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EDITORIAL

Ageing here and now: current research and transformative therapies

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As life expectancy has increased significantly in recent years without a concomitant increase in health span (years of life in good health), there is an urgent need to develop efficient interventions for ageing-associated health issues. With recent significant advances in understanding biological mechanisms underlying the ageing process, we are on the brink of developing and applying such interventions.

The 68th British Society for Research into Ageing (BSRA) annual scientific meeting focused on current research and transformative interventions to tackle ageing-related health issues. This is a very timely topic for lab scientists, clinicians and society as a whole as the landscape of ageing research is changing rapidly. This is due to enormous scientific advances in both basic understanding and translational application, as well as new input from a wide variety of stakeholders including governments, pharma, biotech, SMEs, philanthropists, learned societies, scientists and advocates for older people. For example, the UK government has placed ageing firmly in its strategic focus, both through UKRI funding bodies (BBSRC and MRC) and through its Life Sciences Industrial Strategy (Bell 2017), with Innovate UK about to launch a further funding round on healthy ageing (Innovate 2019). Notably, both the Genetics Society and the BBSRC sponsored sessions of the BSRA scientific meeting, demonstrating strong commitment to promoting excellence in primary research and in knowledge exchange; commercial sponsors also make such meetings financially viable and the role of such companies in promoting scientific exchange should not be undervalued.

This special issue (SI) of Biogerontology ties together some of the exciting research and translational outcomes discussed at the meeting, with a range of papers covering topics including drug discovery pipelines, progeroid diseases, cell senescence, stem cells, inflammation and biomarkers; the conference also provided a context for such work by addressing the global demographic shift and greying of world populations (Harper 2018). The recent call to arms for new and affordable drugs in the ageing space (Bellantuoni 2018) was reinforced at the meeting by inspirational talks from Prof Chas Bountra and Prof Miles Witham. The translational pipeline that facilitates progress, from laboratory science and epidemiology through feasibility testing to clinical trials, is

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discussed in this SI in the article by Witham (2018). The ageing arena continues to progress, with the launch in April 2019 of UK SPINE (https://www.kespine.org.uk), a network drawing together leading institutions within the UK to facilitate knowledge exchange in the ageing sphere and to drive affordable drug discovery.

Ageing is complex and multifactorial. For many years, the most tractable systems for understanding underlying biological processes have been segmental monogenic progeroid diseases, particularly adult onset Werner syndrome and childhood onset Hutchinson Gilford progeria syndrome (HGPS). Lautrup et al. (2019) discuss novel strategies to extend healthy aging and treat—or even cure–human age-related diseases in the context of Werner syndrome (WS), caused by mutations in the gene encoding the Werner (WRN) DNA helicase/exonuclease. Their article summarises the latest progress in molecular understanding of WRN, and highlights the advantages of using different WS model systems, including induced pluripotent stem cells (iPSCs). On the theme of biological understanding to clinical translation, Bikkul et al. (2018) report on testing the efficacy of drugs targeting the mevalonate pathway in HGPS-derived cells—this may provide a useful adjunct to the ongoing clinical trials run by the Progeria Research Foundation using the farnesylation inhibitor lonafarnib (Gordon et al. 2018).

While monogenic diseases may be amenable to treatments based on correcting a single gene deficit, general population ageing presents a different set of challenges, with changes occurring at multiple levels from chromatin organization through splicing to protein localization and post-translational modification. Here, however, the complexity is starting to be resolved by the recognition that cell senescence underlies multiple aspects of ageing: transplantation of senescent cells into young mice rapidly induces age-related disease (Xu et al. 2018), while senescent cell removal from aged mice improved their health and increases longevity (Baker et al. 2011, 2016; Yousefzadeh et al. 2018). Following a keynote by Prof S. Rattan on senescence, the conference covered a number of exciting approaches to address the problem of cell senescence in ageing, particularly through senolytics (agents that selectively kill senescent cells): FOXO4-derived peptides (Baar et al. 2017), nanoparticle targeting to senescent cells (Muñoz-Espín et al. 2018) and compelling preclinical data on the impact of senolytics in improving bone structure and strength in mice, leading to human clinical trials in osteoarthritis (Unity Biotech, ClinicalTrials.gov Identifier: NCT03513016). Several aspects of senescence are dealt with in more detail in this SI.

