personalised AT which will be fit for purpose. This approach will enhance a PwD’s sense of control, as the group will be creating a specific tool together in partnership.
Objective: As we age our bodies ability to repair and regenerate significantly reduces. Tissues in older adults are particularly slow to heal due to a reduced number of active cells. Furthermore, they are more susceptible to infections due to a weakened immune system. Effective implant biomaterials can significantly improve the quality of life and wellbeing of patients in later life through increased mobility and independence. Bioactive glasses have the ability to regenerate living tissue and are widely used in dentistry and orthopaedics. However, the antibacterial efficacy of bioactive glasses remains unclear. The aim of this study was to evaluate the antibacterial properties of bioactive glass doped with 3mol% gallium oxide (Ga2O3) against clinically relevant microorganisms. Methods: 3mol% Ga2O3 bioactive glass was prepared via the melt quench technique and ground into fine particulates (<63 μm). The antibacterial activity was investigated against Escherichia coli NCTC 10533 and Staphylococcus aureus ATCO 6588 over a period of 96 hours. Results: 3mol% Ga2O3 bioactive glass demonstrated significant antibacterial efficacy against both E. coli and S. aureus. Concentrations of 500 and 1000 mg/ml resulted in a 6 log reduction with E. coli within 24hrs whilst a 4 log reduction was demonstrated in S. aureus following exposure to 1000 mg/ml at 96hrs. Conclusion: This study has demonstrated that 3mol% Ga2O3 bioactive glass exhibits antibacterial activity against both Gram negative and Gram positive clinically relevant microorganisms.
Small molecule dietary components can act as mediators of beneficial health effects in later life. The best known of these is probably resveratrol (trans-3,5,4', trihydroxystilbene) a phytoalexin found in high concentrations in a variety of plants consumed as part of the normal human diet. Although consistent evidence of lifespan extension by resveratrol supplementation has so far failed to emerge; the molecule has been reported to produce a variety of physiological effects that are potentially relevant to extended healthspan. These include the suppression of inflammatory processes, cardio and neuro-protection, tumour suppression and protection from the effects of high calorie and high lipid diets. The molecular mechanisms by which these are proposed to occur are diverse but include the induction of enzymes involved in xenobiotic metabolism, the activation of SIRT1, the inhibition of NF-κB and interaction with members of the oestrogen receptor family. The accumulation of senescent cells is now known to play a causal role in the ageing process and accordingly we have proposed that resveratrol exerts a significant component of its beneficial effects on healthy lifespan through modulation of aspects of their phenotype. We report our development of a novel, simple and convenient synthetic method that has generated a wide range of known and novel resveratrol analogues together with our initial results on the cytotoxicity and cytokinetic effects of these compounds on normal and transformed human cells.
Maintaining appropriate nutrition/physical activity levels are key pre-requisites for the maintenance of a healthy muscle mass, the dysregulation of which might contribute to sarcopenia. However, in older women particularly, the regulation of protein metabolism in response to nutrition and exercise remains poorly defined. Herein, we characterized the effects of two distinct feeding regimes in older women (66+3y; N=8/group), either: (i) 20 g Whey protein or, (ii) low-dose leucine enriched essential amino acid (LEAA; 3g [40% leucine]) both at rest and following a bout of unilateral resistance exercise (6×8 knee-extensions; 75% of pre-defined 1-RM). Constant infusions of 13C6-Phenylalanine were used to quantify fractional synthetic rates (FSR; %/h) of myofibrillar proteins (MPS) in muscle tissue. Plasma insulin and AA concentrations were measured by ELISA and ion exchange chromatography respectively, and muscle microvascular blood flow (MBF) by contrast enhanced ultrasound (CEUS). Both feeding modes led to significant plasma insulinaemia and aminoacidemia, but substantially more so after 20g Whey than 3g LEAA (P<0.01). Neither feeding regime modified MBF in the rested leg but MBF increased similarly in both groups after exercise (P<0.05). In the rested leg, both feeding regimes increased MPS similarly 0-2 h (P<0.05) while in the exercised leg, MPS also increased over 0-2 h, but unlike with feeding alone, remained elevated 2-4 h (P<0.05); again independently of nutritional regime. We conclude LEAA provides equal anabolic efficacy to a large Whey bolus in older women at rest and after exercise. This positions LEAA nutritional strategies at the fore of dietary/supplement interventions.
Evidence for reduced visceral nociceptor activation with age during appendicitis

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The ability to sense visceral pain, particularly during appendicitis is impaired in the elderly, leading to difficulties in diagnosis and poorer clinical outcomes (Hall 2002, Am J Physiol 283 G827-32). The aim of the present study was to develop a model of visceral nociceptor activation during appendicitis and investigate the effects of aging. We recorded intestinal mesenteric or colonic lumbar splanchnic nerve activity from isolated intestine and colon perfused with Krebs buffer in young (3month) or old (24month) female mice. Responses to the application of inflamed human supernatants derived from surgically resected appendix from consenting patients (NREC 10/H0703/71) with appendicitis and control supernatants from normal appendix obtained from consenting patients undergoing right hemi-colectomy for cancer. Mechansosensitivity was also assessed by von frey hairs probing (VFH) and chemosensitivity to bradykinin and adenosine. In intestines inflamed supernatant produced a robust increase in mesenteric nerve activity in young but not old mice (p<0.01). Control supernatants produced only a modest increase in nerve activity which was significantly less than inflamed supernatants (p<0.05). Bradykinin produced an increase in nerve activity which was also greatly attenuated in old vs young mice (p<0.01). Responses to adenosine were unchanged with age. In colonic preparations application of inflamed supernatant to serosal nociceptors increased nerve discharge and sensitised the response to mechanical stimuli in young but not old mice (p<0.01). Interestingly baseline mechanosensitivity was unchanged. The sensitivity of visceral nociceptors to mediators derived from the inflamed human appendix is greatly reduced with age.
Profiling of skeletal muscle using high-definition mass spectrometry

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Accurate profiling of the skeletal muscle proteome is challenging but could bring a step increment in our understanding of age-related declines in muscle function. We report automated and time efficient (2 h per sample) profiling of muscle using liquid chromatography (LC) coupled directly with high-definition mass spectrometry (HDMSE). Soluble proteins were extracted from rat gastrocnemius muscle (n=10), digested with trypsin and analysed in duplicate by LC-HDMSE. In total 1,514 proteins were identified. Of these, 811 had at least 3 unique peptides and were used to assess the breadth and reliability of LC-HDMSE label-free profiling. Proteins included in this subset encompass the entire complement of glycolytic, beta-oxidation and tricarboxylic acid enzymes. In addition, numerous components of the electron transport chain and protein kinases important in skeletal muscle regulation were detected. The dynamic range of protein abundances spanned 4 orders of magnitude and the correlation across technical replicates of 10 biological samples was R-squared = 0.9961 ± 0.0036. The coefficient of variation averaged 7.3 ± 6.7 %, and 95 % (767 of 811) of proteins exhibited a coefficient of variation of less than 20 %. Based on these data a sample size of n = 10 would be sufficient to detect a 30 % difference in protein abundance between 2 independent groups with a power of 80 %, α = 0.05. This represents the most sophisticated profiling of skeletal muscle to date.
Intramyocellular fat oxidation is reduced during low-intensity exercise in older men, and can be partially restored by increasing muscle total carnitine content

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Age-related intramyocellular lipid accumulation is associated with insulin resistance and sarcopenia. Increasing muscle total carnitine (TC) content produces adaptations consistent with a carnitine-mediated increase in muscle fat oxidation in young volunteers. Here we hypothesised intramyocellular fat oxidation during low intensity exercise would be lower in older vs. younger men, and that increasing muscle TC in older men would overcome this blunting.

Fourteen healthy older (69±1 yr, BMI 26.5±0.8 kg/m\(^2\)) and 8 younger (22±1 yr, BMI 24.0±1.1 kg/m\(^2\)) men performed 1 hour of cycling (50% VO\(_{2}\)max combined with [U-13C]palmitate infusion, muscle biopsy sampling and indirect calorimetry to determine muscle TC content, plasma, intramyocellular and total fatty acid oxidation. Measurements were repeated in older men following 24 weeks of daily beverage ingestion (220ml; 44.4g carbohydrate, 13.8g protein) containing either placebo (n=7) or 3g L-carnitine (n=7) combined with bi-weekly cycling for 1 hour at 50% VO\(_{2}\)max.

At baseline, there were no differences in muscle TC content (19.3±0.8 vs. 17.9±1.2 mmol/kg/dm) or the relative contribution of fat to total energy expenditure during exercise (41.2±2.7 vs. 43.3±6.1%) between age groups. However, the relative contribution of intramyocellular to total fat utilisation was 50% lower in older compared to younger men (35.0±6.0 vs. 77.0±5.9%, P<0.001), despite similar plasma fatty acid availability. Muscle TC content increased (16%, P<0.05) with carnitine ingestion and was associated with a 21% (P<0.01) increase in total fat oxidation (predominantly intramyocellular fat) during exercise.

