British Society for Research on Ageing

68th Annual Scientific Meeting

Ageing here and now: current research and transformative therapies

Oriel College Oxford 6th-8th September 2018

British Society for Research on Ageing

Oriel College, Oxford
6-8th September
2018

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British Society for Research on Ageing annual scientific conference, Oriel College Oxford 6-8th September 2018

Ageing here and now: current research and transformative therapies

Thursday 6th September 2018

Early career researcher session:
Chairs: Adam Rolt and Terry Davis

10.30 -11.00 Coffee and register

11.00-11.30 Introduction and ideas exchange to identify related research interests
11.30-12.30 Guided workshop: developing a review article or primary research paper
12.30-13.00 Pitch to panel for ideas for a paper for Biogerontology

13.00-14.00 Join other delegates for sandwich lunch

Ageing research in an ageing society
Chairs: David Weinkove and Cathy Slack

12.00-14.00 Arrival and registration for main meeting; sandwich lunch

14.00-14.10 **Welcome**
Lynne Cox, Oxford, UK
14.10-14.40 **Human longevity: myths and possibilities**
Sarah Harper, Oxford, UK

Cells as both cause and treatment of age-related disease
Chairs: Lynne Cox and Jo Bridger

14.40-15.10 **Stem cell therapies in heart disease**
Sian Harding, London, UK
15.10-15.40 **Tracking and targeting of senescent cells**
Daniel Munez-Espin, Cambridge, UK

15.40-16.20 Afternoon tea

16.20-16.50 **Targeted apoptosis of senescent cells against aging and cancer**
Peter de Keizer, Netherlands

16.50-17.20 **Targeting STING in senescence with small-molecule inhibitors**
Andrea Ablasser, Lausanne, Switzerland

17.20-18.05 **KEYNOTE: Senolytic drugs: from mutant mice to human clinical trials**
Nathaniel David, President, Unity Biotechnology, USA

18.05-18.25 Lightning talks (2 minutes each) Even numbered poster presenters

18.25-19.25 Posters with wine reception

19.30-20.45 Dinner in Hall

20.45-23.00 Cash bar

Friday 7th September 2018

Ageing mechanisms (1)
Chairs: Kasia Whysall and John Henderson

09.00-09.30 **Cellular ageing and replicative senescence**
Suresh Rattan, Aarhus, Denmark

09.30-09.45 **Human ageing is associated with reduced natural killer cell cytotoxicity against and migration towards senescent cells**
Jon Hazeldine, Institute of Inflammation and Ageing, Birmingham, UK

09.45-10.00 **The genomic footprint of ageing: epigenetics, replication and somatic mutations**
Benjamin Schuster-Boekler, Oxford, UK

10.00-10.30 **Mitochondria to nucleus retrograde signaling triggers formation of cytoplasmic chromatin fragments and activation of SASP in senescent cells**
Peter Adams, Beatson Institute, Glasgow, UK and San Diego, USA

10.30-11.00 Morning coffee

Ageing mechanisms (2) – immunity, autophagy and mTOR
Chairs: Lorna Harries and Hannah Walters

11.00-11.30 **Autophagy and immune aging**
Katja Simon, Kennedy Institute, Oxford, UK

11.30-11.45 **Genome-wide analysis identifies transcriptional down-regulation of insulin-like growth factor 1 receptor signalling as a major hallmark of ageing in developing B lymphocytes**
Daniel Bolland, Babraham Institute, Cambridge

11.45-12.15 **mTOR signalling in autophagy and ageing**
Viktor Korolchuk, Newcastle, UK

12.15-12.30 **Age-dependent effects of reduced mTor signalling on life expectancy through distinct physiology**
Mirre Simons, Sheffield, UK

12.30-12.45 **Longevity by RNA polymerase III inhibition downstream of TORC1**
Nazif Alic, UCL, London, UK

12.45-13.50 Lunch in hall

13.50-14.30 BSRA AGM (all members requested to attend; several constitutional matters require a quorate membership vote)

Tools and models to study ageing (1)
Chairs: Suresh Rattan and Fiona Mutter

14.30-14.45 **Drosophila as a model to study innate immunity and ageing**
Petros Ligoxygakis, Oxford, UK
14.45-15.15 **Induced pluripotent stem cells: A versatile platform for the study and treatment of age-related diseases**
Paul Fairchild, Oxford, UK
15.15-15.45 **Tissue engineering approaches to modelling Alzheimer's disease**
Eric Hill, Aston, UK

15.45-16.15 Afternoon tea

Tools and models to study ageing (2)
Chairs: Marina Ezcurra and Abigail Otchere

16.15-16.45 **Werner syndrome models implicate DNA damage signalling in premature ageing and identify WRN as a *bona fide* anti-gerontogene**
Lynne Cox, Oxford, UK
16.45-17.15 **NAD^+ repletion inhibits accelerated aging in Werner syndrome through the restoration of mitophagy**
Evandro Fei Fang, Oslo, Norway
17.15-17.30 **Facilitating drug discovery by quantifying early declines in movement in large populations of adult worms**
David Weinkove, Durham, UK
17.30-17.45 **Defining an index for cellular senescence**
Eva Latorre, Exeter, UK
17.45-18.05 Lightning talks (2 minutes each) Odd numbered poster presenters

18.05-19.15 Posters with drinks reception

19.30-21.00 Gala dinner in Hall

21.00-23.00 Cash bar

Saturday 8th September

Ageing in time and place (1): biomarkers

Chairs: Viktor Korolchuk and Luke Pilling

09.00-09.15 **Discovery of a predictive biomarker for death in older adults diagnosed with frailty**
Jorge Erusalimsky, Cardiff, UK

09.15-09.30 **Attenuation of age-related renal lesions in a model of RAGE (receptor for advanced glycation end products) knockout**
Thibault Teissier, University of Lille, France

09.30-09.45 ***HNRNPM*, *HNRNPA0* and *AKAP17A* splicing factor transcript levels demonstrate predictive associations with human ageing phenotypes in peripheral blood**
Ben Lee, Exeter, UK

09.45-10.00 **Applications of deep neural networks to human ageing biomarker development**
Polina Mamoshina, Insilico Medicine, Rockville, USA, and Oxford, UK

10.00-10.15 **Circadian rhythms in immune parameters and functioning in older adults: impact on vaccine responses and inflammatory diseases**
Niharika Duggal, Birmingham, UK

10.15-10.45 Morning coffee

Ageing in time and place (2): systems, trials and drug discovery

Chairs: Claire Stewart and Kay Hemmings

10.45-11.15 **Circadian rhythms in the ageing musculoskeletal system: implications in therapies for osteoarthritis and low back pain**
Qin-Jun Meng, Manchester, UK

11.15-11.45 **Sarcopenia – making the science work for patients**
Miles Witham, Newcastle, UK

11.45-12.00 **Announcement of prizes and awards**
BSRA committee

12.00-12.45 **Open science, partnership with industry and close collaboration between UK universities and the NHS to accelerate treatments for multiple morbidities associated with ageing**
Chas Bountra, Oxford, UK

12.45-13.00 **Closing remarks**
Layla Moran, MP for Oxford West & Abingdon

13.00-14.00 Sandwich lunch and depart

14.00 – 15.30 Guided walking tour of Oxford (if sufficient numbers) - experienced guide and access to many of the very special sights of Oxford.
PLEASE SIGN UP BEFORE LUNCH ON FRIDAY IF INTERESTED

Sponsor details

The following generously provided sponsorship for the meeting and we gratefully acknowledge their support:

BBSRC is part of UK Research and Innovation, a new organisation that brings together the UK's seven research councils, Innovate UK and Research England to maximise the contribution of each council and create the best environment for research and innovation to flourish. The vision is to ensure the UK maintains its world-leading position in research and innovation. Through Bioscience for Health, BBSRC provides sustained research investment to improve health and wellbeing across the life course, reducing the need for medical and social intervention. The four key challenge areas of Bioscience for health are lifelong health, nutrition and health, One health and biotechnology for health.

BBSRC is sponsoring the Mechanisms of Ageing sessions 1 and 2, and also providing ECR bursaries to BBSRC-funded scientists.

The Genetics Society is a registered charity and was founded in 1919 as the world's first society devoted to the study of the mechanisms of inheritance. It is also one of the world's oldest "learned societies". Famous founder members included William Bateson, Edith Rebecca Saunders, JBS Haldane and AW Sutton. Membership includes over 1900 of the UK's active professional genetics, including teachers, researchers and students and is open to anyone with an interest in genetic research or teaching, or in the practical breeding of plants and animals.

The Genetics Society is kindly sponsoring the Tools and Models session.

Lonza provides the pharma market with the tools that life-science researchers use to develop and test therapeutics, beginning with basic research stages on to the final product release. Lonza's bioscience products and services range from cell culture and discovery technologies for research to quality control tests and software that ensures product quality. Lonza Bioscience Solutions serves research customers worldwide in pharmaceutical, biopharmaceutical, biotechnology and personal care companies. The company delivers physiologically relevant cell biology solutions and complete solutions for rapid microbiology.

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Springer has signed an agreement with the British Society for Research on Ageing (BSRA) to enter into an affiliation with the journal **Biogerontology**, which offers a platform for research which aims primarily at achieving healthy old age accompanied by improved longevity. The focus is on efforts to understand, prevent, cure or minimize age-related impairments.

Biogerontology provides a peer-reviewed forum for publishing original research data, new ideas and discussions on modulating the aging process by physical, chemical and biological means, including transgenic and knockout organisms; cell culture systems to develop new approaches and health care products for maintaining or recovering the lost biochemical functions; immunology, autoimmunity and infection in aging; vertebrates, invertebrates, micro-organisms and plants for experimental studies on genetic determinants of aging and longevity; biodemography and theoretical models linking aging and survival kinetics. Biogerontology publishes original research reports, reviews, hypotheses, new methods and interviews, and special issues on topics relating to aging, health and longevity. We are grateful to Springer for offering a special issue of Biogerontology to report on outcomes of this meeting.

https://www.springer.com/life+sciences/cell+biology/journal/10522

The British Society for Research on Ageing was formed as the 'Club for Research on Ageing' by Professor Vladimir Korenchevsky (1880-1959) at some point prior to 1939 and as thus has a valid claim to be the world's oldest scientific society devoted to research into the biology of ageing. The BSRA promotes research to understand the causes and effects of the ageing process. The general aim of the society is to foster an experimental approach to problems of ageing in the biological and medical sciences and to provide a forum for the discussion of current ideas in these two areas.

General information

BSRA helpers
There will be a number of helpers during the conference who will be identifiable by their royal blue BSRA T shirts. They are all scientists who have volunteered to help with the smooth running of the meeting. We are immensely grateful to: **Hannah Walters, Adam Rolt, Terry Davis, Philip Dimitriev, Lorna Harries, Cathy Slack, Anitha Nair, and Sophie Riddell.**

Scientific confidentiality
BSRA conferences aim to encourage the discussion of new and unpublished work, so please treat all communications within the conference as confidential. Do not photograph slides or posters without the express permission of the presenting author, and please do not post any data from others on any social media or other platform. Information contained within abstracts should not be cited directly but treated as personal communication and only referred to in publications with express consent of the authors.

Conference rooms
All lectures will take place in the Harris Lecture Theatre. Tea/coffee breaks, poster sessions and sponsor stands are located immediately adjacent in the Harris Seminar Room.

Sponsors
The meeting is only possible because of the generosity of our sponsors. Please take time to attend their stands and talk to the representatives present.

Meals
Breakfast, lunch and dinner will all be served in Hall (1st quad).
Breakfast (for those staying in college accommodation) is from 8-9am (full cooked English breakfast or continental breakfast).
For lunch and dinner timings on particular days, please consult the programme.

Wifi
Eduroam is available through high-speed wifi around the college. For those without an Eduroam account, we provide internet access through 'The Cloud'. Please follow the simple online instructions on your device to register for an account.

Mobile phones
Mobile phone signals can be erratic around the college because of the nature of the buildings. Please ensure you turn your phone to silent for all of the scientific sessions. For emergency contacts only, the Porters Lodge may be able to relay urgent messages via the conference helpers if necessary – tel 01865 276555.

Check in and check-out
Accommodation will be available from 2pm on day of arrival. The college asks that you check out by 10am on day of departure – since the scientific sessions start at 9am, the BSRA would be grateful if delegates could check out during the breakfast period on their day of departure. All keys and access fobs must be returned to the Porters' lodge.

Luggage
Luggage can be stored in a locked room in staircase 1 (first quad, key from Porters' lodge), or brought at your own risk to the Harris Seminar Room (in use for the Early Career Researcher session 10.30-1pm on 6th September). We will not be able to lock that room as it is accessed by the sponsors at all times.

Fire safety
Please familiarise yourself with the fire safety notices in your accommodation and know the nearest fire exit and meeting point. **DO NOT** ignore any fire alarms; the policy is to evacuate immediately on hearing an alarm – we are not expecting any fire alarm tests during the meeting. Please keep fire doors closed.