It is only by understanding the core drivers of biological ageing that rational drug design becomes possible. Notably, senolytic drug development has benefitted enormously from advances in cancer research, where drug design has shifted away from non-specific tools that cause significant collateral damage towards intelligently targeted drugs based on a precise understanding of molecular mechanisms. Both the Unity UBX drug series and the FOXO4 peptide derivatives benefit from years of research into regulation of apoptosis through the p53 and Bcl2 pathways, critical in cancer. A further key example of cross-fertilization of research areas is in mTOR signaling—while in cancer, this kinase complex drives hyperproliferation, in ageing, mTOR drives the hypertrophy associated with cell senescence. Several presentations at the conference focused on mTOR, including the Koronchevsky award-winning talk by Hannah Walters, describing reversal of multiple senescent phenotypes on pan-TOR inhibition (Walters et al. 2016), a key finding by Nazif Alic that mTOR acts on the RNA polymerase III pathway (Filer et al. 2017) and the paper in this SI by Kucheryavenko et al. (2019), where the authors explore the potential of mTORC1 inhibitors as senolytics. Notably, the mTOR pathway is likely to be one of the first that receives FDA approval for ageing indications, following resTORbio's successful clinical trials showing improved immune function in elderly people following short term treatment with mTORC inhibitors (Mannick et al. 2014, 2018): such drugs provide significant promise for the treatment of a number of age-related diseases (reviewed by Walters and Cox 2018).

While current senolytics and other anti-ageing drugs are based on known targets and known biochemical pathways, discovery of new senomodifying agents requires new tools. Drug screening programmes typically use billions of cells, but senescent cells, by their nature, cannot be grown up in large numbers in the lab. Oncogene-induced senescence (either via BRAF or Ras activation) provides a useful model (Innes and Gil 2019) that makes screening

viable; an alternative approach to mimic another inducing pathway of senescence is reported by Walters and Cox (2019), who demonstrate 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; this provides a potential route for rapidly obtaining large number of senescent cells, but may also prove useful in clinical settings where acute induction of cell senescence would be beneficial.

Another potential intervention for senescence-related pathologies includes suppression of the SASP (senescence-associated secretory phenotype), a cocktail of pro-inflammatory cytokines, chemokines and proteases which mediates the damaging pro-inflammatory state characteristic of senescent cells. Current tools to assess the SASP are expensive and time consuming, with many requiring platforms (e.g. MSD or deep proteomics) out of the reach of most basic science labs. Rolt et al. (2019) describe optimisation and validation of a renewable and relatively inexpensive cell-based biosensor assay for measurement of IL-6, a canonical SASP factor; they describe adaptation of the assay for a 384-well plate format suitable for moderate to high throughput library screening applications, and show that the assay can differentiate between primary human cell populations of different biological ages based on IL-6 levels.

IL-6 is just one of many pro-inflammatory mediators contributing to the multimorbidity of later life, with the state of low-grade chronic inflammation that increases with ageing generally known as "inflammageing" (Franceschi et al. 2000). In this SI, Teissier et al. (2019a) discuss signaling through RAGE (receptor for advanced glycation end-products) as a key contributor to inflammageing and suggest that the pro-longevity effects seen upon blocking RAGE, or upon its deletion, may be the result of reduced inflammageing. This builds upon their latest findings of improved late-life kidney function in RAGE knockout mice (Teissier et al. 2019b). Notably chronic kidney disease accounts for some of the highest health care costs of age-related disease, and is likely only to increase further with the obesity/diabetes epidemic; by understanding the core signaling pathways and pathological outcomes of excess glycation, this work highlights possible new therapeutic targets in age-related disease.

A key requirement for any therapeutic intervention in ageing and age-related disease is a reliable biomarker of ageing/senescence, both for diagnosis and for monitoring therapeutic efficacy. While multiple programmes and international consortia have attempted to address this need (e.g. European Commission 2014), reliable and readily measurable markers have proven elusive; p16 and p21 cyclin kinases inhibitors are widely used but are also elevated in quiescent cells, while senescence-associated beta galactosidase (Dimri et al. 1995), is also found in non-senescent cells experiencing general lysosomal stress. Excitingly, the novel findings from a Europe-wide consortium on identification of a biomarker of frailty are discussed in more depth in the article by Jylhävä et al. (2019). The authors analyse the usefulness of different markers of biological age, finding that frailty index is a strong predictor of the need for care. Frailty is a complex syndrome associated with ageing, a large component of which includes sarcopenia, age-related loss of muscle mass and function (Kemp et al. 2018). As sarcopenia is associated with an increased risk of falls, hospital stay and early death, finding interventions for sarcopenia is an important aim for clinical ageing research (reviewed in Goljanek-Whysall et al. 2016).

While new therapies continue to emerge from ongoing studies, the real future of ageing research lies in the hands of early career researchers (ECRs). Hence capacity building in the ageing sphere is critical for progress. To accelerate this, the BSRA meeting introduced the innovative approach of including ECRs as co-chairs of all major scientific sessions, providing not only training but also enhanced visibility for young researchers. The involvement of Springer and Biogerontology in promoting a writing collaborative for early career researchers will, we hope, also bear fruit in promoting greater interaction between labs at a grass roots level. Such initiatives need to be encouraged throughout the scientific community so that conferences are not simply the domain of already globally respected leaders but also a hot bed for promotion of exciting and ground-breaking new research by the next generation of scientists.

In summary, this special issue brings together a wealth of current research into the mechanisms of ageing and focuses on potentially translational approaches to ageing-related health issues. The recent progress in the field of ageing has shown that

biological mechanisms underlying ageing may be promising targets for the development of novel interventions aimed at extending human healthspan.

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