Intramyocellular fat utilisation during low-intensity exercise is reduced in ageing, and can be partially restored by increasing muscle TC content.
Debilitating neurodegenerative disorders (NDs) are a major public health challenge in increasingly aging societies. Currently approved therapeutics are successful in slowing the progression of NDs but not in reversing or preventing the symptoms of NDs. The simplicity and amenability of the nematode Caenorhabditis elegans (C. elegans) to high-throughput genomic, proteomic and drug screening approaches make this organism an attractive choice for identifying new therapeutic compounds and for understanding their mechanism of action. Indeed, a diverse set of robust C. elegans ND models have been developed to screen for novel genetic and pharmacological modifiers. In this study, we are integrating multiple well-defined C. elegans ND models to uncover generally neuroprotective compounds. Using locomotion behaviour and lifespan as phenotypic readouts, we identified the anticonvulsant ethosuximide as a promising compound with the potential to combat more than one NDs. It not only rescues the short lifespan of a C. elegans null mutant model of a rare autosomal dominant human ND known as adult-onset neuronal ceroid lipofuscinosis (ANCL), but also ameliorates the mobility defect and short lifespan of transgenic worm tauopathy and polyglutamine models. We are currently investigating how ethosuximide might exert its neuroprotective properties. Microarray analysis so far suggests a selective manipulation of aging and metabolic pathways. These findings should encourage further screening and characterisation of other neuroprotective compounds, and ultimately may assist in expediting translational drug research and clinical testing for new therapeutic targets to combat protein conformational disorders in general.
The association of SNAP23 with the mitochondrial network is reduced in skeletal muscle of obese sedentary elderly women

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Introduction This study aimed to investigate whether obesity increases hijacking of SNAP23 by lipid droplets (LDs) in aged women and whether this via reductions in the SNAP23 content of plasma membrane (PM) and mitochondria increases insulin resistance. Methods Biopsies were obtained from the m. gluteus maximus of six aged sedentary non obese (NO) (62±3 years, BMI: 22.6±1.4, HOMA-IR 3.9±1.2) and six aged obese (OB) women (68±3 years, BMI: 33.3±1.6, HOMA-IR: 6.2±1.3) during hip arthroplasty. Cryosections were labelled with antibodies targeting SNAP23, the PM and mitochondria. Lipid droplets were stained using oil red O and images made with immunofluorescence microscopy. Results and Discussion SNAP23 partially colocalised with the PM, LDs and mitochondria in both NO and OB women. The Pearson’s correlations coefficients for pixel overlap (r) were equal for PM (NO: r = 0.39±0.01, OB: r = 0.37±0.03, P=0.640); equal but lower compared to the other sites in LDs (NO: r = 0.12±0.02, OB: r = 0.07±0.02, P=0.277) and significantly lower in the mitochondria (NO: r = 0.34±0.03, OB: r = 0.27±0.03, P=0.037). This study does not confirm the hypothesis that LDs hijack SNAP23 from the PM and thus prevent docking of GLUT-4 and increase insulin resistance. SNAP23’s presence in mitochondria supports its proposed role to channel fatty acids (FA) released from LD hydrolysis into the mitochondria for oxidation. Future research is required to investigate whether the reduced colocalisation of SNAP23 with mitochondria in the obese women limits FA oxidation which would be a potential cause of greater insulin resistance.
The role of SIRTUIN1 in aged and calorie restricted skeletal muscle cells

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Calorie restriction (CR) is considered the only non-genetic dietary intervention implemented that increases lifespan in a variety of species. Advancing age and malnutrition are however coupled with decreases in muscle mass. We have previously shown SIRTUIN1 (SIRT1) to be fundamental in muscle cell survival and regeneration in the presence of apoptotic cytokine TNF-α (Saini et al., 2012). Where loss of SIRT1 has also been shown to abrogate calorie restriction induced lifespan extension (Corbi et al., 2012). We therefore aimed to understand the role of SIRT1 in ameliorating the effect of calorie restriction (low glucose) in young and aged myoblasts originally derived by our group (Sharples et al. 2011, 2012, Deane et al., 2013). Preliminary data suggest low glucose (0.056g/L) reduced morphological and biochemical (CK) differentiation and in both young and aged myoblasts with reductions in corresponding myoD, myogenin, IGF-I, IGF-Ie mRNA, with aged myoblasts undergoing apoptosis by 7 days. We further confirmed that resveratrol (10-15 uM) and SIRT inhibitor (EX-527, 60 uM) were able to successfully activate and suppress respectively the activity of SIRT1 (pSIRT1) in both young and aged myoblasts. We hypothesise for future investigation, in light of our previous work (Saini et al., 2012), that activation of SIRT1 with resveratrol will somewhat reduce the negative impact of low glucose on myoblast differentiation and survival. Future studies will also investigate the cellular signalling events that mediate the morphological and transcript changes observed above and the potential role for SIRT in ageing myoblast stress through nutrient (glucose) restriction.