Smoking
The college is strictly no-smoking (including e-cigarettes), and the non-smoking zone extends to 2m outside the college walls. Rooms are fitted with extremely sensitive smoke detectors.

Safety and security
The college is constrained by the historic nature of its buildings so please do take care on exposed cobbles and uneven surfaces.
Please use your electronic fob for access and ensure that gates and doors close behind you, especially if they open onto public streets. Do not let anyone else into the college. In case of lost/mislaid access cards, please report the loss immediately to the Porters' Lodge. Please do not try to access private staircases – students and some fellows have their homes in college. The college is a working academic community and we ask all delegates to respect that. The quiet period is between 11pm and 8am.

Illness
If you feel unwell during the conference, please notify the Porters' Lodge who will be able to call for medical assistance on your behalf.

Parking
Please note that there is NO PARKING on the college site and parking on adjacent roads is limited to 2 hours per session (with no return within an hour) so is not suitable for the duration of the conference sessions. There is a large central carpark at the Westgate shopping centre a few minutes' walk from college, and several Park and Ride sites around the periphery of the city with very regular bus services running until very late at night/early morning.

WE STRONGLY ADVISE THAT YOU DO NOT TRY TO GET AROUND THE CITY BY PERSONAL CAR: MANY STREETS ARE CLOSED TO THROUGH TRAFFIC AND HEFTY FINES ARE LEVIED ON UNSUSPECTING VISITORS.

Cycling
Oxford has several 'hire to ride' bicycle schemes – simply look out for the brightly coloured bicycles all round the city centre. An app can be downloaded to release and pay for the bicycles.

Taxis
Oxford does not have an Uber service but does have several local taxi companies. There is a dedicated taxi phone in the Porters' Lodge. Examples (without specific recommendations) include:

- Royal Cars 01865 777 333
- GoGreen Taxis 01865 922 222
- OO1 Taxis 01865 240 000 or via app

Coaches to London and Heathrow and Gatwick airports
Oxford has excellent transport links including direct bus services to:

- Heathrow and Gatwick airports *(https://airline.oxfordbus.co.uk/)* – much faster than going via London
- Central London (London Tube and X90)

For details of the location of London/airport coach stops and the railway station, please see the map of Oxford on the back page of the programme.

National Express coach services run from Gloucester Green bus station to many locations in the rest of the UK.

Trains run from Oxford to London and many other parts of the country.

Oriel College
Oriel College was founded in 1326, and is the fifth oldest college in Oxford, with currently around 300 undergraduates and 200 post-graduate students. Oriel, like the other colleges of the University of Oxford, is an independent self-governing academic body, run by the academic Fellows on Governing Body and supported by a strong team of college officers.

The college site is small, based around three quadrangles plus part of the medieval city (the Island site), where the Harris lecture theatre and seminar room are based. The college is able to provide accommodation in college property for all undergraduates for the entire duration of their course, and for all first year post-graduates, either on the main site or at the college's annexe situated at Rectory Road approximately 10 minutes from the main college site, focusing around the modern James Mellon Hall. However, Oriel is far more than a hall of residence for students: within the college, it provides tutorial teaching for undergraduates, mentoring and support for graduate students, and extensive facilities including well-equipped teaching rooms, a lecture theatre, a boat house, three gyms, a chapel, music facilities and a very well-stocked library for the use of college members. There are a number of sporting teams, choirs, drama groups and other cultural activities, with students publishing their own newspaper, and the academic life of the college includes joint sessions involving undergrads, graduate and fellows in the Oriel Talks.

Oxford
The centre of Oxford contains many buildings of historic interest, together with art galleries and the famous Ashmolean Museum and Bodleian Library, all within walking distance of Oriel.

A number of guided walking tours are offered daily – e.g. https://www.oxfordwalkingtours.com

We are hoping to be able to organise a guided tour from 2pm on Saturday, if a sufficient number of people sign up before 1pm on Friday – lists will be up by the lecture theatre.

Oxford is a short distance by bus/taxi from Blenheim Palace, and for those with more commercial interests, the brand-new Westgate Centre offers a huge range of shops, with the world-famous Bicester Village retail outlet only a short bus ride away – or now also accessible via a short train ride from Oxford station (Chiltern Railways to Marylebone).

ECR session

10.30 -11.00 Coffee and register

11.00-11.30 Introduction and ideas exchange to identify related research interests
11.30-12.30 Guided workshop: developing a review article or primary research paper
12.30-13.00 Pitch to panel for ideas for a paper for Biogerontology

13.00-14.00 Join other delegates for sandwich lunch

Chair: Adam Rolt, Elysium fellow, Department of Biochemistry, University of Oxford

Invited speaker biographies

Professor Sarah Harper, CBE

Sarah Harper is Professor of Gerontology at the University of Oxford. She is a Director of the Oxford Institute of Population Ageing which she founded in 1997 with funding from the US National Institute of Aging. Between 2014 and 2017 Sarah served on the Prime Minister's Council for Science and Technology, which advises the Prime Minister on the scientific evidence for strategic policies and frameworks. In 2017 she moved to serve as the Director of the Royal Institution of Great Britain. Sarah is a Director and Trustee of the UK Research Integrity Office and a non-Exec Director of Health Data Research UK. Sarah was appointed a CBE in 2018 for services to Demography.

She chaired the UK government's Foresight Review on Ageing Populations (2014-2016) and has chaired the European Ageing Index Panel for the UNECE Population Unit since 2015. She is a Governor of the Pensions Policy Institute and sits on the Advisory Board, English Longitudinal Study of Ageing (ELSA). She is a Fellow of the Royal Anthropology Institute.

Sarah has a background in anthropology and population studies. Her current research on demographic change addresses the impact of falling fertility and increasing life expectancy, with a particular interest in Asia and Africa. Sarah has just completed a monograph 'How Population Change will Transform our World' Oxford University Press (2016), and is working on her next book for Cambridge University Press on 'Population, Technology and Environmental Change'. Sarah is the founding editor of the Journal of Population Ageing and editor of the Handbook of Ageing and Public Policy (Elgar 2014).

Professor Sian Harding

Sian Harding is interim head of the National heart and Lung Institute, Imperial College London, and Director of the Imperial British Heart Foundation Cardiovascular Regenerative Medicine Centre. Her work has centred on the myocardium in heart failure, especially beta-adrenergic mechanisms. She was Scientific PI on the first UK gene therapy trail in LVAD patients, aimed at improving cardiac contractility. She is now studying the pluripotent stem cell-derived cardiomyocyte, both for disease modelling and cardiac repair. Professor Harding is former President of the European Section of the International Society for Heart Research. She has been elected Fellow of the ISHR, the American Heart Association, European Society of Cardiology, British Society of Pharmacology and the Royal Society of Biology. She is on the board of the British Society of Gene and Cell Therapy.

Dr Daniel Munez-Espin

Daniel Muñoz-Espín studied Biology and Molecular Biology at the Autonomous University of Madrid in Spain, where he also completed his PhD with cum laude honours within the Viral DNA Replication Group at the Centre of Molecular Biology Severo Ochoa (CMBSO), under the supervision of Dr Margarita Salas. During his PhD, he also worked at Sir William Dunn School of Pathology (University of Oxford, UK) as a visiting student. He was then awarded an I3P Fellowship followed by a Spanish National Research Council Fellowship to conduct postdoctoral research on DNA replication, resulting in several first- and corresponding authored papers. Based on his research, a patent was filed on a novel gene delivery system to Sygnis AG Pharma (2013). Dr Muñoz-Espín then moved to Dr Manuel Serrano's group at Spanish National Cancer Research Centre (CNIO), where his productive work culminated with two awarded grants: a Ramon y Cajal Programme Senior Grant and a National Programme Grant for Researched Aimed at the H2020 Societal Changes. His work demonstrated that, in addition to cancer and ageing, cellular senescence also plays a role during normal embryonic development, a process that was termed as "developmentally-programme senescence". This work, published in Cell in 2013, redefined cellular senescence as a tissue remodelling process acting in a physiological context. The scientific community received this novel concept with enthusiasm, as reflected by commentaries in top journal, including Cell, Nature, The EMBO Journal and Nature Reviews Molecular and Cell Biology. In 2016, Dr Muñoz-Espín joined the Department of Oncology at the University of Cambridge as Principal Investigator as part of the Cancer Early Detection Programme of the CRUK Cambridge Centre. Some of his current funding sources include an MRC New Investigator Research Grant (NIRG), a CRUK Early Detection Project Award, and a Royal Society Research Grant. Recently, Dr Muñoz-Espín and colleagues have reported in EMBO Molecular Medicine a versatile drug delivery tool to target senescent cells that has been validated in a model of lung fibrosis, resulting in a remarkable reduction of the fibrotic scar and in the restoration of the pulmonary function, and in a model of cancer, resulting in full tumour regression in combination with senescence-inducing chemotherapy.

Professor Peter L. J. de Keizer

Peter de Keizer is Assistant Professor of Senescence in Cancer and Aging, at the University Medical Center Utrecht, the Netherlands, and is scientific co-founder of Cleara Biotech B.V.

His long-standing aim is to unravel the molecular mechanisms that cause healthy cells to become senescent and to figure out how these cells drive aging. As cancer cells that escape damaging chemo-/radiotherapy can become senescence-like, therapy resistance in late-stage cancer is also a major part of this focus. A specific goal of his current research is to identify subsets of senescent cells

About a decade ago, Peter became intrigued by the observation that FOXO proteins are downstream targets of oncogene and damage-induced senescence (e.g. PhD thesis 2009 and de Keizer, Cancer Research 2010) and discovered that interfering with FOXOs could tip the balance towards cell death. As a postdoc at the Buck Institute for Research on Aging in Novato, California, he continued this research in 2009 and generated the first and second generation of FOXO4-based compounds to eliminate senescent and therapy-resistant cancer cells (e.g. patent US20130288981 A1; 2012). In 2012, he joined the Erasmus Medical Center in Rotterdam, where he designed the third generation of anti-senescence drugs: the FOXO4-DRI peptide, aka Proxofim. This proved to be effective in counteracting signs of chemotoxicity and, excitingly, was able to restore healthspan in models for fast and natural aging, e.g. fur density, behavior and renal function (Baar et al., Cell, 2017).

In January 2018, Peter joined the University Medical Center Utrecht as assistant professor to investigate heterogeneity in senescence and the role of individual senescence subtypes in disease development. Furthermore, together with other senescence experts and molecular, cellular and pharmacological biologists, he started a biotech company (www.clearabiotech.com) to develop the fourth generation of anti-senescence drugs, through which it is truly hoped to translate these academic findings to benefit patients suffering from senescence-driven diseases and target the negative aspects of aging itself.

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Dr Andrea Ablasser

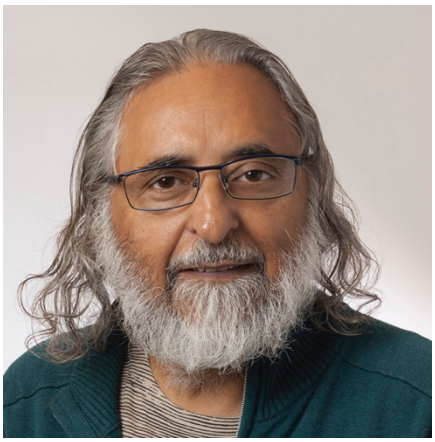
Andrea Ablasser studied Medicine at the University of Munich and received her M.D. in 2010. Her post-doctoral studies at the University of Bonn, GER, focused on deciphering molecular mechanisms of innate DNA sensing. Since 2014 she has been heading a research group at the Ecole Polytechnique Fédérale de Lausanne (EPFL), CH. Her work has identified a mechanism of innate immune sensing that triggers cellular senescence.

Dr Nathaniel David

Co-Founder and President, UNITY Biotechnology

Ned co-founded UNITY in 2011, largely because he thought it was “simply the coolest biology he had ever seen.” Before UNITY, Ned co-founded four other biotechnology companies that together raised over $1.5 billion in financing and today employ over 400 scientists, engineers, and business people. Ned builds companies because he sees company creation as a means to create technologies that change the world. Ned is a co-founder of Syrrx (acquired by Takeda), Achaogen (AKAO), Kythera Biopharmaceuticals (KYTH, acquired by Allergan), and Sapphire Energy. Ned holds pending and issued patents in fields such as nanovolume crystallography, antibiotic resistance, aesthetic medicine, and cellular senescence. He has served on the board of directors of Kythera Biopharmaceuticals, Sapphire Energy, and the Buck Institute for Research on Aging and is a member of the board of trustees of the University of California Foundation. Ned was named one of the Top 100 innovators in the world under 35 by the MIT Technology Review. He holds a Ph.D. from the University of California, Berkeley in Molecular and Cellular Biology and an A.B. in Biology from Harvard University.