References


Introduction: Reduced muscle function is a complex disorder which affects a wide spectrum of individuals, including older people. Raised local and systemic pro-inflammatory cytokines seen in the older population can act as inhibitory modulators of muscle force production through a cascade of events including raised levels of reactive oxygen species (ROS) [2]. Current evidence suggests cytokines such as Tumour necrosis factor-α (TNF-α) plays a major role in modulating the function of muscle cells. Increased levels of dietary polyphenols have been associated with a reduction in systemic inflammation and ROS damage [3] and may potentially alleviate symptoms of muscle dysfunction. Methods: To assess the effect of resveratrol on TNF-α induced release of pro-inflammatory cytokines and muscle viability, a suitable dose and time course for TNF-α treatment was established in C2C12 myotubes. Cells were pre-treated with 1µM or 10 µM resveratrol for 24 hours followed by 5ng/ml or 25ng/ml TNF-α for 24 hours. Results: Data support previous findings [4] showing a significant release of pro-inflammatory cytokines IL-6, MCP-1, RANTES/CCL5 and Keratinocyte Chemoattractant (KC) from C2C12 muscle cells in response to 5 and 25ng/ml TNF-α, compared with untreated control cells. Pre-treatment with 1µM Resveratrol reduced the release of IL-6, MCP-1, RANTES/CCL5 and KC released from C2C12 cells induced by 25ng/ml TNF-α treatment. Discussion: These preliminary data suggests that antioxidant rich polyphenols may inhibit the actions of TNF-α by reducing the release of pro-inflammatory cytokines from C2C12 muscle cells. Funded by BBSRC, MRC and the ME Association.
Ageing is the predominant cause of disease worldwide, yet its biological basis is poorly understood. We are using the nematode C. elegans to study the genetic control of ageing as a means to understand its biological mechanisms. Our working definition of ageing is the set of endogenously generated pathologies that increase in later life, resulting in physical and cognitive decline. Our main question is to understand what causes the development of these pathologies. The transparency of C. elegans allows the study of age-related pathologies in intact animals, without the need of dissection. Previous studies have identified a range of age-related pathologies in C. elegans, such as formation of tumor-like masses in the uterus, sarcopenia, accumulation of large yolk pools in the body cavity and severe atrophy of the intestine. The development of these pathologies is slowed down in long-lived mutants, suggesting that the pathologies are important to the aging process. We have developed an assay, which allows us to study how the pathologies develop in living animals, and how they affect healthspan and lifespan. Our initial studies have yielded exciting results regarding the kinetics and the variation of pathology development, and the effect of different pathologies on lifespan. Our working hypothesis is that run-off developmental processes result in hypertrophy and age-related pathologies, ultimately causing the death of the animal. We are in the process of studying age-related changes in animals of different genotypes and in different conditions, in order to dissect the mechanisms of how age-related changes develop.
Ageing is the predominant cause of disease worldwide, yet its biological basis is poorly understood. We are using the nematode C. elegans to study the genetic control of ageing as a means to understand its biological mechanisms. Our working definition of ageing is the set of endogenously generated pathologies that increase in later life, resulting in physical and cognitive decline. Our main question is to understand what causes the development of these pathologies. The transparency of C. elegans allows the study of age-related pathologies in intact animals, without the need of dissection. Previous studies have identified a range of age-related pathologies in C. elegans, such as formation of tumor-like masses in the uterus, sarcopenia, accumulation of large yolk pools in the body cavity and severe atrophy of the intestine. The development of these pathologies is slowed down in long-lived mutants, suggesting that the pathologies are important to the aging process. We have developed an assay, which allows us to study how the pathologies develop in living animals, and how they affect healthspan and lifespan. Our initial studies have yielded exciting results regarding the kinetics and the variation of pathology development, and the effect of different pathologies on lifespan. Our working hypothesis is that run-off developmental processes result in hypertrophy and age-related pathologies, ultimately causing the death of the animal. We are in the process of studying age-related changes in animals of different genotypes and in different conditions, in order to dissect the mechanisms of how age-related changes develop.
Finding viable ways for increasing movement patterns in older adults requires that hitherto unexplored avenues be examined. Dancing is a form of artistic expression that combines rhythmic movements and motor/cognitive challenge. It is also one that has long been pursued by humans for its unique intrinsically motivating properties (i.e., pleasure, enjoyment, self-rewarding effects). The potential advantages of dance programmes for older adults as a means of encouraging physical activity in this population segment have been greatly underexploited. A health promotion approach focusing on dance can be based on a potentially more effective message, namely that dance elicits short-term (as opposed to long-term) affective benefits, such as pleasure and enjoyment (as opposed to reducing the future risk of chronic disease). The proposed study aims to explore the psychological and physiological improvements associated with regular participation in a dance programme among older adults. Researchers propose to design and deliver accessible and enjoyable dance sessions that combine gentle contemporary dance techniques with Pilates exercises and creative movement explorations to improve movement memory, body coordination, strength, flexibility, balance and confidence. An integral aim of the programme is also to help participants through active movement explorations while engaging positively with their emotions. The study will be based on a quasi-experimental design where participants enrolled in the experimental (dance) group will participate in a dance intervention for 12 weeks with a control group continuing to follow their normal lifestyle patterns. Pre and post psychophysiological assessments will be used to measure any changes.
Human ageing is associated with decreased cellular plasticity and adaptability. Changes in alternative splicing with advancing age have been reported in man, which may arise from age-related alterations in splicing factor expression. We determined whether the mRNA expression of key splicing factors differed with age, by microarray analysis in blood from two human populations and by qRT-PCR in senescent primary fibroblasts and endothelial cells. Potential regulators of splicing factor expression were investigated by siRNA analysis. Approximately one third of splicing factors demonstrated age-related transcript expression changes in two human populations. Ataxia Telangiectasia Mutated (ATM) transcript expression correlated with splicing factor expression in human microarray data. Senescent primary fibroblasts and endothelial cells also demonstrated alterations in splicing factor expression, and changes in alternative splicing. Targeted knockdown of the ATM gene in primary fibroblasts resulted in up-regulation of some age-responsive splicing factor transcripts. We conclude that isoform ratios and splicing factor expression alters with age in-vivo and in vitro, and that ATM may have an inhibitory role on the expression of some splicing factors. These findings suggest for the first time that ATM, a core element in the DNA damage response, is a key regulator of the splicing machinery in man.
Maximal heart rate (HRMAX) decreases with age. As a result, age adjusted equations have been developed. However, the validity of these equations have not been established for upper body exercise in the elderly. The purpose of this study was to investigate the accuracy of age-prediction equations of HRMAX to estimate actual HRMAX, specifically for upper body exercise. This study compared measured vs. age-predicted HRMAX in 20 healthy older adults (age; 67 ± 6 years). Maximal HR was measured during maximal incremental exercise tests using a cycle ergometer (CYC) and arm crank ergometer (ACE). Age-based HRMAX was predicted using the Fox [1971] (220 – age) and Tanaka [2001] (208 – 0.7 * age) equations used for lower body exercise. One-way ANOVA was used to determine differences between measured HRMAX and age prediction equations. Measured HRMAX for ACE (144 ± 16 beats•min-1) was significantly lower compared to the Fox (P = 0.009) and Tanaka (P = 0.001) equations, which over predicted HRMAX by 10 ± 4 beats•min-1 and 18 ± 4 beats•min-1, respectively. For CYC, measured HRMAX (159 ± 5 beats•min-1) was not different to the Tanaka (162 ± 4 beats•min-1) or Fox (154 ± 6 beats•min-1) equations (P > 0.05). These preliminary findings show that age adjusted equations based on lower body exercise over estimate HRMAX for upper body exercise. In practical application, subtracting ~ 20 beats•min-1 from the Tanaka equation provides a reasonable estimate of HRMAX for ACE.
We have previously shown that older adults with a high risk of falling, tend to look away prematurely from targets for safe foot placement to view future hazards. This behaviour, which has been linked to anxiety, results in a decrease in stepping accuracy and a corresponding increase in the likelihood of a trip. This study aimed to determine the effectiveness of training older individuals to preview a route prior to initiation of walking in reducing the incidence of maladaptive gaze behaviours and improving associated stepping performance. Nine young and nine older adults completed six walks with three obstacle arrangements over two sessions. Participants starting with eyes closed, on hearing a verbal signal, opened their eyes and initiated walking (session 1), or stood previewing the route for 10 seconds before walking (session 2). Body kinematic data were collected using a Vicon motion analysis system. Gaze behavior was sampled using an Ergoneers Dikablis system. ANOVA revealed a significant interaction between age group and session in the mean fixation duration of stepping target. Older adults fixated targets for significantly longer during walking when they had previewed the route prior to walking compared to the condition when they had not previewed the route. Conclusion: Previewing the route prior to walking can ameliorate the gaze behavior of older adults previously shown to be causally linked to increased falls risk. Carry over effects on stepping accuracy are currently under investigation.
We have previously highlighted the ability of testosterone (T) to improve hypertrophy in population doubled (PD) murine myoblasts (Deane et al. 2013), which display an ageing phenotype in monolayer and bioengineered skeletal muscle cultures (Sharples et al. 2011; 2012) vs. their parental controls (CON). We next sought to investigate the role of the AR vs. IGF-I related signalling in mediating the effects of testosterone in this muscle cell model. Cells were exposed to low serum conditions in the presence or absence of T (100 nM) ± AR (flutamide) ± IGF-IR (Picropodophyllin) inhibitors for 72 hrs and 7 days (early/late muscle differentiation respectively). The presence of the IGF-IR inhibitor had no effect on abrogating the substantial hypertrophic effects of T in either cell type. However, the addition of the AR inhibitor (flutamide) attenuated T induced increases myotube differentiation and hypertrophy in both cell types. T significantly increased AR protein levels and Akt phosphorylation, with a heightened response observed in PD ‘aged’ myoblasts compared to CON cells. The increases in Akt phosphorylation still occurred following T administration in the presence of upstream IGF-IR inhibition, suggesting activation of T induced Akt in aged cells. Interestingly, the presence of the AR inhibitor lead to significant increases in myostatin mRNA levels resulting in a detrimental effect on myotube formation. The present study demonstrated T’s ability to improve hypertrophy in aged myoblasts predominately via increases in AR and activation of Akt independently of upstream input from IGF-IR.
Histone protein acetylation has a regulatory effect on gene expression1; the presence of acetyl groups typically promotes gene expression whilst their removal by deacetylase proteins inhibits expression. The sirtuin family of NAD+ dependent deacetylase proteins modulates the cellular inflammatory response by deacetylating inflammatory gene promoter regions and P65 in the NF-κB complex2. Sirtuin deacetylase activity is regulated by energy availability, suggesting a potential link between inflammation associated with metabolic conditions and nutrient availability3. To investigate this further, THP1 monocytes were treated with increased concentrations of glucose (0-50mM) in order to measure its effects on SIRT1 deacetylase activity, P65 acetylation status and TNFα mRNA production and secretion. To confirm whether the in vitro effects of glucose mimicked ex vivo effects on primary monocytes, whole blood or primary monocytes isolated from whole blood were taken from consenting healthy volunteers and supplemented with glucose (50mM) for 6 and 24 hours and the effect on TNFα mRNA production and TNFα secretion in response to LPS measured by quantitative PCR and ELISA respectively. All statistical analysis was performed using one-way ANOVA, significance against control groups (5mM D-glucose treated) determined with Dunnett’s multiple comparison test. THP1 monocytes treated with 50mM glucose had no effect on sirtuin 1 activity over 6 hours but over a 24 hour period resulted in decreased sirtuin1 activity (10% decrease, P≤0.05). However, P65 acetylation was increased after 6 h of incubation with 50mM glucose (60% increase, P≤0.001) (Fig. 2.). Whole blood and isolated primary monocytes supplemented with 50mM glucose showed an increase in TNFα mRNA production and TNFα secretion (Fig. 2.) in response to LPS compared to those supplemented with 5mM glucose. The increase in TNFα secretion in response to LPS in high glucose may reflect increased P65 acetylation and gene expression.
Ligament and tendon are prone to degeneration through ageing and injury and current therapies are largely ineffective. The recent identification of a cell population within tendon with stem cell-like characteristics holds potential for regeneration of tendon and ligament. The local stem cell environment (niche) is important for stem cell maintenance and function. This study aims to characterize extracellular matrix (ECM) components of the stem cell niche in equine tendon and canine cruciate ligament, which are prone to age-related degeneration and rupture. Putative stem cells were isolated from equine tendon by low-density plating and differential adhesion to plastic and fibronectin substrates. Cells were analysed by flow cytometry using antibodies to mesenchymal stem cell markers CD90, CD73 and CD105. A subpopulation of tendon cells expressed CD90 in both freshly isolated cells and putative stem cells, but were CD105 and CD73 negative. Antibody cross-reactivity is currently being validated with equine mesenchymal stem cells. We plan to identify ECM components of the stem cell niche by mass spectrometry and microarray comparison of tendon/ligament tissue, stem cells and fibroblasts. qRT-PCR and Western blotting will be used for validation. To specifically label newly synthesized ECM, cells were labeled with 14C-labelled amino acids prior to differential extraction of cells and ECM. Similar protein labeling profiles of tendon fibroblasts and putative stem cells currently indicates that further testing of stem cell isolation procedures is required. Alternatively it is possible that the equine tendon cell population consists of a heterogenous mixture of cells at different stages of differentiation.
Sequencing the genome of the longest-lived mammal to identify longevity assurance mechanisms

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Sequencing the genome of the longest-lived mammal to identify longevity assurance mechanisms. The bowhead whale (Balaena mysticetus) has not only been estimated to live over 200 years, making it the longest-lived mammal, but these animals remain disease-free until much more advanced ages than humans can. The mechanisms for the longevity and resistance to aging-related diseases of bowhead whales are unknown, but it is clear they must possess aging prevention mechanisms. In particular in the context of cancer, bowhead whales must have anti-tumour mechanisms, because given their large size and longevity their cells must have a massively lower chance of developing into cancer when compared to human cells. In this project, we are sequencing and analyzing the genome of the bowhead whale to identify longevity assurance mechanisms. We are also performing analyses to identify promising candidate genes for further study and identify possible mechanisms that may explain the long lifespan and resistance to age-related diseases of bowhead whales. Overall, this project will provide a key resource for studying the bowhead whale’s exceptional longevity and resistance to diseases. Studying a species so long-lived and with such an extraordinary resistance to age-related diseases will help elucidate mechanisms and genes conferring longevity and disease resistance in mammals that in the future may be applied to improve human health.
Effect of resveratrol on skeletal muscle adaptation and viability: potential impact on sarcopenia.

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Skeletal muscle mass and function deteriorates considerably with age, although the mechanisms responsible for this deterioration are poorly understood. There is considerable evidence that the increased inflammation and oxidation associated with ageing results in muscle dysfunction. The dietary polyphenol, resveratrol is a potentially beneficial intervention due to its ability to reduce oxidation and inflammation, possibly through up-regulation of sirtuin 1 (SIRT1). The aim of this study was to determine levels of resveratrol necessary to have a functional effect on muscle. Myoblasts and myotubes isolated from Sprague Dawley rats were treated with 0.1, 1 or 10µm of resveratrol, stained with Syto10/DeadRed to determine cell viability or harvested for western blotting. Resveratrol treatment did not affect the viability of myoblasts, however the highest dose (10µM) of resveratrol resulted in reduced viability of myotubes after 5 days of treatment. Myoblasts treated for 24hrs with 0.1 and 1µM of resveratrol demonstrated an increased content of SIRT1, this was not evident following treatment with 10µM resveratrol. All concentrations of resveratrol resulted in an increased catalase content. Treatment of myoblasts with 0.1, 1 and 10µM of resveratrol resulted in an increased content of MnSOD 3hrs after treatment which was maintained for 12 hrs following treatment with 1 and 10µM resveratrol. Data suggest that 1µM and 10µM resveratrol may result in functional changes in skeletal muscle cells and provide a potential intervention to improve muscle function in older mammals. This is the focus of future studies. The authors would like to thank BBSRC DRINC for funding this study.
Skeletal muscle ageing is associated with an altered oxidative status of redox sensitive proteins within the muscle fibre. Reactive oxygen and reactive nitrogen species (ROS/RNS) are generated by contracting skeletal muscle and are necessary for a regulatory effect on the activity and function of redox proteins. ROS/RNS are not blunt instruments involved in non-specific oxidation but are fundamental in the specific adaptive response to exercise and many proteins require a certain level of ROS/RNS for correct protein function, signalling and adaptation. Using gastrocnemius muscles from adult and aged mice we have undertaken a label free quantitative proteomic approach that includes a differential Cysteine labelling step that allow simultaneous identification of up and down regulated proteins between samples and also the identification and quantification of the reversible oxidation state of susceptible redox Cysteine residues within samples. Our results indicate significant changes in chaperone, glucose metabolism and cytoskeletal regulatory proteins between adult and aged mice, and also a reduction in the identification of redox responsive proteins from aged mice skeletal muscle tissue.
Musculoskeletal changes in superoxide dismutase 1 (SOD1) null mice

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SOD1 null (SOD1/-/-) mice are a powerful model to study the effects of ageing on musculoskeletal tissues. The aim of this study was to determine the effect of lack of SOD1 in mice on mechanical changes in bones compared with old mice and to determine whether changes are due to a direct effect of the deletion in bone or indirectly muscle changes. The study used adult and old wild-type (WT), adult SOD1/-/- and SOD1/-/- mice with expression of SOD1 rescued in nerve (SynTgSod1/-/-) or specifically deleted in the muscle (mKO). Muscles force generation was measured and MicroCT analysis performed on tibia. Finite Element (FE) models were developed to map strain across the tibia and these data were compared with MicroCT data. Old WT mice showed a 20+/-3% loss of muscle mass, thinning of cortical bone and a 37 +/-1% loss of trabecular bone compared with adult mice. Loss of muscle in adult SOD1/-/- mice was associated with a 29+/-1% loss of trabecular bone. FE analyses indicated that this loss of muscle led to 50+/- 0% reduction in tibia strain which was mirrored by microCT data. SynTgSod1/-/- mice preserved muscle mass but showed loss of tibia trabecular bone. Muscles of mKO mice had a reduced specific force but tibia displayed normal structure. Data suggest that loss of trabecular bone in SOD1/-/- mice is due to the direct effect of lack of SOD1 in the bone. Funded by MRC-ARUK Centre for Integrated research into Musculoskeletal Ageing and NIA (AG-20591).
The impact of obesity on bone mineral density changes with ageing in sedentary women

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Obesity is associated with increased maximal torque (1,2), through an effect attributable to greater total lean mass (1). Similarly, the obese have a specious bone strength advantage (3). This study examined the relationship between ageing and bone mineral density (BMD), to determine whether any beneficial impact of increased load is offset by high adiposity. 94 untrained healthy women were categorised by age into young (Y) (mean ± SD: 22.4 ± 4.4 yrs) versus old (O) (64.0 ± 9.6 yrs), and by adiposity into average (<40%) vs. high (≥40%) body fat. Participants were assessed for total and segmental body composition using dual energy x-ray absorptiometry.

Total BMD decreased with ageing in the high adiposity group (-0.0029 g/cm² per year; r = 0.517, P<0.001). This subgroup in fact exhibited 12% leg (1.28 ± 0.11 vs. 1.13 ± 0.13 g/cm², p=0.001) and 8% arm (0.85 ± 0.12 vs. 0.78 ± 0.11 g/cm², p=0.001) BMD differences in Y vs O (see Figure 1). These BMD changes were in line with the lean tissue content losses (-14% in total body (p=0.01), -20% in leg (p<0.01) and -14% in arm (p=0.05) musculature of O vs Y). There were no ageing-related changes in the average adiposity group.

Our findings suggest that mechanical loading is not the primary mediator of the effects of obesity on bone strength adaptations. In fact, the increased mechanical demands of high adiposity are inadequate to modulate equivalent muscle and bone adaptations, particularly in the older person, likely leading to eventual osteosarcopenic obesity.

References

Figure 1: Age differences in appendicular BMD by adiposity. Data shown are Mean ± SD. * Denotes P<0.05.
The thymus is the first organ to undergo age-related degeneration in normal healthy individuals. As a consequence, thymic production of new naïve T cells progressively declines throughout adulthood, reducing the capacity of the immune system to respond to previously unencountered pathogens. Thymus degeneration, or involution, is thus a major cause of inadequate immune system function in the elderly and acts to prolong the period of morbidity at the end of life. Sex steroid signaling has been suggested as a primary cause of age-related thymic involution and sex steroid ablation (SSA) can transiently reverse some aspects of thymic atrophy (Griffith et al., Aging Cell 2012). However, the mechanism of SSA-induced rebound is not known, and it remains unclear how sex steroid signaling interacts with other regulators of thymic function during involution. We have investigated the effect of ablating androgen receptor (AR) in the developing and adult thymus, and show that while AR signaling negatively regulates thymus size, it is not required to initiate or sustain age-related thymic involution. In contrast, our recent data reveal that up-regulation of the transcription factor FOXN1 in the aged murine thymus is sufficient to restore thymus architecture and function, but not size, to a pre-involution state (Bredenkamp et al., Development 2014). We have therefore tested whether SSA and FOXN1 up-regulation synergise to drive complete and sustained thymus regeneration. The potential of this combined approach as a novel method of improving immune function in the elderly will be discussed.
During ageing, there is a loss of bone mineral density and lean mass with a concomitant increase in body fat mass. In turn, increased body fat mass is associated with a redistribution of adipose tissue, a decrease in lower body subcutaneous fat storage and an increase in the plasma non-esterified fatty acids (NEFA). We have investigated the hypothesis that the age-associated increase in NEFA drive an inflammatory phenotype in monocytes during ageing. Peripheral blood was taken from fasting, consenting healthy male volunteers from young (18-30 years old, n=29) and midlife (50-65 years old, n=21) cohorts. The plasma NEFA profile acid profile were analysed for SFA, monounsaturated (MUFA) and polyunsaturated (PUFA) fatty acids by GC and plasma cytokines (IL-6, IL-10, TGF-β and TNF-α) by ELISA. In older adults, circulating SFA, MUFA and PUFA were significantly altered, with the greatest effect of age seen in fatty acids palmitate (C16:0; decreased), γ-linoleic acid (C18:3n6; increased) and nervonic acid (C24:0; increased). TNF-α and IL-6 concentrations were significantly higher and IL-10 concentrations were significantly lower in the plasma from older men than in healthy younger men. Using linear regression analysis γ-linoleic acid was found to be a positive predictor of IL-6 and TNFα. Together these findings support the hypothesis that a change in lipid metabolism with ageing may promote an inflammatory phenotype.
Functional cellular imaging of immune responses during ageing using intravital multiphoton microscopy