Dr Suresh Rattan



Suresh Rattan, Ph.D.,D.Sc., is Professor of Biogerontology and Head of the Laboratory of Cellular Ageing, at the Department of Molecular Biology and Genetics, Aarhus University, Denmark. His research areas and expertise include ageing of human cells and application of the concept of mild stress-induced hormesis as a modulator of ageing. He is the recipient of the Lord Cohen Medal in Gerontology from the British Society for Research on Ageing (BSRA), and an Honorary Doctorate from the Russian Academy of Medical Sciences (St. Petersburg). He is the discoverer of the healthy-ageing effects of kinetin and zeatin, for which he holds world-wide patents. He has published more than 250 scientific articles, and has edited/co-edited 15 books, including books for children, general public and research scientists. He is the founder and Editor-in-Chief of *Biogerontology* – an international peer-reviewed journal published by Springer-Nature. He is the present Chairman of the Biological Section of the European Region of the International Association of Gerontology and Geriatrics (IAGG-ER). His personal website is: www.sureshrattan.com

Professor Peter D. Adams

Peter Adams obtained his PhD from Imperial Cancer Research Fund London in 1993 and did post-doctoral work with William G. Kaelin, Jr. at Dana-Farber Cancer Institute Boston, 1993-1999. Peter had is own lab at Fox Chase Cancer Center Philadelphia from 1999-2008, and then moved to the Beatson Institute for Cancer Research (BICR), Glasgow, where he was head of the Epigenetics Unit at University of Glasgow and BICR (2008-2017). Recently, Peter relocated to Sanford Burnham Prebys Medical Discovery Center and his lab in Glasgow is winding down. Over the years, Peter has studied signal transduction, cell cycle control, cell senescence and its control by chromatin and epigenetics, mostly in the context of cancer. Peter is now passionate to understand the molecular mechanisms underlying the exponential increase in cancer incidence with age – an important but understudied problem. In particular, Peter is interested in the contribution of age-associated epigenetic changes to onset of age-associated cancer, and the mechanisms by which cells harness the dynamic epigenome to permit phenotypic stability and healthy aging (a process for which his lab coined the term “chromostasis”, for chromatin homeostasis). Peter is also exploiting the new generation of small molecule epigenetic inhibitors for development of novel cancer therapies. In the UK, Peter’s lab is funded by CRUK, BBSRC and MRC and in the US by NIA. Peter Adams is co-editor-in-chief of Aging Cell.

Professor Katja Simon

Katja Simon is a Professor at Oxford University at the Kennedy Institute of Rheumatology. She trained as an Immunologist under Mitchison at the DRFZ Berlin and showed in her PhD that TH1 cytokines are found in excess in rheumatoid arthritis (EULAR Award). As a postdoc at the Centre d'Immunologie Marseille Luminy, she investigated transcription factors regulating thymic cell death. During her second postdoc in Oxford she pursued her interest in cell fate, studying cell death molecules in thymic selection, inflammation and tumour immunity. As a Principal Investigator, she turned her attention to autophagy. She is a Wellcome investigator and recipient of the 2018 EFIS Ita Askonas prize for outstanding European female group leaders in Immunology.

Over the last 8 years The Simon lab has studied the role of autophagy in the development and function of hematopoietic cells. It pioneered a technique detecting autophagy in human primary cells and showed a decrease in autophagy levels in ageing T lymphocytes (Phadwal et al, Autophagy 2012, 8(4):677-89). In vivo red blood cells need autophagy to degrade mitochondria for their final maturation (Mortensen et al, PNAS 2010, 107 (2) 832-837). Autophagy maintains hematopoietic stem cells (Mortensen, J Exp Med et al, 2011 208(3): p. 455-67), and in the absence of autophagy, a mild pre-leukemic phenotype was observed. Her lab measured low levels of autophagy in human acute myeloid leukemia samples, and demonstrated that this provides a growth advantage to AML growth in vivo (Watson et al, Cell Death Discovery 2015). The survival of memory T cells is also reliant on autophagy. They find that inducing autophagy in the aged T cells with a drug reverses an inefficient memory T cell response to influenza vaccination (Puleston et al, elife, 2014, **3**). Lastly autophagy provides free fatty acids to differentiating neutrophils (Riffelmacher et al, Immunity, 2017 47(3): p. 466-480) and promotes B1 cell self-renewal (Clarke et al J Exp Med, 2018, 215(2): p. 399-413). Her lab are now investigating the role of autophagy in aging for the identification of novel druggable pathways of autophagy in hematopoietic cells and immune cells.

Dr Viktor Korolchuk

Victor is an Associate Professor (Reader) at Newcastle University Institute for Ageing, Newcastle University, UK, since 2017. He obtained his PhD in Biochemistry at the Institute of Biochemistry, Kiev, National Academy of Sciences, Ukraine, 2000, then conducted two postdoctoral fellowships, with Dr. Cahir O'Kane, Department of Genetics, Cambridge University, UK, (2003-2006) then Prof. David Rubinsztein, Cambridge Institute for Medical Research, Cambridge University, UK, (2006-2011). His research interests include autophagy and its regulation by mTOR signalling in the context of cellular and organismal ageing; the role of autophagy in the maintenance of protein, DNA and organelle homeostasis; and autophagy as a mechanism of oxidative stress response

Professor Paul Fairchild

Paul Fairchild began his research career in Oxford, where he studied for a doctorate in the Nuffield Department of Surgical Sciences, focussing on the dual role of dendritic cells in allograft rejection and immunological self-tolerance. After spending five years as a Post-doctoral Fellow investigating the aetiology of autoimmune disease in the Department of Pathology, University of Cambridge, he returned to Oxford, where he is currently Associate Professor within the Sir William Dunn School of Pathology and a Fellow of Trinity College. In 2008, Paul Fairchild founded the Oxford Stem Cell Institute (OSCI), for which he served as Co-Director until the end of 2015. His current research continues to draw on his background in transplantation immunology, in order to investigate the nature of the immune response to tissues differentiated from pluripotent stem cells and to develop approaches to the induction and maintenance of immunological tolerance. Furthermore, he has developed a programme of research aimed at exploiting the properties of pluripotent stem cells to address unmet medical needs with an immunological basis and has filed several patents focussing on the derivation of dendritic cell subsets from human iPSC for use in immunotherapy.

Dr. Eric Hill

Dr Hill is a senior lecturer at Aston University and is programme director for the MSc Stem cells and regenerative medicine. His research interests include the development of tissue engineering strategies to model stem cell behaviour in the development of neuronal networks and also in neurodegeneration. He is currently engaged in developing stem cell derived models of the CNS in an attempt to study complex cellular interactions that occur in diseases including Alzheimer's disease, Rett syndrome and Seizure.

Professor Lynne S. Cox

Lynne Cox studied at Cambridge for both her undergraduate degree and PhD (supervised by Prof Ron Laskey, CBE), followed by a post-doctoral position with Prof Sir David Lane in Dundee on the tumour suppressor p53. She was then awarded a Royal Society of Edinburgh Research Fellowship, leading to identification of the PCNA-interacting peptide motif, or PIP, and several patents based on that discovery, which contributed to the formation of the spin-out company Cyclacel. Her studies on p53, p21 and PCNA in DNA replication control in cancer led to an interest in ageing that she has pursued since setting up her own lab in Oxford in 1996, studying the molecular basis of ageing using longitudinal proteomics and functional approaches, as well as phenotypic screening to identify agents that can suppress deleterious phenotypes in senescent cells. She also has a strong interest in premature ageing Werner syndrome (WS); her lab identified a DNA replication defect in patient-derived WS cells that could be corrected by Holliday junction resolution, and studies are ongoing to attempt to modulate premature senescence in human WS. In collaborative projects with Dr Robert Saunders (Open University) and Prof Alison Woollard (Biochemistry, Oxford), she has developed whole organism models of Werner syndrome in fruit flies and the nematode worm *C. elegans*, allowing integration of data from molecular biology and biochemical studies with whole animal biology. She is a Trustee of the British Society for Research on Ageing, Fellow and Tutor in Biochemistry at Oriel College, Oxford, Fellow of the Royal Society of Biology, and co-founded (with Katja Simon) the Oxford Ageing Network, OxAgeN. In 2015, she received the US Glenn Foundation award, presented at the House of Lords, for research into the biological mechanisms of ageing.

Dr Evandro F. Fang

Dr. Evandro F. Fang is investigating the molecular mechanisms of one of the most fundamental and fascinating topics in current biology: human aging. After finished his Ph.D training in Biochemistry at the Chinese University of Hong Kong in 2012, he started a 5-year postdoctoral fellowship at the National Institute on Aging USA with Dr. Vilhelm Bohr, focusing on the roles of the "human power house" mitochondria in human aging and age-related diseases, especially the role of DNA damage in neurodegeneration.

In September 2017, he established his independent laboratory at the University of Oslo, Norway. His laboratory is focused on the molecular mechanisms of how cells clear their damaged and aged mitochondria, a process called "mitophagy", as well as the roles of mitophagy in Alzheimer's disease. He is fascinated with and actively engaged in moving his laboratory findings to translational applications, with the overarching goal to establish novel and safe biological approaches to promote longer and healthier human lives.

He has published over 55 papers in peer-reviewed journals with an H index of 23. He has received several awards including The NIH Fellows Award for Research Excellence 2014, 2015, and an awardee of the prestigious Butler-Williams Scholar on Aging 2016 (USA), an FRIMEDBIO Young Research Talent 2017(Norway), and a finalist of the 2017 ERC Starting grant.

Professor Miles Witham

Miles Witham is Professor of Trials for Older People in the NIHR Newcastle Biomedical Research Centre, Newcastle University. He also works as a consultant Geriatrician working in both primary and secondary care. His research aims to improve physical function and quality of life for older people, using a wide range of interventions, including pharmacological agents, nutrition, exercise and strategies of care.

Improving the translation of discoveries from laboratory science and epidemiology into clinical practice is a key aim for the Newcastle BRC, and as part of this work, Professor Witham is developing a programme of trials both to test interventions targeting sarcopenia and physical frailty, but also to improve the way that we design and run trials for older people. He is also co-founder on the British Geriatrics Society Sarcopenia and Frailty Research Group, which aims to both support research and ensure that the results influence clinical practice.

He tweets at @OlderTrialsProf

Professor Qing-Jun Meng

Qing-Jun Meng is a Professor and an Arthritis Research UK (ARUK) Senior Research Fellow in the Faculty of Biology, Medicine and Health, University of Manchester. He started his post-doctoral training in 2003 at the University of Manchester to investigate the molecular mechanisms and pharmacological resetting of the biological clocks. In 2009, he received a MRC Career Development Fellowship and started his own research group, focusing on circadian clocks, ageing and age-associated diseases. In 2015, he was awarded an ARUK Senior Fellowship to continue his work into the roles of circadian clocks in the musculoskeletal system. He was promoted to a Professor of Chronobiology in 2017. Qing-Jun is a Committee member and Bursary Chair for the British Society for Matrix Biology, Theme Leader of the Chrono-Matrix Theme within the Wellcome Trust Centre for Cell Matrix Research, Management Board member of ShARM UK, International Advisory Board member of Matrix Biology Europe 2018, MRC College of Reviewers for the Newton Fund, ARUK College of Experts.

Professor Chas Bountra OBE

Chas Bountra is Professor of Translational Medicine in the Nuffield Department of Clinical Medicine and Associate Member of the Department of Pharmacology at the University of Oxford. He is also a Visiting Professor in Neuroscience and Mental Health at Imperial College, London. Chas is an invited expert on several government and charitable research funding bodies, and an advisor for many academic, biotech and pharma drug discovery programmes.

Prior to coming back to Oxford, Chas was Vice President and Head of Biology at GlaxoSmithKline. He was involved in the identification of more than 40 clinical candidates for many gastro-intestinal, inflammatory and neuro-psychiatric diseases. More than 20 of these molecules progressed into patient studies and more than five of these delivered successful "Proof of Concept" data and hence progressed into late stage development. He was involved in the launch and development of the first treatment for Irritable Bowel Syndrome (Alosetron) and was the first to show that neurokinin NK1 antagonists are anti-emetic in preclinical and clinical studies.

His current interests are i) using X ray structures of novel human proteins to generate small molecule inhibitors, screening in human cells to identify novel targets for drug discovery, and then developing clinical candidates for evaluation in patients, pre-competitively ii) focussing on epigenetic and genetically identified proteins, because these are likely to represent better targets for drug discovery, for many cancer, inflammatory, metabolic and neuro-psychiatric diseases iii) working with colleagues in Oxford to build major programmes in rare diseases and in Alzheimers Disease, and creating a "BioEscalator" for the rapid translation of SGC science and iv) building stronger links with local hospitals, patient groups, regulatory agencies, private investors, CROs, biotechs and large pharma companies, to create a new, more efficient ecosystem for pioneer drug discovery.

Chas believes the SGC has become a leader in human protein structural biology and epigenetics chemical biology, and is arguably one of the most successful open innovation, public – private partnerships in the world. Furthermore, with the many recent local developments (Target Discovery Institute, Kennedy Institute, Dementia Institute), he believes Oxford is emerging as one of the major academic drug discovery centres in Europe.

He has given over 300 invited lectures. In 2012 he was voted one of the "top innovators in the industry".

Layla Moran, MP for Oxford West & Abingdon

Layla Moran is a Physics teacher by profession, formerly working in a state secondary school, as a Head of Year in an international school and latterly with an Oxford-based Education organisation. She read Physics at Imperial College and holds an MA in Comparative Education. She is a school governor at a primary school in her constituency.

Layla was inspired to go into politics by her passion to see that every child, no matter their background, should have a fair chance of making the best of this world. She overturned a 9,500 vote Conservative majority to win Oxford West & Abingdon in June 2017.

She is the Liberal Democrat spokesperson on Education, and sits also on the Public Accounts Select Committee.

Layla has an international background; she has lived in many countries including Belgium, Greece, Ethiopia, Jamaica and Jordan and speaks French fluently along with some Spanish, Arabic and Greek.

Abstracts for talks

Human longevity: myths and possibilities

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There have always been long lived individuals. The challenge facing the 21st century is the sheer number of us and our children who are projected to survive to a century and more. As death has been pushed back across the life course, so that most people in high income countries can expect to reach age 80 and over, so our societies and communities need rethink our lives and the institutions which frame them. How did we attain such long lives? Will they be healthy or frail? Is there a maximum age a human can live to? And importantly how we can ensure that current and future societies are able to maintain wellbeing across these long lived lives, as well as equity within and between the generations.

Stem cell therapies in heart disease

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Endogenous repair of cardiac muscle is modest in young and middle-aged adults and drops further in age. There is still intense debate as to whether the reparative cells are cardiac stem cells or existing cardiomyocytes which dedifferentiate and redifferentiate. Both stimulation of endogenous repair and addition of exogenous cardiomyocytes or cardiac stem cells are being explored as potential regenerative strategies. Mesenchymal stem cells (including bone-marrow derived cells) have been tested in a large number of clinical trials. They have been shown as safe and modestly beneficial in cardiac repair but provide this by immunosuppressive and other paracrine effects rather than generation of new muscle. Human pluripotent stem cells, both embryonic and induce pluripotent stem cells, robustly generate cardiomyocytes (hiPSC-CM) through defined manipulation of the Wnt pathway. These hiPSC-CM can be formed into substantial sheets of engineered heart tissue or combined with biomaterials for cardiac patches. Delivery, vascularization and retention remain challenges in the field, to which advanced tissue engineering methods are being applied.

Tracking and targeting senescent cells

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Senescent cells accumulate in multiple ageing-associated diseases [1] and eliminating these cells has recently emerged as a promising therapeutic approach [2]. Here, we take advantage of the high lysosomal β-galactosidase activity of senescent cells to design a targeted drug delivery system based on the encapsulation of drugs with galacto-oligosaccharides [3]. We show that gal-encapsulated fluorophores are preferentially released within senescent cells in mice. In a model of chemotherapy-induced senescence, gal-encapsulated cytotoxic drugs target senescent tumor cells and improve tumor xenograft regression in combination with palbociclib. Moreover, in a model of pulmonary fibrosis in mice, gal-encapsulated cytotoxics target senescent cells, reducing collagen deposition and restoring pulmonary function. Finally, gal-encapsulation reduces the toxic side effects of the cytotoxic drugs. Drug delivery into senescent cells opens new diagnostic and therapeutic applications for senescence-associated disorders and during ageing.

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Targeted apoptosis of senescent cells against aging and cancer

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Aging is a major risk factor for the development of diseases. For long, it remained unclear what causes aging at a cellular and a molecular level. We now know that as we age, our cells accumulate damage, which can eventually cause them to become "senescent" [1]. Senescent cells cease to divide, but chronically secrete a wide range of factors that permanently alter their environment. As such, they are thought to impair tissue function and promote cancer progression, migration and therapy resistance by permanently enforcing a state of stemness [2, 3]. Senescent cells are now established as a cause for at least some aspects of aging and pose exciting candidates for therapeutic removal.

I will discuss how we identified the interaction between the damage-associated proteins FOXO4 and p53 as a pivot in senescent cell viability. Inhibition of FOXO4, or interference with its interaction with p53 using cell penetrating peptides could selectively eliminate senescent cells and target signs of aging *in vivo* [4]. This shows that, at least to an extent, it may be possible to restore healthspan once it has already declined. It will be crucial to dissect senescence heterogeneity and identify molecular mechanisms that dictate sensitivity or resistance. Our current research is focused on these mechanisms and optimizing our FOXO4-p53 drugs for clinical translation.

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Targeting STING in senescence with small-molecule inhibitors

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Senescence, a cellular program triggered by various distinct stresses, has emerged as an important contributor to aging-associated diseases. One critical feature, which underlies some of the maladaptive effects of senescent cells, is their inflammatory secretome, collectively referred to as the senescence- associated secretory phenotype (SASP). Recently, we have defined a critical role for the innate DNA sensing pathway comprising cyclic GMP-AMP synthase (cGAS) and Stimulator of interferon genes (STING) in the regulation of the SASP. Briefly, we found that cGAS recognizes aberrant cytosolic chromatin fragments (CCFs) in senescent cells and, in turn, triggers the production of SASP factors through STING. Our finding of aberrant activation of innate immune signalling in senescence raises the possibility that targeting this pathway may provide beneficial effects in senescence-associated pathologies. However, the development of pharmacological inhibitors that specifically act on molecules of the innate DNA sensing pathway has remained a major challenge. In this talk, we report the discovery of highly potent and selective small molecule antagonists of stimulator of interferon genes (STING). In depth characterisation of the compounds uncovered an entirely unexpected mechanism to pharmacologically antagonise STING signalling. We show that the discovered compounds reduce STING-mediated inflammatory cytokine production in various contexts *in vitro* and, moreover, we demonstrate their therapeutic utility in autoinflammatory disease in mice. Finally, we discuss the effect of acute inhibition of STING in contexts of cellular senescence. In sum, our work describes the first ever reported STING antagonists and provide a proof-of-concept of the realization of anti-STING therapies. We propose targeting STING with small molecules may be beneficial for diseases caused by chronic inflammation, potentially also diseases driven by the SASP.

Senolytic drugs: from mutant mice to human clinical trials

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In the nearly seven years since Baker *et al*. demonstrated that clearing senescent cells (SnCs) blunted aging in mice [1], the field of cellular senescence has leapt forward: more than 20 beneficial phenotypes have been observed when SnCs are eliminated, favorably impacting diseases as far reaching as glaucoma, osteoarthritis [2], lung fibrosis [3], and heart disease [4]. Our recently initiated clinical trial with a senolytic drug (UBX0101) for osteoarthritis represents the first effort in humans to deliberately eliminate SnCs for a widespread disease of aging. Our recent work has demonstrated that the SnCs that accumulate in aging tissues are both necessary and sufficient to drive multiple age-associated diseases and that their clearance can blunt disease progression. Such insights have allowed us to pick clinical indications amenable to safe and efficient senescent cell clearance. Selecting the right molecules for the right diseases is an ongoing challenge and will ultimately enable the creation of senolytic drugs to make particular features of aging treatable conditions.

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Cellular ageing and replicative senescence

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The 1961 discovery that cultured normal diploid cells have a limited proliferative capacity, and that this phenomenon is associated with the origins of ageing, is best known as the "Hayflick limit" and the "Hayflick phenomenon", respectively. Beginning with the demonstration of the occurrence of ageing in cells outside the body, this model system became focused on the ultimate state of cell cycle arrest in the form of replicative senescence, which is in opposition to the dysregulation and continuous proliferation of cancerous and immortalized cells. Until these finding occurred the focus of research on ageing was mostly descriptive, and the cause of ageing was thought to be driven by extracellular events. The Hayflick phenomenon of cellular ageing and replicative senescence redirected the focus on the cause of ageing toward intracellular events. Thus began the field of cytogerontology. The origin of age changes has more recently evolved to include fundamental events that occur at the molecular level and that involve the flow of energy. The Hayflick system has contributed to a change of paradigm from anti-ageing to health maintenance by underlying that ageing is not a disease; there are no ageing causing gerontogenes; and there is no enemy within our cells. Ageing occurs in spite of the presence of complex pathways of maintenance, repair and defence. Among various approaches towards ageing interventions, a promising strategy is that of mild stress-induced hormesis, which stimulates cellular defence systems. Novel hormetins based in the principles of hormesis are in development for cosmeceutical, nutriceutical and other applications for maintaining and strengthening health, and extending health-span.

Human ageing is associated with reduced natural killer cell cytotoxicity against and migration towards senescent cells

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Senescent cell accumulation is a well described phenomenon of physiological ageing that has been linked to the development of several age-related pathologies [1]. Recently, data has emerged demonstrating that senescent cells are subject to immunosurveillance, with a prominent role assigned to natural killer (NK) cells [2-3]. Here, we show NK cells from older adults exhibit reduced cytotoxicity and migration towards senescent cells, and propose that these defects contribute to the increased frequency of senescent cells in aged tissue. Compared to younger adults, interleukin-12 (IL-12) primed NK cells from older adults induced significantly less apoptosis of senescent fibroblasts during a 1-hour *in vitro* co-culture. Critical for NK-mediated elimination of senescent cells is the activating receptor NKG2D. Whilst no age-associated differences were found in NKG2D expression, downstream signaling defects were detected, with NK cells from older adults exhibiting impaired activation of extracellular signal-regulated kinase 1/2 following NKG2D ligation. Further evidence of age-related defects in NK cell signaling was shown by reduced up-regulation of the activation marker CD69 on NK cells from older adults following IL-12 stimulation. Alongside the impairment in NK cell killing, an age-associated reduction was detected in NK cell transmigration towards senescent fibroblasts in a 3D co-culture system. Flow cytometric analysis of NK cells revealed reduced surface expression of the chemokine receptors CCR1 and CCR5 with age, offering a potential mechanistic explanation for the impairment in migration. In summary, our data is the first to suggest that innate immunesenescence is a potential factor underlying the age-associated accumulation of senescent cells.

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The genomic footprint of ageing: epigenetics, replication and somatic mutations

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The accumulation of somatic mutations is an important driver of aging, and can lead to aging-related diseases such as cancer. Many processes influence the accumulation of mutations in the genome (Garinis et al., 2008). While some carcinogens, like tobacco smoke, are lifestyle-dependent, others are intrinsic to the cell. Most importantly, epigenetic modifications on cytosines are known to increase the frequency of mutations to thymine (C>T mutations) (Tomkova and Schuster-Böckler, 2018). Due to the strong correlation of these mutations with age, the frequency of C>T mutations at CpG dinucleotides (CpG>T) is in fact often referred to as the "aging signature" (Alexandrov et al., 2015).

It is generally assumed that the aging signature is the result of spontaneous deamination of methylated cytosine, producing thymine. This reaction occurs at a higher rate on methylated C than on other nucleotides. However, recent genomic data points at another potential pathway for the accumulation of C>T mutations at methylated cytosines.

We investigated the relationship between DNA replication and the accumulation of mutations in the somatic genome. We noticed that patients with defects in proofreading during DNA replication, or with deficiencies in mismatch-repair, exhibit a marked increase in the rate of C>T mutations at methylated cytosine. This is highly surprising, since neither of these error-suppression mechanisms are thought to be involved in the repair of spontaneous deamination. In the same patients, we also observed a bias for CpG>T mutations to occur on the continuously synthesized leading strand, relative to the discontinuously synthesized lagging strand. Together, these finding support a model where polymerase ε, the main leading-strand polymerase, incorporates adenine opposite methylated cytosine at a higher frequency (Tomkova et al., 2018). This phenomenon could help to explain the differences in somatic mutation burden between different tissue types in a single individual, and improve our understanding of genomic degradation with age.

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Mitochondria to nucleus retrograde signaling triggers formation of cytoplasmic chromatin fragments and activation of SASP in senescent cells.

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In response to diverse molecular stresses cells enter a proliferation arrested and pro-inflammatory state called senescence. Senescence is an important tumor suppression mechanism. However, chronic expression of the pro-inflammatory senescence-associated secretory phenotype (SASP) also promotes tissue aging. The mechanism underlying SASP has not been well defined. Inhibitors of SASP may have value to suppress the pro-aging phenotypes of senescent cells, without abrogating tumor suppression.

We previously showed that senescent cells expel fragments of chromatin from the nucleus to the cytoplasm, so-called cytoplasmic chromatin fragments (CCF) [1]. We further showed that CCF are generated by a mechanism that depends on a pre-existing lamin B1/LC3 interaction in the cell nucleus and CCF trigger activation of the cytoplasmic DNA sensing anti—viral cGAS/STING pathway to activate the SASP [2, 3]. Unpublished data will be presented demonstrating that initiation of CCF depends upon a mitochondria to nucleus retrograde signaling pathway.