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The immune system protects us against bacteria, viruses and other pathogens, and if compromised can result in susceptibility to infection. Immunosenescence refers to age-related immune impairments in immune function that may contribute to increased prevalence and severity of infectious disease in the elderly. Despite increasing understanding of molecular and cellular age-related immune alterations, knowledge is incomplete, particularly on dynamic and functional cellular changes. Multiphoton microscopy is a technique optimised to visualise and quantify dynamic cell behaviour in vivo under near physiological conditions. To date, multiphoton microscopy has enabled us to visualise important immune events in lymphoid tissues, including antigen capture and transport, interactions between immune cell populations, and lymphocyte proliferation and egress into the periphery [1-4]. Our aim is to use multiphoton in vivo imaging of ageing mice to study how age affects important immune responses. Initial studies have immunohistochemistry and flow cytometry to define key structural and cellular changes occurring at 3, 12 and 22 months of age; this information will be used to identify selected cell populations of interest. The effect of ageing on dynamic activity of these cell populations and trafficking of antigen necessary for response to pathogen challenge will then be determined using multiphoton in vivo imaging. An improved understanding of how ageing affects functional activity in the immune system may reveal novel targets for intervention to alleviate age-related immune dysfunction and possibly lighten the medical burden of ageing. 1. Swirski, F.K., et al., Identification of Splenic Reservoir Monocytes and Their Deployment to Inflammatory Sites. Science, 2009. 325(5940): p. 612616. 2. Phan, T.G., et al., Immune complex relay by subcapsular sinus macrophages and noncognate B cells drives antibody affinity maturation. Nature Immunology, 2009. 10(7): p. 786U153. 3. Arnon, T.I., et al., Visualization of splenic marginal zone B cell shuttling and follicular B cell egress. Nature, 2013. 493(7434): p. 6848. 4. Heesters, B.A., et al., Endocytosis and recycling of immune complexes by follicular dendritic cells enhances B cell antigen binding and activation. Immunity, 2013. 38(6): p. 116475.
A cross-sectional study was undertaken to compare leg power and strength in older (25 male and 20 female; (Mean(SD)) 69(4), 70(3) years; 76.4(11.7), 62.4(9.0) kg) and younger (15 male and 15 female; 25(4), 26(4) years; 75.5(10.4), 61.6(5.2) kg) individuals. Vastus Lateralis (VL) muscle thickness was measured by ultrasonography and leg power by an incremental leg press test to failure (~10 repetitions) performed on a pneumatic leg press (Keiser A420) at maximum voluntary velocity for every repetition. VL thickness was lower for older than younger males (19.7(4.4) vs. 24.3(3.9) mm, p<0.01), and females (16.5(2.7) vs. 20.6(2.2) mm, p<0.01). Peak power and peak power relative to VL thickness were lower in older than younger males (530(143) vs. 1074(164) W, p<0.01; 27.6(7.9) vs. 43.7(9.1) W/mm, p<0.01) and females (312(89) vs. 595(150) W, p<0.01; 19.3(5.4) vs. 27.3(6.9) W/mm, p<0.01). Peak force and peak force relative to VL thickness were lower in older than younger males (1031(193) vs. 1657(282) N, p<0.01; 53.9(12.4) vs. 68.8(9.8) N/mm, p<0.01), and peak force was lower in older females (680(108) vs. 954(166) N, p<0.01), but peak force relative to VL thickness was not different (41.5(7.7) vs. 46.4(6.7) N/mm, p=0.08). In conclusion, both leg power and strength were lower in older compared to younger individuals. When expressed relative to a marker of muscle size, strength was different between older and younger males but not females.
Changes associated with the decline of muscle mass and function with increasing age, including substantial loss of motor neurons and changes in reactive oxygen species (ROS), are widely described in rodent models. Nerve transection has been shown to cause dramatic increases in mitochondrial hydrogen peroxide (H2O2) generation and we hypothesise that even small, partial denervation, such as that described in muscle of old rodents, could influence the entire muscle. Mice which express yellow fluorescent protein (YFP) in neuronal cells (with no expression in non-neuronal cells and no apparent toxic effects) provide a novel approach to assessment of individual nerves in muscle. In our initial studies, the peroneal nerve was transected and a small section removed under anaesthesia. Following recovery for 1, 3, 7 or 10 days, bundles of muscle fibres from the anterior tibialis (AT) muscle were analysed for H2O2 using amplex Red and immuno-fluorescent staining for published markers of denervation. Amplex Red assays demonstrate that a fully denervated AT had significantly higher levels of H2O2 compared with the contralateral limb (sham). The increase was apparent by 3 days after surgery and the trend remained even after 10 days of denervation. Fluorescent imaging confirmed loss of innervation while immuno-fluorescent staining for markers of denervation revealed neuronal cell adhesion molecule (NCAM) positive fibres following surgery, however, numbers of positively stained muscle fibres appeared low. Ongoing work has established a method for achieving partial denervation of the AT. Although preliminary amplex red data is variable, our long term goal is to utilise the partial denervation model to examine how increased ROS generation associated with partial denervation in a specific area of muscle can influence the entire muscle.

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Loss of appetite amongst the elderly population is common and can lead to malnutrition, contributing to the frailty of older individuals. Gut hormones, produced by enteroendocrine cells (ECs) of the intestinal mucosa, play a key role in appetite regulation, and also in gastrointestinal functions such as gastric emptying. Alteration to gut hormone levels in ageing has been reported in some previous studies. Ghrelin, produced by a subpopulation of ECs of the stomach, stimulates appetite, while other peptides, including somatostatin, produced by different stomach ECs, decreases appetite. Here, we investigated possible changes in the numbers of ghrelin- and somatostatin-immunoreactive (IR) ECs in the stomach of male C57BL/6 mice at 4-5, 12-13, 18-19 and 24-25 months of age. Stomach mass and tissue morphology were also measured. No significant changes in stomach mass, muscle thickness or mucosal area were seen, although the greatest stomach mass was seen in 18 month animals. Ghrelin-IR cell density tended to be greater in the fundus than the pylorus (except in the oldest animals), and did not change significantly during ageing. In contrast, somatostatin-IR cell density was similar in both stomach regions but significantly decreased in the fundus of 24-25 month old animals. Somatostatin delays gastric emptying and inhibits ghrelin release. These results indicate that changes in the EC populations of the mammalian stomach may occur during ageing, and may contribute to alterations in gastrointestinal functions and appetite seen in many old people.

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Mitochondrial function and ROS generation in permeabilised skeletal muscle fibre bundles from young, middle-aged and older subjects


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Oxidative damage has been reported to be involved in the loss of tissue function that occurs during ageing, and the potential role of mitochondria as a source of increased ROS generation has been attributed to the impaired mitochondrial function and oxidative damage to mitochondrial components that occurs with advancing of age. Experimental data on this topic have predominantly been obtained from studies using rodents as an ageing model and there is limited information on the role of mitochondrial ROS generation in skeletal muscle from older humans. To determine the role of mitochondrial ROS in the muscle decline that occurs with ageing, muscle biopsies from young (20-30 years) middle-aged (45-55 years) and older (>60 years) healthy volunteers were taken from the vastus lateralis muscle. A combination of analyses were performed in small bundles of permeabilised fibres including mitochondrial ROS changes in the presence of various ETC substrates and inhibitors, changes in mitochondrial respiration and membrane potential and changes in maximum calcium-activated tetanic force. No differences in fibre cross-sectional area or absolute and specific force in response to calcium stimulation were observed in fibres between age groups. Respiratory function, mitochondrial membrane potential and ROS generation, assessed via changes in superoxide and hydrogen peroxide, were not significantly different between age groups. Our data challenge the concept that mitochondrial ROS generation plays a key role in human skeletal muscle ageing.

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Tumour-Necrosis Factor Alpha (TNF-α) is a pleiotropic cytokine that is chronically elevated in ageing/aged related disease states (Sarcopenia, Cachexia); where higher TNF-α levels are strongly correlated with morbidity and mortality in later life. We have extensively shown that TNF-α impairs regenerative capacity in mouse and human muscle cells (Meadows 2000; Foulstone 2001, 2004; Stewart 2004; Al-Shanti 2008; Saini, 2008; Sharples 2010). Recently, we have established a SIRT1 (histone deacetylase) mediated mechanism regulating survival of myoblasts in the presence of TNF-α (Saini, 2012). We therefore wished to extend this work and investigate the epigenetic consequences of repeated doses of TNF-α on DNA methylation. C2C12 myoblasts were cultured in the absence or presence of TNF-α (40 ng.ml-1), followed by multiple population doublings (25 doublings; Sharples et al., 2011, 2012) in the absence of TNF-α, prior to the induction of differentiation in the absence or presence of a second dose of TNF-α (20 ng.ml-1). Interestingly, the cells that received a pre- and post-population doubling dose of TNF-α were more susceptible to the cytokine and exhibited a larger reduction in morphological and biochemical (CK) differentiation vs. cells that had not been exposed to TNF-α previously. Interestingly, CpG island methylation of 3 different regions of myoD were increased in cells that have undergone the ‘early life’ TNF-α dose with corresponding reductions in myoD gene transcription. Overall, myoblasts seem to have a memory of earlier life encounters of TNF-α when exposed to a further catabolic stimulus in later life, potentially through increased CpG methylation of myoD.
Background Increasing physical activity (PA) reduces cardiovascular disease (CVD) risk but the underlying molecular mechanisms are poorly understood. Previous studies indicate that PA exerts epigenetic effects by altering the DNA methylation status of genes implicated in age-related disease. The aim of the present study was to investigate the relationship between PA and the methylation status of CVD risk genes in an aged population. Methods Blood samples were collected at baseline and after 8 years from 253 females (70.7 ± 0.3 yrs) and 137 males (71.4 ± 0.4 yrs) in the Cardiovascular Health Study (CHS). The DNA methylation status of eight genes and LINE-1 was analysed in leukocytes. Self-report PA level collected at both time points was used to estimate physical activity energy expenditure (PAEE; kcal/wk). Participants were stratified by the extent of change in PAEE during the study; those who decreased PAEE by ≥ 500 kcal/wk (DEC), increased by ≥ 500 kcal/wk (INC), or showed no overall change (NOC). Results DEC showed reduced methylation of TNF; whereas increasing PAEE showed a trend toward reduced IL10 methylation. SERPINA5 methylation was reduced in men in INC. There were gender-specific differences in SNCG and LINE-1 methylation in INC. The effects of PAEE on DNA methylation were independent of ageing or change in waist circumference. Conclusions Altering PAEE was significantly associated with the differential methylation of CVD risk genes and LINE-1 in leukocytes of aged subjects. PA-induced effects on DNA methylation could therefore underpin the associations between PA and CVD risk.
**Structural evolution of photo-polymerised dimethacrylate dental resin systems**