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Autophagy and immune aging

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With extension of the average lifespan, ageing has become a heavy burden in society. Immune senescence is a key risk factor for many age-related diseases such as cancer, neurodegeneration and increased infections in the elderly, and hence, has elicited much attention in recent years. As our body's guardian, the immune system maintains systemic health through removal of pathogens and damage. Autophagy is an important cellular "clearance" process by which a cell internally delivers damaged organelles and macromolecules to lysosomes for degradation. Here, we discuss the most current knowledge of how impaired autophagy can lead to cellular and immune senescence. We will provide an overview, with examples, of the clinical potential of exploiting autophagy to delay immune senescence and/or rejuvenate immunity to treat various age-related diseases.

Genome-wide analysis identifies transcriptional down-regulation of Insulin-like Growth Factor 1 receptor signalling as a major hallmark of ageing in developing B lymphocytes

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Ageing is characterized by widespread loss of function of the adaptive immune system, leading to reduced vaccine response and impaired ability to fight infection in the elderly. The bone marrow progenitor B lymphocyte compartment, which generates the primary antibody repertoire, has reduced cell numbers in ageing, which contributes to reduced diversity of the antibody response, but the underlying causes remain poorly understood. To assess the molecular effects of ageing on B lymphocyte development, we have profiled gene expression and chromatin features, including histone modifications and chromatin conformation (HiC, promoter Capture HiC) genome-wide, in murine bone marrow pro-B and pre-B cells. Our analyses have revealed surprisingly narrow changes in B cell precursors in young versus old mice. We identified transcriptional down- regulation of several components of the insulin-like growth factor 1 receptor (IGF1R) signalling pathway, as a signature of the aged phenotype, suggesting a role for the IGF1 signalling pathway in B cell ageing. Remarkably, these expression changes involved alterations at several levels, including miRNA regulation and polycomb-mediated repression. We conclude that components of the insulin-like growth factor signalling pathway are key targets of epigenetic regulation of ageing in bone marrow B cell precursors and that dysregulation of this pathway may underpin loss of progenitor B cell numbers in ageing.

Role of mTOR and autophagy in cell senescence

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The mammalian target of rapamycin complex 1 (mTORC1) is the key signalling hub that regulates cellular protein homeostasis, growth, and proliferation. Activation of mTORC1 leads to the suppression of the catabolic process of autophagy where damaged cellular components are degraded via lysosomal proteolysis. mTORC1 is also intimately linked to cellular senescence and organismal aging. Inhibition of mTORC1 is the best-known intervention to extend lifespan, and recent evidence suggests that clearance of senescent cells can also improve health and lifespan. mTORC1 is important for the development of characteristic phenotypes of senescence, although the underlying mechanisms by which mTORC1 contributes to the acquisition of senescence are not well understood. Our data indicate that cellular senescence induced by stress, replicative exhaustion, or oncogene activation results in the perturbation of amino acid and growth factor sensing by mTORC1. In senescent human fibroblasts mTORC1 becomes constitutively active and resistant to serum and amino acid starvation. This is driven by depolarization of senescent cell plasma membrane and a resultant failure to inhibit growth factor signalling. Furthermore, increased autophagy promoting high levels of intracellular amino acids may also contribute to the persistent mTORC1 activity in starvation conditions. Interventions that correct these phenotypes restore sensitivity of mTORC1 to growth promoting signals in senescent cells and cause their death, indicating that persistent signalling supports senescent cell survival. These findings suggest how mTORC1 signalling contributes to cellular and organismal senescence and may inform interventions aiming to delay ageing.

Age-dependent effects of reduced mTor signalling on life expectancy through distinct physiology

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Reduced mTor (mechanistic target of rapamycin) signalling increases lifespan in model organisms. We have recently demonstrated, using meta-analysis of the resultant demography of mortality, that in mice, flies and yeast mTor signalling modulates the total level of mortality, whereas in worms the rate at which mortality increases with age is affected. This suggests that mTor signalling could potentially modulate mortality instantly and transiently. Such transient control of mortality could mean that reducing mTor signalling late in life results in marked improvements in lifespan and is therefore of high relevance for translational purposes. Moreover, recent experiments in mice have suggested that short- term reduction of mTor signalling in early life extends lifespan. We have now tested these hypotheses using large sample size (N > 2,000 per comparison) demography in fruit flies. We used inducible knockdown (GeneSwitch x RNAi) of mTor for their whole lives, early-life only and late-life only. We find that indeed reduced mTor can reduce mortality risk at old age. Surprisingly, but in line with recent suggestive results in mice, we also find life- extending effects of short-term mTor suppression. These experiments were fully controlled by positive (conditional overepression of hid and rpr, causing death through apoptosis) and negative controls (non-active RNAi). Together these results show evidence for age-dependent effects of mTor signalling that mediate life expectancy possibly through distinct physiological actions of the mTor network. Age-dependent RNAseq experiments demonstrate distinct physiology is responsible for both early and late life effects of mTor suppression.

Longevity by RNA polymerase III inhibition downstream of TORC1

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Three distinct RNA polymerases (Pols) transcribe different classes of genes in the eukaryotic nucleus. Pol III is the essential, evolutionarily conserved enzyme that generates short, non-coding RNAs, including transfer RNAs (tRNAs) and *5S* ribosomal RNA (rRNA). Historical focus on transcription of protein-coding genes has left the roles of Pol III in organismal physiology relatively unexplored. The prominent regulator of Pol III activity, Target of Rapamycin kinase Complex 1 (TORC1), is an important longevity determinant, raising the question of Pol III's involvement in ageing. Here we show that Pol III limits lifespan downstream of TORC1. We find that a reduction in Pol III extends chronological lifespan in yeast and organismal lifespan in worms and flies. Inhibiting Pol III activity in the adult worm or fly gut is sufficient to extend lifespan, and in flies, longevity can be achieved by Pol III inhibition specifically in the intestinal stem cells (ISCs). The longevity phenotype is associated with amelioration of age-related gut pathology and functional decline, dampened protein synthesis and increased tolerance of proteostatic stress. Importantly, Pol III acts downstream of TORC1 for lifespan and limiting Pol III activity in the adult gut achieves the full longevity benefit of systemic TORC1 inhibition. Hence, Pol III is a pivotal output of this key nutrient signalling network for longevity; Pol III's growth-promoting, anabolic activity mediates the acceleration of ageing by TORC1. The evolutionary conservation of Pol III affirms its potential as a therapeutic target.

Innate immunity and ageing in Drosophila

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During aging, innate immunity progresses to a chronically active state. However, what distinguishes those that "age well" from those developing age-related neurological conditions is unclear. We used *Drosophila* to explore the cost of immunity in the aging brain. We show that mutations in intracellular negative regulators of the IMD/NF-κB pathway predisposed flies to toxic levels of antimicrobial peptides, resulting in early locomotor defects, extensive neurodegeneration, and reduced lifespan. These phenotypes were rescued when immunity was suppressed in glia. In healthy flies, suppressing immunity in glial cells resulted in increased adipokinetic hormonal signaling with high nutrient levels in later life and an extension of active lifespan. Thus, when levels of IMD/NF-κB deviate from normal, two mechanisms are at play: lower levels de-repress an immune-endocrine axis, which mobilizes nutrients, leading to lifespan extension, whereas higher levels increase antimicrobial peptides, causing neurodegeneration. Immunity in the fly brain is therefore a key lifespan determinant.

Induced pluripotent stem cells: a versatile platform for the study and treatment of age-related diseases

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The progressive loss of function and depletion of endogenous stem cell populations that accompanies the ageing process underlies many of the chronic and degenerative diseases of old age. However, studies of the genetic and molecular basis of such disease states has traditionally lacked suitable in vitro models and is in critical need of new treatment paradigms. The advent ten years ago of induced pluripotent stem cells (iPSC) offers the prospect of exploiting pluripotency on an individual basis to recreate disease symptoms in vitro to facilitate drug discovery and toxicology, while providing a ready source of replacement cell types for transplantation purposes [1]. Here we review these developments and discuss their likely future impact on clinical medicine. Furthermore, we shall discuss our own research into the use of iPSC as a novel source of rare populations of leukocytes for use in immunotherapy [2]. In particular, we describe the directed differentiation of $CD141^{+}XCR1^{+}$ dendritic cells from patient-specific iPSC not normally accessible from patients and their application both to cancer vaccination [3] and the induction of immunological tolerance [4], thereby providing a broad platform for immune intervention.

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Tissue engineering approaches to modelling Alzheimer's disease

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Alzheimer's Disease (AD) affects more than 35 million people worldwide. Neurons derived from induced pluripotent stem cell (iPSC) may enable Alzheimer's to be modelled in vitro. We have recently shown that membranes containing microscopic holes allow these brain cells to contact each other across the membrane, but do not allow the whole cell to pass through. This will allow us to grow diseased tissue in close proximity to healthy tissue in order to monitor the spread of disease. We have also shown that neurons derived from iPSC demonstrate electrical activity thus demonstrating the potential of the assay to track degradation in communication between cells. This model can be used to model disease progression, increasing our understanding of AD and facilitating the development and screening of new drugs and treatments.

Werner syndrome models implicate DNA damage signalling in premature ageing and identify WRN as a *bona fide* anti-gerontogene

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Progeroid syndromes have yielded informative insights into the mechanisms of human ageing. The causative gene in premature ageing human Werner syndrome (WS) is the dual function WRN helicase/exonuclease that has been implicated in many aspects of DNA metabolism. We have previously shown that DNA replication fork progression is defective in WS patient-derived cells and that this is likely to arise from Holliday junctions that form when replication forks stall or collapse in the absence of functional WRN, since ectopic expression of an HJ nuclease can correct the defect. We have developed fly and worm models of WS lacking the exonuclease and helicase activities of human WRN, respectively. Both organisms show marked DNA damage and anaphase bridges during mitosis, leading to high levels of illegitimate genomic recombination, premature ageing and shortened lifespan. Notably, preventing the signalling of such damage in worms (by loss of function mutation of p53) dramatically and highly significantly extends their lifespan and improves health in later life. Hence it is not the accumulation of DNA damage *per se* but the response to such damage that adversely impacts worm longevity.

However, the evidence that progeroid syndrome genes normally serve a role in preventing ageing is still at best only correlative. To test whether WRN can indeed improve ageing outcomes, we have generated transgenic *C. elegans* worms which overexpress the worm orthologue of WRN, *wrn-1*. We find that *wrn-1* overexpression not only corrects lifespan defects in *wrn-1*- mutant worms, but that overexpression in a wild type background extends lifespan significantly over than of control wild type animals. Moreover, *wrn-1* overexpression results in improved morphology, tissue integrity and movement throughout the life course - the first demonstration that a progeroid-associated gene product is effective in delaying ageing pathologies. Hence we conclude that *wrn-1* protects against ageing phenotypes and moreover that normal levels may be limiting for lifespan and health, with significant implications for human ageing.

NAD^+ repletion inhibits accelerated aging in Werner syndrome through the restoration of mitophagy

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Metabolic dysfunction is one of the most common symptoms and promotes accelerated aging in the disease Werner syndrome (WS). WS is genetically linked to mutation of the gene *WRN*, which encodes the RecQ DNA helicase; however, the relationship between *WRN* mutation and its severe metabolic phenotypes is unclear(*1*). Here we report mitochondrial dysfunction and depletion of NAD^+, a fundamental ubiquitous cofactor(*2, 3*), in WS patient samples and WS animal models. NAD^+ repletion restores NAD^+ metabolic profiles and improves mitochondrial quality through DCT-1 and ULK-1-dependent mitophagy. At the organismal level, NAD^+ repletion remarkably delays accelerated aging, including stem cell exhaustion in both *C. elegans* and *Drosophila* models of WS. Mechanistically, WRN physically binds to a key NAD^+ biosynthetic enzyme nicotinamide nucleotide adenylyltransferase 1 (NMNAT1) and facilitates NAD^+ production. Our findings reveal a novel anti-aging mechanism of WRN that integrates its new function of NAD^+ synthesis to coordinate mitochondrial maintenance and energy expenditure, and suggest therapeutic potential.

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Facilitating drug discovery by quantifying early declines in movement in large populations of adult worms

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Animals, including humans, slow down as they age. However, accurate measurement of the long-term decline in movement requires frequent monitoring because animals do not move constantly, and large populations because rates of ageing vary considerably between individuals. While *C. elegans* have a lifespan of 2 or 3 weeks, their movement declines substantially in the first few days of adult life. We have developed a robust automated method to measure this change. A series of inexpensive cameras are each focused on a conventional 6cm petri dish of worms and connected to a Raspberry Pi single board computer. This computer controls the camera to take a series of images taken every 0.8 seconds, and then processes the images to allow movement to be detected. The pre-processed data is sent to a central computer for further analysis. Using this technique, we can reliably measure movement decline in large populations in a way that it is very sensitive to the addition of compounds that either accelerate or slow ageing. We can also screen a large range of concentrations, making this methodology useful to screen lead compounds in drug discovery.

Defining an index for cellular senescence

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Senescent cells provide a good model to study ageing. However, cultures of "senescent" cells are a mix of cell populations (proliferative, senescent and growth-arrested). Determining the proportion of genuinely senescent cells is crucial. The ability to compare the efficacy of anti-senescent therapies relies on accurate measures of senescence. Commonly used markers (population-doubling, SA-βgal, Ki67, γ-H2AX and TUNEL) are diverse, and none is purely specific for measuring senescence. Therefore, our aim is to merge these markers to build a reliable senescence index, which may be used to compare the level of senescence in cell cultures.

We used primary human dermal fibroblasts (nHDF) as a cell model. Cells were "aged" *in vitro* from PD22 to PD71. A newly developed dynamical systems model (DSM) captures the transition to replicative senescence. It keeps tracks of population-doubling and the proportion of cells that are in proliferating, quiescent, apoptotic or senescent states. The accrual of DNA damage following successive division is represented. Independent of division, cells can move directly to the senescent, quiescent or apoptotic populations with population-doubling dependent rates. Based on assumptions relating the cell states to experimental markers, the DSM produces a good fit to data with a minimal set of parameters.

In combination with data on the 5 markers discussed, the DSM will be used to 1) refine assumptions relating cells states to markers, 2) assess whether any given marker is redundant, and 3) establish independent marker combinations that provide a reliable index for senescence across cell cultures.

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Discovery of a predictive biomarker for death in older adults diagnosed with frailty

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Introduction: Frailty is a major cause of poor survival in elderly individuals. Biomarkers related to excess mortality in this condition have not been extensively investigated despite the fact that these could be of clinical value. The receptor for advanced glycation-end products (RAGE) and it soluble forms (sRAGE) have been implicated in the pathogenesis of chronic metabolic and inflammatory disorders. As chronic inflammatory mechanisms could potentially affect the evolution of frailty, we investigated the relationship between sRAGE and mortality in a prospective study of elderly subjects living in the community.

Methods and Results: Participants from two European cohorts (ETES and AMI) enrolled in 2013 to the FRAILOMIC study (n=691, mean age 75.2±6.0), for whom blood and full baseline sociodemographic and clinical data were available, had their serum sRAGE levels measured. Based on Fried's criteria 141 participants were classified as frail and 550 as non-frail. Frail individuals who died within a 4-year follow-up had significantly higher sRAGE levels at baseline compared to those that survived (1959 [1195-2674] pg/mL vs 1213 [871-1683] pg/mL, P<0.001). In contrast, no difference in sRAGE levels was observed between non-survivors and survivors of the non-frail group (1245 [998-1705] pg/mL vs 1186 [921-1550] pg/mL, P = 0.337). Cox multivariate proportional hazards regression analysis with adjustment for potential confounders demonstrated that in frail individuals sRAGE was an independent predictor of death (HR=3.07 per unit ln sRAGE increment, 95%CI 1.32-7.14, P = 0.009). Furthermore, comparisons by different cut-off levels of sRAGE showed that frail participants in the highest quartile of sRAGE (>1887 pg/mL) were on average over 6-times more likely to die than those in the lowest quartile (HR=6.25, 95%CI 1.32-29.55, P = 0.021). Additionally, Kaplan Meyer survival analysis demonstrated that the incidence of death was significantly higher in the highest sRAGE quartile than in the three lower quartiles (P=0.002). In contrast, sRAGE showed no association with future death in non-frail individuals. Integrated area under the curve analysis demonstrated that inclusion of sRAGE in the hazard model increased its predictive accuracy.

Conclusions: These results demonstrate that elevated serum sRAGE is an independent predictor of early death in frail elderly individuals. Determination of sRAGE could be useful for stratification of frail subjects to guide the selection of suitable therapeutic treatments.

Attenuation of age-related renal lesions in a model of RAGE (receptor for advanced glycation end products) knockout

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Pro-ageing effects of endogenous advanced glycation end-products (AGEs) have been reported, in particular through binding with RAGE (the main receptor for AGEs) that engenders pro-inflammatory and pro-fibrosis effects. The role of dietary AGEs (dAGEs) remains uncertain; however, the predominantly renal accumulation of the dAGE carboxymethyllysine (CML) (Tessier et al., 2016) suggests kidneys may be particularly affected. We here report effects of RAGE deletion and dCML on renal ageing.

Two-month-old wild-type (WT) and RAGE$^{-/-}$ C57Bl/6 mice were fed a control or a CML-enriched diet (200µg CML/g_{food}) for 18 months. Compared to controls, we observed higher CML levels in the kidneys of both CML WT and CML RAGE$^{-/-}$ mice, with a predominantly tubular localization. The CML-rich diet had no significant impact on the studied renal parameters – only a trend to worsening glomerular sclerosis was detected. Irrespective of diet, the RAGE$^{-/-}$ mice were significantly protected against nephrosclerosis lesions (hyalinosis, tubular atrophy, fibrosis and glomerular sclerosis) and renal senile apolipoprotein A-II (ApoA-II) amyloidosis ($p < 0.001$). A positive linear correlation between sclerosis and ApoA-II amyloidosis (r=0.92) was observed. The attenuation of these lesions was associated with decreases in inflammation markers and AKT activation, as well as increased *Sod2* and SIRT1 expression in the old RAGE$^{-/-}$ mice.

Overall, nephrosclerosis lesions and senile amyloidosis were significantly reduced in RAGE$^{-/-}$ mice, indicating a protective effect of RAGE deletion with respect to renal ageing. This could be due to lower levels of inflammation and oxidative stress in RAGE$^{-/-}$ mice, suggesting a significant role of RAGE in so-called inflamm-ageing.

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HNRNPM, *HNRNPA0* and *AKAP17A* splicing factor transcript levels demonstrate predictive associations with human ageing phenotypes in peripheral blood

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Correct regulation of mRNA processing is critical for successful ageing, as it confers genomic plasticity. Splicing decisions are made by the binding of splicing factors; levels of transcripts encoding these factors has previously been implicated in ageing and senescence both *in vitro* and *in vivo*.

We measured the mRNA transcript levels of an *a priori* panel of 20 splicing factors previously associated with senescence in cell models or with age population studies. Cross-sectional and predictive relationships were then assessed in relation to cognitive decline (Mini Mental State Examination; MMSE), frailty (hand-grip strength) and combined parental longevity score (PLS) at two time points.

We identified both cross-sectional and predictive associations between *HNRNPA0*, *HNRNPM* and *AKAP17A* transcript levels and multiple ageing phenotypes. *AKAP17A* expression was predictively associated with severe cognitive decline as measured by MMSE score (β-coefficient -0.153; p = 0.007), and nominally associated with a decline in mean hand-grip strength, a measure of frailty (β-coefficient -0.006; p = 0.023). *HNRNPA0* and *HNRNPM* transcript levels were predictively associated with severe decline in MMSE (β-coefficients -0.083 and -0.082; p = 0.001 and 0.008 respectively).

These data suggest that changes in *HNRNPM*, *AKAP17A* and *HNRNPA0* levels may lie upstream of phenotypic changes characteristic of cognitive decline and frailty. Our observation that transcript levels are associated with ageing phenotypes in human peripheral blood raises the possibility that they may have utility as potential biomarkers of cognitive decline or frailty in the ageing population.

Applications of deep neural networks to human ageing biomarker development

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The rates of ageing may vary substantially among different individuals and population groups, and they are significantly influenced by environmental and hereditary factors. Multiple attempts have been made to develop biologically-relevant biomarkers of human ageing. However, the biomarkers proposed so far usually focus on monitoring a restricted number of processes known for being directly correlated with the chronological age such as the telomere length-based or DNA methylation. There is a need for biologically-relevant quantifiable, interpretable and therapeutically-targetable multi-modal biomarkers of ageing. The common blood test is one of the simplest tests used by physicians to evaluate the health state of patients. The biomarkers from blood biochemistry and blood cell counts can potentially be sensitive indicators of chronological ageing-related changes. In 2015 Zhavoronkov et al. proposed using deep learning predictors of chronological age trained on both the static and dynamic data types for multi-modal data integration, analysis and target identification (Zhavoronkov, 2015). In 2016 we published the first demonstrated the capabilities of the deep neural network (DNN)-based methods to accurately predict the biological age and identify a set of the most relevant biomarkers for tracking physiological processes related to ageing using the common clinical blood tests (Putin, 2017). This work was extended by Mamoshina et al into a multi-population haematological ageing clock trained on the large combined dataset of Canadian, South Korean, and Eastern European populations (Mamoshina, 2018).

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Circadian rhythms in immune parameters and functioning in older adults: impact on vaccine responses and inflammatory diseases

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Immune cell components present daily variations, which are essential in maintaining body homeostasis and defence. However, whether immune cells' circadian oscillations are affected with age still remains unexplored. In this study, we recruited healthy young (n = 20) and old volunteers (n = 18) aged > 60 and bled them at two time points; morning, (8:00-8:30) and afternoon, (15:00-15:30) to assess circadian variations in innate and adaptive immune parameters. Firstly, we observed a significantly higher circulating neutrophil count (p =.04) and neutrophil phagocytosis (p =.03) at the afternoon time point in healthy old. Monocytes displayed an elevated phagocytosis (p = .03) and TNFα production post LPS stimulation (p =.03) in the afternoon. The circulating frequency of natural killer cells was elevated in the morning but only in young (p = .04) and not in old donors (p = .22). Next, on assessing circadian variations in adaptive immune parameters, we observed an elevated frequency of naïve CD4 T cells (p = .04) and a higher Th1 response in the morning (p = .002) in old donors. These might be factors contributing towards the improved responsiveness to the influenza vaccine when administered in the morning, compared to the afternoon that we have previously reported. Interestingly, we also observed an elevated Th17 response (p = .04) and elevated circulating levels of IL6 (p =.001) in the morning, which might be contributing towards the elevated joint pain and stiffness reported in rheumatoid arthritis patients on awakening in the morning.

Circadian rhythms in the ageing musculoskeletal system: implications in therapies for osteoarthritis and low back pain

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Osteoarthritis (OA) is the most prevalent joint disease, causing severe pain, deformity and a loss of mobility. Low back pain (LBP), frequently associated with degeneration of the intervertebral disc (IVD), is the No.1 cause of Years Lived with Disability, with over 80% of the population predicted to experience back pain within their lifetime. Age is a major risk factor for both skeletal conditions. However, the reasons why susceptibility to these conditions increases with age are still not fully understood. Consequently, current treatments are limited focusing solely on symptomatic pain relief rather than correcting the underlying pathogenesis and aberrant cell biology. The circadian (24 hourly) clocks in the brain and periphery direct key aspects of physiology through rhythmic control of tissue-specific sets of downstream genes. Symptoms of both conditions are known to show time-of-day effect, suggesting a possible involvement of the clock mechanisms. Work from our group focuses on the roles of circadian clocks in the articular cartilage and IVD. We have shown that the daily rhythms in these tissues become dampened and out-of-phase during ageing. Further, our data identify circadian clock disruption in cartilage and IVD as a new target of inflammation. Moreover, we show that mice with targeted knockout of an essential clock gene (BMAL1) in chondrocytes and disc cells have profound, yet tissue-specific degeneration in the articular cartilage and IVD. These findings implicate the skeletal circadian clock as a key regulatory mechanism for tissue homeostasis. This new avenue of research holds potential to better understand, and eventually treat these debilitating conditions. In this seminar, I will summarize our key findings on skeletal clocks and their potential implications in health and disease of the joint/spine.

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Sarcopenia – making the science work for patients

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Sarcopenia – the age-related loss of skeletal muscle mass and strength – is a major public health issue. Sarcopenia is associated with an increased risk of falls, disability, dependency, institutionalization, hospital stay and early death. Finding interventions to stabilize, reverse or prevent sarcopenia is therefore a key goal for clinical ageing research.

If patients are to eventually benefit from discovery science on ageing skeletal muscle, we need to build a translational pipeline that facilitates progress from laboratory science and epidemiology, through feasibility testing to early-phase, and eventually late-phase clinical trials. A number of barriers need to be overcome to make this pipeline work – in particular challenges around identifying people with sarcopenia in routine clinical practice, developing capacity to run trials for older people, and selecting trial outcomes of relevance to older people. A further key point is that interventions should ideally have pleiotropic actions – i.e. beneficial actions across multiple organ systems, rather than treating sarcopenia alone. Such pleiotropic interventions may be the only way to avoid the perils of polypharmacy and drug interactions that bedevil care for many older people.

To date, evidence for interventions to improve sarcopenia in clinical practice is scanty, with the exception of resistance training. Progress is now being made however; the Leucine and ACE inhibitor for sarcopenia trial (LACE) provides one example of how sarcopenia trials are evolving. Evidence from trials, particularly those with embedded mechanism and biomarker studies, will also help to develop our understanding of sarcopenia, thus further accelerating the development and targeting of interventions.