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**Purpose/Aims:** In later life we typically produce less saliva which reduces the mouths’ ability to buffer and neutralise oral acidity thus resulting in increased tooth decay. Good oral hygiene is very important in older adults: e.g. consuming sufficient nutrients and immune system less responsive to oral infections. Resin-based-composites (RBC) are extensively used in dental restoration; however information on structural changes on an atomic length-scale is noticeable absent. This study aimed to understand the evolution of the molecular structure in RBC during photo-polymerisation. **Methods:** Bis-GMA / TEGDMA composites with Lucirin TPO or Camphorquinone (CQ) photo-initiators were photo-polymerised at different rates whilst undertaking simultaneous synchrotron small-angle X-ray scattering (SAXS) to measure changes in cross-linking distances and relative orders. **Results:** SAXS measurements revealed a broad-peak feature at Q=1.4Å⁻¹ which shifted to lower Q during polymerisation, indicative of molecular extension. TPO initiated systems polymerised more rapidly and displayed greater extension than CQ samples. However, rapidly cured systems exhibited a subsequent relaxation to shorter lengths not evident in most CQ resins. CQ systems demonstrated the greatest relative order within the matrix. **Conclusion:** Resins cured with low polymerisation rates generated smaller initial strains and greater subsequent atomic order which is considered to be structurally favourable. We demonstrate for the first time that polymerisation rate can introduce structural differences that influence residual strains, mechanical properties and ultimately clinical performance of RBC restorative materials.
Introduction: Dysregulated iron homeostasis, leading to oxidative stress and mitochondrial damage, may be a significant contributor to the senescent brain. Iron-sensitive MR relaxometry has frequently been used to suggest elevated iron in the ageing human brain. However, no study has demonstrated correlation of age-related changes in MR relaxometry with direct measures of brain iron levels. Methods: Paraformaldehyde-fixed brains from male C57BL/6J mice aged 2, 19 (n= 11/age group) and 27 months (n= 8) underwent MRI at 7T. Relaxivity maps, R2 and R2*, were generated and regions of interest (ROIs) placed within several brain regions. Following MRI, brain samples were sectioned and underwent synchrotron radiation X-ray fluorescence (SR-XRF) elemental iron mapping. Results: Significantly higher R2 and R2* was observed in the basal ganglia (P<0.0001) of aged mice. Interestingly, a significant increase in R2*, but not R2, was seen between 19 and 27 month old brains in the striatum (P<0.0001) and globus pallidus (P<0.0001). Preliminary SR-XRF elemental iron maps showed relatively higher iron levels in the basal ganglia compared to cortical iron levels in the 19 month compared to the 2 month old mice. Conclusions: MR relaxometry changes in the aged C57BL/6J mouse basal ganglia are concordant with the human brain and these changes are related to the iron levels. MR relaxometry may therefore be a valuable non-invasive measure to track age-related alterations in brain iron homeostasis and subsequent testing of anti-ageing therapies. Further investigations are needed however to determine the role of the age-related increased iron in detrimental ageing.
Normal ageing is associated with decline in cognitive and motor functions. There is, however, large variation across individuals in level of performance, rate of decline, and response to training programs. One hypothesis is that variations in the efficiency of the mechanisms of neuroplasticity underlie the large individual differences performance and learning in older age. Recently, non-invasive brain stimulation (NIBS) techniques have been used to induce short-term changes in LTP and LTD-like plasticity. The aim of the present research is to examine the relationship between NIBS-induced neuroplasticity and motor and cognitive function in older adults. Baseline cognitive and motor function was measured using the NIH Toolbox for Assessment of Neurological and Behavioral Function. NIBS-induced neuroplasticity was assessed by response to anodal transcranial direct current stimulation (atDCS) as measured by sets of single transcranial magnetic stimulation pulses from 0-30 minutes post stimulation in 5 min intervals. Genotyping was performed for BDNF polymorphisms and an estimate of physical fitness was obtained from a combination of self-reported physical activity index, age, sex, BMI, and resting heart rate. Preliminary analyses of data from 36 participants (mean age = 67.3 years, BDNF: Val/Val = 25, Met carriers = 11) in the ongoing study showed a significant increase in cortical excitability of 21.2% following anodal tDCS. BDNF Met carriers showed a significantly greater response to atDCS than Val/Val. Correlation analyses between cognitive/motor measures and response to atDCS revealed a negative correlation between age-adjusted working memory test scores and response to atDCS (r = -0.423, p = 0.01).
The muscles that mediate sphincter closure and copulatory behaviour are innervated by spinal motoneurons (MNs) located within the dorsolateral nucleus (DLN), spinal nucleus of the bulbocavernosus (SNB), and sacral parasympathetic nucleus (SPN). In aged rats, the number of synapses contacting these MNs is reduced. Similar data for mice is lacking. Hence, the current study sought to identify age-related changes in terminals containing serotonin (5-HT), substance P (SP) and glutamate (identified by vesicular glutamate transporter 2, VGLUT2) in the DLN and SNB of male C57BL/6 mice. Terminals located in the SPN containing corticotropin-releasing factor (CRF), a neuropeptide involved in facilitating voiding behaviour, were also studied. Spinal cord sections from 3-4.5, 24 and 30-31 months mice were immunofluorescently labelled for the neuronal markers MAP2 or ChAT, in combination with 5-HT, SP, VGLUT2 or CRF. In 3-4.5 months mice, labelling for immunoreactive (IR) terminals appeared uniform in signal intensity, size and distribution. By contrast, IR terminals from 24+ months mice varied in intensity and size. Some IR terminals that were enlarged, and irregular in shape, were observed. This was most apparent for 5-HT inputs to SNB MNs. Ultrastructural studies are also being undertaken to determine the synaptic connectivity of 5-HT-, SP- and VGLUT2-IR terminals. These studies will provide insight into structural alterations of MNs, innervating muscles that promote sphincter closure and mediate sexual behaviours, and how these changes may contribute to disrupted muscle contraction in relation to ageing. Supported by BBSRC grant BB/(BB/G015988/1) to MJS and RNR.
In *C. elegans* the *skn-1* gene encodes a transcription factor that resembles mammalian Nrf2 and activates the detoxification response. *skn-1* promotes resistance to oxidative stress and also protects against ageing, and it has been suggested that the former causes that latter - consistent with the theory that oxidative damage causes ageing. While long-lived strains are often stress resistant, they are not always. Moreover, a number of studies suggest that molecular damage may not in fact be the cause of ageing, particularly in *C. elegans*. Here we present work suggesting that effects of SKN-1 on stress resistance and longevity can be dissociated. We focus on the role of SKN-1 downstream of DAF-16/FoxO, another key *C. elegans* transcription factor that controls growth, metabolism and ageing. Over-expression of DAF-16 promotes stress resistance and can increase longevity. Recent analysis of transcript and chromatin profiling implies that DAF-16 regulates relatively few genes directly, many of which encode other regulatory proteins. We show that one of these targets is *skn-1* and that this transcription factor is required for the stress resistance caused by over-expressing DAF-16. However *skn-1* is not required for DAF-16-mediated lifespan extension. Moreover, knock-down of *skn-1* expression can increase molecular damage levels without decreasing lifespan. These findings suggest that SKN-1 mediates lifespan extension by a means other than protection against damage, and elucidate the gene-regulatory network centered on DAF-16. We also present evidence that the mechanisms of life extension by daf-2 mutation or DAF-16 over-expression are mechanistically different.
As the average age of our population continues to climb the burden on the health system increases. This is due in part to the decreased ability of the aged immune system to deal with infection and disease. Aging results in increased immunosenescence and along with this an increased susceptibility in aged individuals towards opportunistic pathogens and inflammatory conditions. B cells are critical immune cells whose role is to respond to foreign antigens and fight disease. To determine the effect of aging on the B cells in the immune system spleens and lymph nodes of aged (>2 years) female mice were compared with young (<2 months) female control mice and an analysis of the B cell populations performed via FACS and IHC. A relative decrease in the total number of B cells was observed in the spleens of aged mice via FACS compared to young mice. However, within the mature B cell population of the aged mice, whilst the representation of Follicular B cells decreased the representation of Marginal Zone (MZ) B cells increased. When IHC analysis was performed on the spleen and lymph nodes there was a significant disturbance to the structure of the B cell follicles in both tissues. Furthermore, the MZ of the spleens in the aged mice was severely disrupted as demonstrated by the delocalisation of the MZ macrophages. Further research will be performed to determine the effect of this delocalisation on the functioning of the marginal zone B cells with respect to mounting immune responses.