Open science, partnership with industry and close collaboration between UK universities and the NHS to accelerate treatments for multiple morbidities associated with ageing

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The discovery of new medicines is too risky, too slow and too costly. There is massive duplication and wastage in biomedical research, there are questions being asked about the reproducibility of published work, and for many increasingly important therapeutic areas we are simply not producing what society and patients want.

The validation of pioneer targets for drug discovery, remains a major challenge. We have therefore:

- worked with a large number of pharmaceutical companies, to develop high quality small molecule inhibitors, using structure based drug design
- focussed only on novel targets, or those deemed to be 'difficult' or intractable
- and given these inhibitors to a large and growing international network of academic collaborators, to crowd source new biology, disease understanding and 'target discovery'.

These endeavours have facilitated proprietary efforts in pharma, catalysed the creation of new biotechs, and accelerated numerous clinical studies.

More recently we have been

- generating 'Target Enabling Packages' (comprising purified proteins, biophysical or biochemical assays to assess function, three dimensional X ray structures and chemical starting points) for novel, high priority, disease linked genes
- building platforms of primary human cells, for screening novel inhibitors, in order to identify new 'better' targets for drug discovery
- building major collaborations with patient groups and hospitals, in order to catalyse these studies and enhance dissemination into the best disease labs across the world

We are now building a national effort to accelerate new treatments for multiple morbidities associated with ageing. To catalyse this project we have partnered with Universities of Dundee and Birmingham, the Medicines Discovery Catapult and the Crick Institute. We aim to work with any academic, clinician or industrial scientist in the UK, to identify new drug targets, generate industry standard clinical molecules, and then evaluate these in stratified patient cohorts using novel, longitudinal biomarker platforms. Critical to the success of this project is close working with the pharmaceutical industry. We have started to engage several such organisations.

Together, we aim to create a new ecosystem for drug discovery. One which we believe will accelerate the generation of more novel medicines, more quickly. We hope such medicines will also more affordable.

Poster abstracts

P01: Exploring a gut-brain axis in constitutively active immunity

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The secretion of antimicrobial peptides (AMPs) is the final step of the *Drosophila* inflammatory response. This is achieved via two NF-kB regulated signalling pathways: The Toll and the IMD pathway. A number of studies have illustrated the importance of a tightly regulated immune system in Drosophila [1]. This strict regulation in the gut helps the fly maintain a healthy gut microbiome and a normal lifespan. We have shown previously that during healthy aging, an age-dependent decrease of intracellular negative regulators results in an increase of NF-κB controlled AMPs [2]. Moreover, absence of intracellular NF-kB negative regulators has been linked to immune-dependent neurodegeneration and a reduced lifespan. However, our study revealed that this increase in AMPs was largely rescued in germ-free conditions [2]. This led to the hypothesis that age-dependent increase in AMPs may be microbiome dependent. Since sleep patterns are known to be disrupted in individuals with neurodegenerative disorders [3], we used sleep profiling as a method to estimate the extent of neurological effects in flies mutant for *pirk* a negative regulator of NF-kB. We observed a significant increase in sleep in 6 day old and 28-day old *pirk* mutant flies. Our results establish the presence of an association between a constitutive immune response and sleep and a need to explore these parameters in germ-free (GF) conditions.

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P02: Lack of gene movement in old human cells, and a molluscan model organism.

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Whole chromosomes, and the genes housed upon them, are non-randomly positioned within the interphase nuclei of many different organisms, including the molluscan model organism – *Biomphalaria glabrata*. We and others have shown that this strict organisation is altered in old human cells. We now have evidence that this change in genome organisation is also occurring in old whole *B. glabrata* snails. Furthermore, specific movement of genes can be stimulated in young human cells by nutrition deprivation or heat shock and in young *B. glabrata* snails by heat-shock or infection, through nuclear motor activity. However, in senescent human cells and old snails this directed and specific gene relocation is not apparent with any of the stimuli we have tested.

P03: Leucine and β-Hydroxy β-methylbutyrate enhance replicatively aged C2C12 myoblast migration but not fusion

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Introduction: With ageing the ability to retain skeletal muscle mass and function declines (sarcopenia), with associated "anabolic resistance" being reported. Since, the migration and fusion of resident myoblasts are critical to these processes, we hypothesised that these would be compromised with age. Our ultimate aim is to implement models of ageing muscle degeneration and regeneration to enable interventions targeting sarcopenia by enhancing repair and maintaining muscle mass. Methods: Confluent control and replicatively aged [1] myoblasts were damaged in the absence or presence of 10mM leucine or HMB. Migration velocity, directionality and distance were assessed (0-48h). Myotube formation was assessed morphologically and biochemically (creatine kinase (CK), lactate dehydrogenase (LDH)) and gene expression all at 0, 24 and 96h.
Results: Surprisingly, aged myoblasts migrated more efficiently versus control, with significant (all $P<0.001$) increases in velocity, directionality and distance and near significance in increased expression of ADAMS10 ($P=0.056$). Supplementation significantly impacted on aged cell velocity ($P<0.001$) and in the presence of HMB only, distance ($P=0.041$). Although control cells showed significant fusion with time ($P<0.001$), aged myoblasts did not fuse in the absence or presence of supplementation and displayed significant reductions in CK ($P<0.001$) and myogenin expression ($P<0.001$) and significant increases in LDH ($P<0.001$) and myostatin expression ($P=0.06$), vs control. LDH levels were significantly attenuated with leucine at 48h ($P=0.002$) and 96h ($P=0.007$).
Conclusion: These novel data suggest that improved migration (potentially linked to increased ADAMS10 expression), but not fusion (linked to reduced myogenin and elevated myostatin expression) occur in aged vs. control myoblasts with "anabolic resistance" being constrained to hypertrophy only.

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P04: Reproductive processes cause intestinal senescence – a central age-related pathology in *C. elegans*

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Although many genes have been shown to influence lifespan in *C. elegans*, the chain of events between altered gene function and effects on lifespan remains unclear. Given that aging leads to death by causing disease, it is likely that gene action on *C. elegans* lifespan is attributable to effects on senescent pathology. To explore this, we have conducted a screen of interventions affecting lifespan, comparing their effects on senescent pathology. Simultaneous analysis of the rate of development of five major pathologies in wild-type hermaphrodites defines a coordinated burst of pathogenesis in early-mid life. By contrast, this early burst of senescent pathogenesis was not seen in males. Testing a range of interventions that affect lifespan revealed some treatment-specificity in terms of which senescent pathologies are altered. However, all treatments that extended lifespan suppressed intestinal pathology, and vice versa. These results imply that treatments that alter hermaphrodite lifespan do so particularly through effects on intestinal senescence. The early, rapid onset and severity of senescent pathology in hermaphrodites is not typical of animal senescence, but resembles that of semelparous species that exhibit reproductive death (e.g. Pacific salmon, male marsupial mice), suppression of which can cause large increases in lifespan. Our work suggests that in *C. elegans* hermaphrodites reproductive processes result in pathology, ageing and death and shows that identifying the underlying causes of age-related pathologies holds the key to understanding the biology of ageing.

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P05: Do redox-regulated microRNAs play a role in age-related muscle wasting?

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There is currently a disproportionate increase in age-related health issues, with one of the major problems being the age-related loss of muscle mass and function - sarcopenia. Redox and epigenetic factors are key regulatory pathways associated with ageing. MicroRNAs, stable RNAs with half-life >24h, regulate muscle homeostasis post-transcriptionally. Oxidative modification of microRNAs could result in the regulation of non-native targets. Redox balance is disrupted during ageing and the accumulation of oxidised, most likely pathogenic, microRNAs in muscle leads to their disrupted specificity for regulating protein content.

We have validated microRNAs/mRNAs/proteins networks affected by ageing in muscle and have shown that modifying microRNA expression improves muscle function, but there is currently no research into the function of oxidized microRNAs in ageing.

Integrating epigenetic/redox experimental approaches with functional studies, we have studied key oxidized microRNAs and targets in human and mouse muscle and have shown that inhibiting one of the oxidized microRNAs in old mice positively affects myofibre size and muscle strength. We have shown that improvement of muscle force following inhibition of oxi-microRNA is associated with changes in mitochondrial dynamics and has no overall off-target effects. This provides proof-of-principle for the use of specific oxi-microRNA inhibitors for improvement of muscle function during ageing.

P06: Does aberrant exosomal signaling by skeletal muscle promote neuromuscular ageing?

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Muscle mass and function are reduced with age in mammals and this is associated with disrupted neuromuscular interactions. Muscle mounts a robust response to contractions by the increased expression of Heat Shock Proteins (HSPs), which facilitate muscle remodeling, promote protein folding and clearance of damaged proteins. In contrast, other tissues, including neurons are unable to mount a stress response and it is proposed that cells, including muscle, may transfer HSPs to these other cell types by secretion in exosomes to maintain proteostasis in the recipient cells. HSP generation in muscle following contractions is attenuated in old mice and humans. We hypothesise that the inability of muscles of old mice to produce HSPs in response to contractions results in a failure of proteostasis maintenance in neighbouring motor neurons, resulting in neuronal and muscle degeneration[1].

Muscle fibres from adult (6 month) mice were isolated and initiated to contract using a non-damaging electrical stimulation protocol. Media was collected for up to 24hrs, exosomes were purified from the media using differential centrifugation, and HSP content analysed.

Data demonstrated that the exosomes released by muscle of adult mice contained HSPs. Further studies will use a lipophilic carbocyanine to label the exosomes. Uptake of these exosomes by neuronal cells will be monitored using fluorescent imaging. Additional studies will also examine the effect of age on exosome production.

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P07: Modulating SIRT1 activity through inhibition of other NAD+ dependent enzymes

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The histone deacetylase SIRT1 and its yeast homologue Sir2 have been well established as regulators of longevity in various model organisms(Cantó and Auwerx, 2009). The naturally occurring compound resveratrol has thus far been the conventional SIRT1 activator used in most studies to date, however its efficacy in vivo has been hindered by its low bioavailability (Berman et al., 2017).

As such, identifying other ways to enhance SIRT1 activity is key, one approach being to increase the availability of SIRT1's essential cofactor NAD+.

NAD+ is a coenzyme which is necessary for a wide array of cellular activities – some perhaps more important than others. Hence, in addition to increasing NAD+ levels through treatment with NAD+ precursors, we have targeted NAD+ consuming enzymes such as PARP1 and CD38 for inhibition to increase the NAD+ pool available to SIRT1.

So far this approach has been applied to skin fibroblasts in vitro, with tissue from PARP1$^{-/-}$ mice also used to assess the feasibility of increasing SIRT1 activity via PARP1 knockout. The results so far have been mixed, suggesting inhibition of individual NAD+ consuming enzymes offers limited enhancement of SIRT1 activity and thus a more nuanced approach is required which is currently being worked on.

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P08: The sex-based differences in the age-related changes in isolated locomotory (soleus & EDL) and respiratory (diaphragm) skeletal muscle contractile function using the work loop technique

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Little is currently known about the sex-based and muscle-specific occurrence of sarcopenia and dynapenia in relation to the contractile performance of isolated skeletal muscles. The present study furthers the work conducted by Tallis et al. [2] by implementing the work loop technique to closely replicate in vivo contractile function [1] to examine the age-related changes in skeletal muscle contractile performance of whole isolated mouse soleus, extensor digitorum longus (EDL) and diaphragm for males and females at various timepoints. Measurements of maximal absolute force, isometric stress (force/cross-sectional area), absolute power and power normalised to muscle mass are compared in 3-, 10-, 30- (male only), 52-, and 78-week-old male and female CD-1 mice. Soleus and EDL muscle mass, absolute force and power was lowest at 3 weeks and was greatest at 52 weeks and was maintained until 78 weeks, with muscle mass and absolute power greater for males than females. Isometric stress and normalised power declined progressively from 10 weeks for all skeletal muscles, with the magnitude of decline greater in males than females for power, but not stress. Between 10 and 52 weeks, the loss of isometric stress exceed that of normalised power, though this relationship was inversed between 52 and 78 weeks. These results indicate that dynapenia, but not sarcopenia, accounts for age-related declines in normalised performance that can be attributed to a poorer muscle quality, particularly for males. Reduced muscle quality is likely to be due to a greater non-contractile mass, fiber atrophy and poorer cross-bridge kinetics.

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P09: 8-oxoG:OGG1 repair pathway alters inflammatory signature in C2C12 myoblasts in vitro

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An imbalance of intracellular redox state occurs during ageing and leads to increased presence of oxidised DNA. The most abundant DNA base lesion seen is 8-oxo-7, 8-dihydroguanine (8-oxoG). In mammals, 8-oxoG is repaired by the 8-oxoguanine DNA glycosylase-1 (OGG1)-initiated DNA base excision repair pathway. In ageing tissue, the 8-oxoG:OGG1 repair pathway is associated with chronic activation of NF-kB. This study examined the role of ROS, 8-oxoG and OGG1 in the activation of NF-kB and release of NF-kB induced pro-inflammatory chemokines/cytokines in C2C12 myoblasts.