Disruption of B cell localisation in aged murine spleen and lymph nodes

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GeneFriends: an online co-expression analysis tool to identify novel gene targets for aging and complex diseases

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Although many diseases have been well characterized at the molecular level, the underlying mechanisms are often unknown. Nearly half of all human genes remain poorly studied, yet these genes may contribute to these disease processes. Additionally many other genetic factors, such as non-coding RNAs may play a crucial role in the understanding of these mechanisms. With the rapid evolution of sequencing technology it is now possible to measure the expression of such factors. Using a large range of expression data it is possible to analyze which genes/factors tend to be co-expressed. Using this approach we created a tool that allows users to associate these factors with well annotated genes and assigned a putative function. Genes involved in common biological processes and diseases are often co-expressed. Applying this theory to previously unidentified features, such as non-coding RNAs, it is possible to associate these with disease. We tested our tool on a set of genes previously associated with aging, which we used to investigate their co-expression with other genes. Interestingly this revealed several C/ebp genes as candidate regulators of transcriptional modules in aging. Our tool, GeneFriends, employs a gene co-expression network for candidate gene prioritization, based on a seed list of genes and for functional annotation of unknown genes in humans and model organisms. Both a microarray and an RNAseq based co-expression tool are available on www.genefriends.org.
Major predictors of the gradual decrease in Left Ventricular Diastolic Function with increasing age: the Physical Activity and Health Ageing Study (PAHA)

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Introduction: Healthy ageing results in a gradual decrease with age in left ventricular diastolic function (LVDF; attenuated ability to fill the LV with blood). This among others limits exercise capacity. Aim: Identify the main predictors of the decrease in LVDF. Hypotheses: High physical activity (PAL) is a positive predictor, while systemic inflammation (plasma CRP) and obesity are negative predictors. Cohort and statistical analysis: 175 Healthy elders (mixed gender) had variables measured playing key roles in the (patho)physiology of LVDF. Initially, correlation analysis was performed, followed by univariate analysis of candidate predictors against LVDF. Significant predictors were then included in multiple hierarchical regression analyses. Function measurements: LVDF was measured as E/A ratio (ratio between early and late LV filling), PAL using triaxial accelerometry, Mean Arterial Pressure (MAP), BMI, and plasma CRP. Results: PAL (steps per day) was 4564±1230 and 10318±2664 in lowest and highest quintile. Full cohort univariate analysis indicated that PAL was main positive predictor of LVDF (2% of variance), while MAP was main negative predictor (28%). Multivariate analysis indicated that PAL positively predicted 5% and MAP negatively 5%. Model 2 (adjusted for age and gender) indicated that MAP and BMI negatively predicted 7% and 5%, respectively; PAL did not predict significantly. Systemic inflammation was not a significant negative predictor in any of the analyses. Conclusions: The interpretation of these data is complex as there is a dependency with a high PAL having a health promoting effect on all negative predictors.

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The blood-brain barrier (BBB) is formed by tight junctions present between the endothelial cells of the capillaries at the microvasculature, which controls the molecular traffic between the blood and brain to maintain the neural microenvironment. MicroRNAs (miRs) are endogenous non-coding small RNAs that have emerged as important regulators of gene expression. BBB leakage in cerebral cortex has been reported in normal ageing and age-related diseases in both humans and rodents. Our preliminary data and other studies suggest that deregulation of miR levels, especially miR155, in cerebral endothelial cells (CECs) may be critical in BBB dysfunction. To date information on the mechanisms underlying age-associated BBB dysfunction and the possible role of miRs in these processes, in particular in CECs, is lacking. The prime goal of this project is therefore to determine the role of endothelial miRs in modulating BBB function in ageing. In this study, we characterized the age-related changes in BBB function in ageing C57/BL6 mice. BBB integrity of brain and spinal cord was assessed at 3, 12, 18 and 24 months of age using albumin Evans Blue assay. We found that the BBB permeability significantly increased at ageing mouse cerebra, cerebellum and spinal cord. We also studied vessels and the expression of tight junction proteins using antibodies to CD31 and ZO-1, respectively, on ageing mouse brain. Alteration in the expression of tight junction proteins resulting in increased BBB permeability may contribute to BBB dysfunction in ageing. ACKNOWLEDGMENTS: This work is supported by BBSRC ‘Role of microRNAs in ageing at the blood-brain barrier: integrated studies in human and mouse models’ funding: BB/J021687/1. We are grateful to the staff of the OU BRU.
The effects of ageing, obesity and pro-inflammatory cytokines on human skeletal muscle size and strength in vivo

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\textbf{Introduction}: Obesity exacerbates the age-related loss of muscle strength (1,2). The purpose of this study was to determine whether circulating pro-inflammatory cytokines, elevated with increased fat mass (3) and ageing (4,5), were associated with muscle properties in young and older people across the BMI spectrum. \textbf{Methods}: Seventy-five young (18-49 yrs) and 67 older (50-80 yrs) healthy, untrained men and women (BMI: 17-49 kg/m\textsuperscript{2}) performed plantar flexor maximum voluntary contractions (MVCs). Volume (Vm), fascicle pennation angle (FPA), and physiological cross-sectional area (PCSA) of m. gastrocnemius medialis (GM) were measured using ultrasonography. GM specific force was calculated as GM fascicle force/PCSA. Percentage body fat (BF\%), body fat mass (BFM), and lean mass (BLM) were assessed using DEXA. Serum concentration of 13 cytokines was measured using luminometry. \textbf{Results}: Despite greater Vm, FPA, and PCSA (p<0.05), young individuals with BF\% $\geq$40 exhibited 37\% less GM specific force and 24\% less MVC/body mass compared to young BF\% <40 (p<0.05), while circulating cytokine concentrations correlated inversely with young muscle properties (r$\geq$0.324, p$\leq$0.044). Older people with BF\% $\geq$40 expressed greater isokinetic MVC compared to older BF\% <40 (p=0.019) but this was reduced by 26\% when normalised to body mass (p<0.001), while serum cytokine concentrations correlated positively with older muscle properties (r$\geq$0.378, p$\leq$0.027). \textbf{Discussion}: Our data suggest that obesity has an anabolic effect on young but not older muscle, and that it reduces muscle quality differently with age. This could be due, in part, to potentially different effects of pro-inflammatory cytokines on young vs. older muscle.

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**Increased habitual physical activity maintains neutrophil migratory dynamics in the elderly: the Physical Activity and Healthy Ageing Study (PAHA)**

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**Background:** The increased risk of morbidity and infections in the elderly is accompanied by reduced immune function (immunesenescence) and increased systemic inflammation (inflamm-ageing). Neutrophils represent critical first-line mediators in the fight against bacterial infection and systemic inflammation through functions including migration to the site of infection, killing of bacteria and resolution of infections. With ageing there are significant reductions in these functions. Physical activity (PA) has many health benefits, of which many may be mediated by reduced inflammation and improved immune function. Little is known about the effects of PA on neutrophil function in the elderly. **Methods:** To address this, healthy elders (66.9±4.9yrs; n=211) were assessed for habitual PA using accelerometry. The 20 elders with the highest and lowest PA levels were then evaluated. 10 young (23±3.8yrs) control participants were assessed. Neutrophil function was assessed: migration towards the chemokine IL-8 by novel time-lapse video-microscopy, bactericidal activity (phagocytosis, ROS generation) and chemokine receptor expression. Systemic inflammation was also determined. **Results:** Neutrophils from high PA donors had more efficient migration than cells from low PA donors (p=.001) and comparable to young donors. No differences were observed for expression of chemokine receptors CXCR1 or CXCR2 or phagocytosis of bacteria (all p>.05). Neutrophils from low PA donors produced more superoxide (p=.044) and these subjects had increased signs of inflamm-ageing: raised IL-6 (p=.043), IL-8 (p=.037), PAI-1 (p=.019) and reduced IL-10 (p=.040). **Conclusions:** Increased PA in later life maintains neutrophil migratory dynamics and reduces age-related systemic inflammation, which may contribute to improved health in older adults.
Introduction: Older adults adopt altered movement control strategies to cope with the demands of stair descent, particularly between different buildings, where stair rise may differ. Exercise training may help older people meet these demands. Therefore, this study examined the effects of lower-limb exercise training on the postural stability and movement control strategies of older adults descending stairs of different step height. **Methods:** Fifteen older individuals (11 women; 75 ± 3 yr, 162 ± 7 cm, 69 ± 11 kg) descended an instrumented four-step staircase, configured to either standard (17 cm) or increased rise steps (25.5 cm), before and 16 weeks after exercise training. Kistler force platforms and a VICON motion capture system were used to collect and compare data on: centre of mass (COM)-centre of pressure (COP) separation COM jerk (the rate of change of COM acceleration). Exercise training involved two sessions per week of leg-press, knee extension and calf-press exercises (three sets of ~8 repetitions at 80% 3RM), and plantarflexor static stretching (45 s per leg, 3 repetitions). **Results:** Post-training, anterior COM-COP separation increased (P < 0.01) and posterior separation decreased when descending standard stairs (P < 0.01), but not increased rise stairs. Medial (P < 0.05) and lateral separations (P < 0.05) increased when descending standard stairs, but not increased rise stairs after training. Anterior-posterior COM jerk increased, with vertical jerk unchanged, when descending standard stairs (P < 0.01). Training did not affect COM jerk for increased rise stairs. **Discussion:** These results demonstrate that the biomechanical and postural adaptations conferred from 16 weeks of resistance exercise and stretching training are constrained by step rise during stair descent in older adults. **Acknowledgements:** This research was funded by the NDA programme, grant ES/G037310/1.
**Objective:** Catheter associated Urinary tract infections (UTI’s) are prevalent in elderly patients particularly those in hospitals or nursing homes and are one of the most common nosocomial infections in hospitals. These infections are caused due to the attachment of microorganisms on the catheter surface which then invade into epithelial cells of the urinary tract and thus cause infection. The aim of the current research project is to develop novel antimicrobial coatings which will not only prevent the attachment of microorganism on the catheter surface but also kill them thus preventing and eliminating catheter associated UTI’s. **Methods:** The antimicrobial properties of six pure metals (Cu, Zn, Co, Ni, Ga, Ag) against Gram negative bacterium (Escherichia coli) and Gram positive (Staphylococcus aureus) were investigated. Bacterial cultures were incubated at 37°C with metal powders and the killing effect was determined at different time points (24, 48, 72 and 96 hours). **Results:** The results show that antimicrobial properties of the metals very considerably. From the metals studied, cobalt and copper were found to be the most effective with high killing effect both on Gram positive and Gram negative bacteria. Gallium and silver did not show any antimicrobial properties however, zinc and nickel exhibit varied properties depending upon the bacterial species. **Conclusion:** These results although suggest that copper, cobalt and zinc are strong antimicrobial metals however further work is required to develop novel coating for urinary catheters.
Low-grade systemic inflammation, evident as raised IL6 levels, is characteristic of ageing. Using 2 independent human population studies (the InCHIANTI Study and the Framingham Heart Study) we aimed to identify which gene transcripts statistically explained the relationship between age and increasing interleukin-6 (IL6) levels in blood. We used microarrays which measured expression of >9000 genes from peripheral blood sample RNA in both studies. We then used statistical mediation models to estimate the proportion of the age~IL6 association mediated by each gene. Many genes (>4000) were associated with age or IL6 levels, but very few mediated the age-IL6 association. We found 7 genes in both cohorts mediating more than 5% of the age~IL6 association, after accounting for the different leukocyte cell types and other confounding factors. The largest effect mediator explained 35.6% of the age-IL6 association in InCHIANTI and has not previously been linked to ageing. Several of the mediator genes have known functional relevance to immune ageing (including Perforin, a cytolytic protein released by T-cells). Very few cytokine or interleukin-related transcripts were significant mediators. In particular, IL-6 expression in blood did not mediate the association between age and IL-6 protein levels. These results suggest that age related inflammation is characterised by specific expression changes, far more focussed than the general IL6 related inflammatory response. Most circulating inflammatory markers in ageing may be coming from tissues other than blood white cells. We are now characterising the novel genes and attempting to identify their cell subtypes of origin.
Daily physical activity characteristics of older versus younger individuals

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Maintaining physical activity into older age is likely an important strategy to retain muscle function, and thus an independent lifestyle. We investigated habitual physical activity characteristics in older (25 male and 20 female; (Mean(SD); 70(4), 70(3) years; 76.4(11.7), 62.4(9.0) kg) and younger (15 male and 15 female; 25(4), 26(4) years; 75.5(10.4), 61.6(5.2) kg) individuals. Participants wore an Actiheart™ combined accelerometer and heart rate monitor for 6-days. Physical activity level as a ratio of total energy expenditure to basal metabolic rate (PAL) of older and younger males was not statistically different, (1.53(0.15) vs. 1.68(0.26), p=0.06, d=0.7), but was lower in older compared to younger females (1.66(0.19) vs. 1.80(0.19), p<0.05, d=0.7). Minutes per day spent in sedentary/light activity (<3 METs/min) and moderate activity (≥3-6 METs/min) were not different between older and younger males (1340(45) vs. 1298(86), p=0.10, d=0.6; and 85(40) vs. 111(78) min, p=0.23, d=0.4), or females (1295(75) vs. 1282(56), p=0.56, d=0.2; and 145(75) vs. 119(49) min, p=0.37, d=0.4). Daily vigorous activity (≥6 METs/min) was lower in older than younger males (12(13) vs. 23(17) min, p<0.05, d=0.7) and likewise in females (7(7) vs. 30(22) min, p<0.01, d=1.3). Older males had lower PAL than older females (p<0.05, d=0.8), engaging in more sedentary/light activity (p<0.05, d=0.7) but less moderate activity (p<0.01, d=0.9). In conclusion, older individuals engaged in less vigorous activity than younger individuals, and tended to expend a lower proportion of daily energy through activity, however older females were more active than older males.
Validations of a systems approach for cytokine stimulation of MMP1 in chondrocytes

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The proteolytic degradation of articular cartilage is a major component in the development of Rheumatoid and Osteoarthritis. People with these conditions have been shown to have elevated levels of pro-inflammatory cytokines oncostatin M (OSM) and Interleukin 1 (IL1) in their synovial fluid and this corresponds with a synergistic loss of cartilage. These findings led to the creation of microarray data from SW 1353 cells which have been treated with OSM and IL1. Combined treatment of the two cytokines leads to the upregulation of many genes. Particularly interesting is their combined effect on metalloproteinases (MMPs), since MMPs can lead to breakdown of cartilage components. The presence of OSM by itself has little effect on MMP expression and although IL1 does increase expression, this is greatly exacerbated when both cytokines are added. This experimental data led to a computer model recently being published in arthritis and rheumatology that shows how OSM and IL1 can control cartilage collagen breakdown. Using a systems biology approach we aim to identify, other genes from the data with similar expression patterns that may cause damage by themselves or affect the MMPs in some way. Starting with functional enriching programmes, we aim to extract processes that are relevant to collagen breakdown in order to determine genes with potential for further study and possible addition to the model. Our initial aim however is to test the reliability of the data due to its age. Simultaneously we aim to test drug compounds generated by the Broad institute website (http://www.broadinstitute.org/cmap) which have similar effects to the cytokines. This will hopefully confirm our results and give us some idea to the validity of the broad institute programme to our experiments.
Effect of Recording Location on MUNIX Values in the Bicep Brachii of Humans

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Background: The motor unit number index (MUNIX) provides an index value relative to motor unit number from surface electromyography (EMG). It has been used in investigations of larger muscles, although very large ranges of values have been reported in the biceps brachii (BB) (Neuwirth et al, 2011). The MUNIX calculation relies on the surface interference pattern (SIP) from voluntary contractions and the compound muscle action potential (CMAP) from a supra-maximal stimulation of the nerve, both of which may vary when measured at different sites across a muscle. Aim: Investigate the effects of recording electrode position on SIP and CMAP area and power, and resulting MUNIX values from the BB muscle in healthy adults. Methods: Participants gave written informed consent, and a 4-channel monopolar linear array surface EMG electrode was placed on both the medial and lateral heads of the BB of 10 participants, nine young; 24.8(4.2) yrs and one old; 70 yrs. The linear array on the medial head was placed over the motor point, defined as the area of muscle with the highest excitability from the smallest electrical stimulus. The remaining linear array was placed in line and parallel to this on the lateral head. EMG signals were recorded during maximum voluntary isometric contractions and at 5, 10, 20, 30, 40, and 60% of the maximum. The CMAP was obtained with a supramaximal stimulation of the musculocutaneous nerve. SIP and CMAP area and power, and MUNIX values were calculated for each of the 8 channels. Results: MUNIX values differed significantly across different proximal-distal locations of the BB when analysed with a two-way repeated measures ANOVA (p<0.001), but did not differ between sites side by side on medial and lateral heads (p=0.532). Mean MUNIX across all channels was 131. Conclusions: Site selection is important when obtaining a MUNIX from the BB. Medial-lateral variations are less important than proximal-distal variations when considering a recording location. Similar values can be obtained from the same locations on the medial and lateral heads. A value recorded at a given location is unlikely to be representative of the entire muscle. This consideration should be applied when studying other larger muscles with the MUNIX method.

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Figure 1: MUNIX values across 8 separate channels on the medial and lateral heads of the BB (*p<0.05, **p<0.001).
Exercise Effects on Bone are More Pronounced in Younger People, Men and Childhood Starters – A Study of Master Tennis Players

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Whilst exercise can improve bone strength, effects of age, gender and starting age on exercise benefits are unknown. In tennis players the non-racquet arm can act as a control for the exercising racquet arm without confounding factors, e.g. genotype. Therefore, muscle-bone side asymmetries were examined in master tennis players to investigate age, sex and starting age effects on the osteogenic potential of exercise. Eighty-eight tennis players (51m, 37f; age 63.8±11.8y) were recruited - peripheral quantitative computed tomography (pQCT) scans of both arms were taken at radius, ulna and humerus mid-shaft and distal radius. Thirty-two ‘old starters’ began playing in adulthood; remaining players began during childhood and were termed ‘young starters’. Pronounced asymmetries in muscle and bone in favour of the racquet arm were observed; most notably racquet arm humeral bone area was 23±12 % greater (P<0.001). Despite no or gender age effect on training volume diaphyseal asymmetries were larger in younger players and men – particularly in the humerus where bone mass, cortical thickness and bending/torsional stiffness asymmetries were 41-48% greater in 40- than 80-year olds and 28–34 % greater in men (all P<0.05). However, asymmetries in distal radius bone mass (a common fracture site) were not affected by age (P=0.863) or sex (P=0.9544). Bone area and periosteal circumference asymmetries were larger in young starters at all sites (all P<0.01); most strikingly, no distal radius asymmetry was found in old starters (0.4±3.4 %). Results suggest a greater potential for exercise benefits to bone in men, younger people and young starters.