The model of oxidative damage was established by treating myoblasts with H_2O_2 (10 µM -100µM). The effects of H_2O_2 on 8-oxoG and oxidative DNA damage repair responses (OGG1 poly(ADP-ribose) polymerase-1 (PARP-1), cleaved-PARP-1, NF-kappa-B activation and inflammatory cytokine production were determined.

OGG1 levels were increased at 24 hours following treatment with low concentrations of H_2O_2 (10 µM -50µM). PARP-1 was expressed 24 hours after H_2O_2 treatment (10 µM) and cleaved at 48 hours. Hence, earlier stage evaluation into effects of acute oxidative stress on 8-oxoG:OGG1 related protein expression is imperative. At higher concentrations of H_2O_2 (50 µM -100µM) levels of PARP-1 were increased by 48 hours with cleaved PARP-1 evident at 72hours following treatment.

Further studies will examine NF-kB activation in this model. A computational model of DNA damage and repair has been designed to discover druggable target(s) to intervene in 8-oxoG:OGG1 pathway related NF-kB-driven production of cytokines.

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P10: A novel 3D muscle construct for assessing muscle contraction: application to studying ageing.

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Skeletal muscle ageing is characterised by the loss of individual muscle fibres and a weakening of remaining fibres. The mechanisms by which this occurs are unclear although transplant studies suggest that this is, at least in part, driven by changes in the local environment which lead to a resistance to adapt to contractions[1].
The aim of this study was to establish a reproducible 3D muscle construct to examine the effect of altered environments on muscle cell function, including the effect of a reduced gravity (e.g. using rotating-wall vessel bioreactors).
Muscle cells were seeded in a collagen matrix and plated into a 3D printed scaffold. Myoblasts were induced to differentiate at which time they spontaneously attached to anchor points and formed a cylindrical structure. After 10 days in culture, the 3D constructs comprised of aligned myotubes and expressed early markers of muscle differentiation including *Myogenin* and *Myf5*. The 3D constructs were electrically stimulated to contract via platinum electrodes and contractions monitored. Constructs contracted in a similar manner to isolated muscles and post-contraction analysis highlighted activation of the adaptive responses, such as increases in *Hsp70*. This preparation provides a rapid and simple test system to determine the effect of changes in environment on muscle function and adaptive responses *in vitro.* The system also allows examination of the potential interventions to rescue such changes.

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P11: A role for metabotropic glutamate receptors in healthy ageing.

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Metabotropic glutamate receptors (mGluRs) are G-protein coupled receptor which are activated by the amino acid, L-glutamate to modulate intracellular signal transduction cascades. This includes the PI3K and MAP/ERK signaling pathways which play evolutionary conserved roles in animal ageing. *Drosophila melanogaster* has a single mGluR, and preliminary studies from our group have shown that loss of mGluR activity in flies causes sex-specific differences on longevity. The mechanism whereby this occurs is currently unknown. We aim to find the mechanism(s) by which loss of mGluR activity in flies leads to longer lifespan and in particular, investigate the basis for the sex-specific effects of mGluR activity on longevity. Such studies could reveal novel cellular targets against which we could develop pharmacological interventions that can not only extend lifespan but also maintain health during old age. In our present study, utilising a null mutation of the gene encoding the single fly mGluR, *DmGluRA*, we confirm that loss of *DmGluRA* activity promotes longevity irrespective of genetic background but that the sex specific effects appear to be background-dependent. Interventions that extend lifespan tend to be associated with other phenotypes including increased stress resistance, reduced female fecundity, and improvements in climbing ability with age. We have characterised some of these phenotypes in this long-lived mutant and report those findings. Our data indicates that loss of mGluR activity in flies leads to longevity and present some age related-phenotypes which may give insight into the mechanisms by which this mutation extends lifespan.

P12: Human ageing outcomes of the SH2B3 (Lnk) insulin/IGF1 pathway genetic variant

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Introduction & Aim

SH2B (Lnk) is a major regulator of lifespan through modulation of the insulin/IGF1 (insulin-like growth factor) pathway in fruit flies and mammalian organisms. A common amino-acid substituting variant in humans (rs3184504) has been identified, by our group and others, to be associated with longevity, cancer, and cardiovascular disease risk. In the current study we aimed to characterise the SH2B3 rs3184504 T to C missense variant associations with ageing outcomes in 451,000 UK Biobank community volunteers, using data from the assessment, and hospital inpatient records.

Results

The lifespan-increasing (C) allele was associated with lower incident rates of coronary heart disease (Hazard Ratio 0.91: 0.87 to 0.96), diabetes (HR 0.94: 0.89 to 0.99), and hypertension (HR 0.96: 0.92 to 0.99). However, the C allele was also associated with higher BMI at baseline, and substantially higher incidence of breast (HR 1.20: 1.10 to 1.30) and colorectal cancer (HR 1.22: 1.10 to 1.35) during follow-up. The study included many other ageing-related phenotypes. Given the potential of this pathway for intervention in humans we highlight the important pleiotropic effects of this variant on ageing outcomes, and welcome discussion on this pathway during the meeting.

P13: Developing new tools to identify senescent cells and measure the SASP

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Cell senescence, resulting in permanent cell cycle arrest with marked metabolic alterations, is a physiological response to a variety of cell stresses, and provides an important barrier to tumorigenesis. However, senescent cells contribute to ageing, as demonstrated by the improved health and increased longevity of mice treated with senolytic agents [1]. However, the use of senolytic agents requires an understanding of the senescent cell burden, which is likely to vary significantly between tissues. In cases where the ratio of senescent: non-senescent cells is very high (e.g. it has been estimated that senescent cells may comprise 20-60% of aged primate skin [2, 3]), suppression of the pro-inflammatory senescence-associated secretory phenotype (SASP) may be preferable to senolytic treatment. However, measuring the senescent cell burden and particularly the SASP is currently hampered by a shortage of experimental methods that are sensitive, reliable, robust and cost-effective.

We report the development of simple methods to identify senescent cells in cell culture and to measure IL-6 as a canonical factor of the SASP, with the eventual aim of exploiting such findings in point-of-care devices to assess senescent cell presence and the impact of therapy *in vivo*. Here we discuss optimization of a procedure to determine IL-6 levels secreted by senescent cells, which we have applied during high throughput library screening to identify factors that suppress the SASP. By combining such assays with other readouts of senescence, we can identify the impact of agents on core features of senescence including cell morphology, proliferation, oxidative stress and SASP production.

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P14: Senescence in myoblasts; role in age-related muscle dysfunction

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Loss of muscle mass and function are critical factors in the development of frailty although the mechanisms involved are poorly understood. The number of senescent cells increases with age[1-2]. It is proposed that the presence of these cells plays a role in age-related muscle dysfunction via chronic activation of the nuclear factor k-B (NF-kB) mediated inflammatory pathway[3]. We hypothesise that resident satellite, or potentially other cells local to muscle, become senescent and exert detrimental effects on mature muscle fibres; including the chronic activation of NF-kB via the senescence associated secretory phenotype molecules (SASP) by the bystander effect[4].

In vitro studies have also investigated whether C2C12 myoblasts could become senescent, whether senescence associated cyclin-dependent kinase inhibitors (CDKI) are upregulated, and to determine the nature of the SASP. Myoblasts were treated with Etoposide to induce senescence. Treated myoblasts exhibited significantly altered morphology consistent with a senescent phenotype, increased SA-β-Gal activity, CDKI levels, and SASP factors (IL-6, IL-12(p40), and RANTES), compared with untreated cells.

Additional studies examined muscles from old (24 months) and young (3 months) C57BL6 Wild-Type (WT) mice for evidence of increased senescence markers. Muscles from old mice had a significantly increased (4-fold) content of senescence CDKIs compared with muscles of young mice ($p<0.05$).

Data suggest that myoblasts can develop a senescent phenotype. Further work will investigate the effect on mature myotubes co-cultured with senescent myoblasts on NF-kB activity. Furthermore, we will determine the role of senescence *in vivo* on skeletal muscle and NF-kB activity in muscle using p16-3MR mice and senolytic agents.

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P15: Inhibition of SIRT1/2 by Tenovin-6 induces premature senescence

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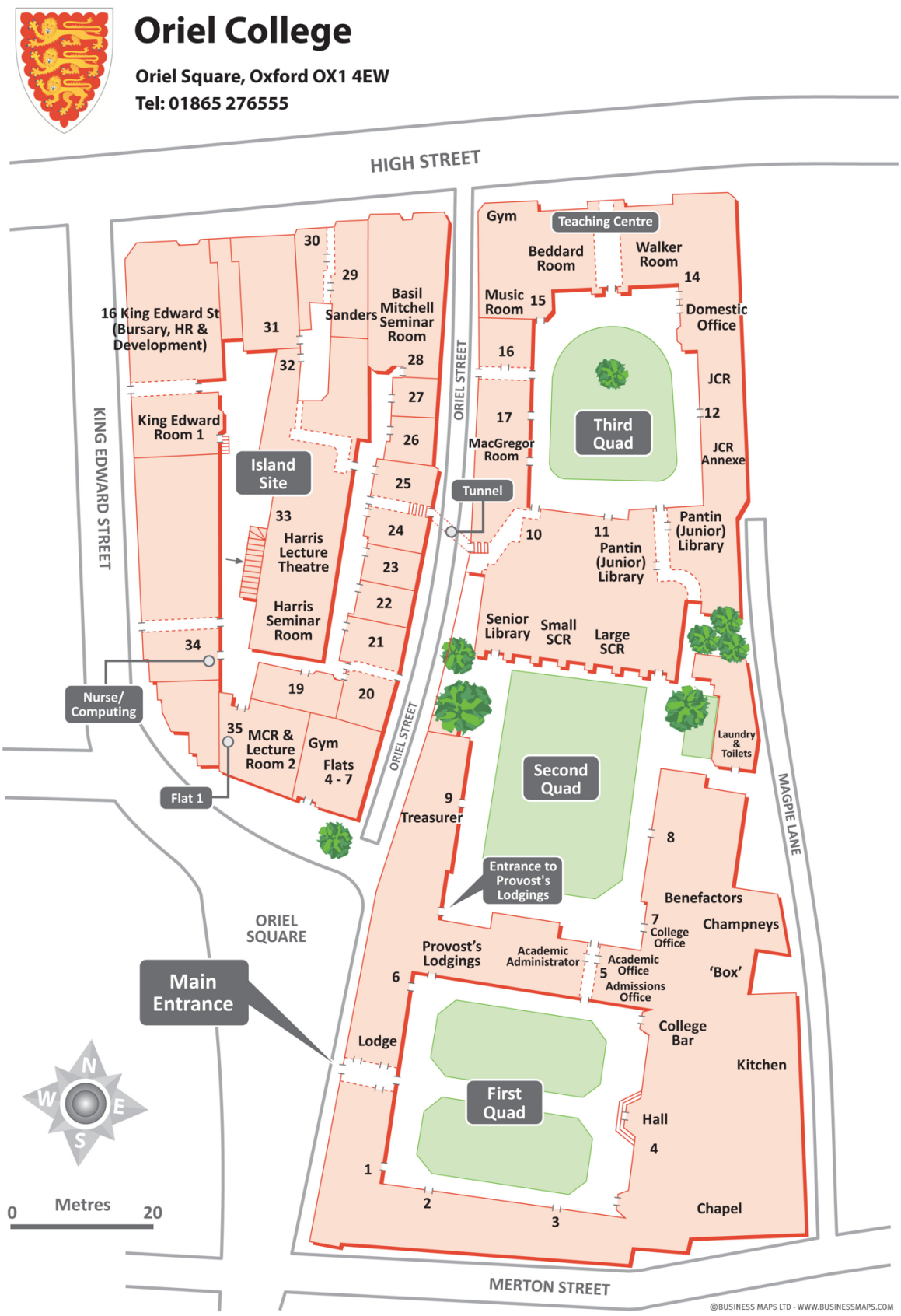
Cell senescence, a state of cell cycle arrest and altered metabolism with enhanced pro-inflammatory secretion, underlies at least some aspects of organismal ageing. The sirtuin family of deacetylases has been implicated in preventing premature ageing; overexpression or resveratrol-mediated activation increase longevity. Here we show that sirtuin inhibition by short-term, low-dose treatment with the experimental anti-cancer agent Tenovin-6 (TnV6) induces cellular senescence in primary human fibroblasts. Treated cells cease proliferation, and arrest in G1 of the cell cycle, with elevated p21 levels, DNA damage foci, high mitochondrial and lysosomal load and increased senescence-associated β galactosidase activity, together with actin stress fibres and secretion of IL-6 (indicative of SASP upregulation). Consistent with a histone deacetylation role of SIRT1 and 2, we find nuclear enlargement, probably resulting from chromatin decompaction on sirtuin inhibition. These findings highlight TnV6 as a drug that may be useful in clinical settings where acute induction of primary cell senescence would be beneficial but provide the caveat that even non-genotoxic anticancer drugs can have unexpected and efficacy-limiting impacts on non-transformed cells.



Map of Oriel College

Map of central Oxford