Meeting report

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Healthspan versus lifespan: new medicines to close the gap

On 27 and 28 June 2022, the UK SPINE network (www.kespine.org.uk) held an in-person conference focusing on how new medicines could contribute to improving healthspan (healthy life years). The event facilitated knowledge exchange within the broader geroscience community by bringing together researchers and stakeholders from multiple sectors, including industry, academia, entrepreneurs, small-to-medium-sized enterprises, regulators, patients and carers, investors and policy makers.

Human aging is a complex process with many contributing genetic, environmental and socioeconomic factors. Data show that, despite a trajectory of increasing lifespan, healthspan has not shown a similar rate of improvement, with patients experiencing prolonged periods of poor health and often managing multiple age-related conditions.

Over the past decade, research in this field — buoyed by the publication of the nine hallmarks of aging[1] — has exploded, opening up the potential to develop therapeutics to treat, and potentially prevent, the onset and progression of multiple age-related conditions. The UK SPINE conference sought to showcase this research and provide a platform for discussions about the challenges and opportunities it presents for a multitude of stakeholders.

This report presents the main research themes, followed by an exploration of some of the discussions surrounding the development, approval and adoption of therapeutics to treat multiple age-related conditions.

The aging research landscape

Three main research themes arose, showcasing some of the most promising approaches to therapeutics development, senolytics and drug repurposing, as well as discussing potential targets and biomarkers, and strategies to further progress their development.

Senolytics. Senescence, and the ability of compounds to modify it therapeutically, was highlighted by a number of speakers. Keynote speaker Jesus Gil (Imperial College London) described the processes that underlie cellular senescence, a phenotype caused by changes in cells induced by stressors, such as cell cycle arrest, chromatin remodeling, morphological changes, metabolic reprogramming, lysosomal increase, senescence-associated secretory phenotype and resistance to apoptosis. Senolytics have the potential to eliminate senescent cells, and in model organisms can extend lifespan, improve healthspan and positively affect more than 20 pathologies with limited side effects.

Gil described work to screen for compounds that modulate senescence, such as 3-deazaadenosine, which alleviates senescence and has been found to improve phenotypes associated with age (in particular in muscle stem cell models)[2]. His laboratory has also carried out drug repurposing screens that identified cardiac glycosides such as ouabain as senolytics, and showed them to be active in a variety of cell types and able to eliminate senescent cells from old mice with benefits in metabolic and physical phenotypes[3].

Satomi Miwa (Newcastle University) presented data that demonstrate that mild electron transport chain 'uncoupling' could act synergistically with senolytics, improving their sensitivity and specificity both in vitro and in mouse models. For instance, the toxicity of the putative senolytic navitoclax was reduced in human dermal fibroblasts using the oxidative phosphorylation uncoupler FCCP. Frailty index, cognitive function and neuromuscular function were measured in mouse models, with results indicating that the effects of the senolytic combined with FCCP were enhanced compared with navitoclax alone. These findings can now be applied to the translation of novel senolytic drugs and the development of tools to diagnose and evaluate the therapeutic efficacy of senolytics, using a minimally invasive senescence biomarker.

Potential for repurposed drugs and supplements. James Edwards (University of Oxford) provided an overview from the literature of the nonskeletal effects of bisphosphonates. Bisphosphonates are widely prescribed to treat conditions such as osteoporosis, and recent meta-analyses have shown them to be clinically active in several other conditions. For example, they have been found to reduce risk of all-cause mortality by 29% over time in a hip fracture trial[4]; cause a 67% reduction in cardiovascular mortality and a 45% reduction in myocardial infarcts[5]; reduce heart attacks by 28%[6]; provide a 39% reduction in deaths from colon cancer[7]; reduce in-hospital mortality by 59% in patients treated with bisphosphonates before admission to intensive care units[8]; and reduce the risk of developing pneumonia by 24%[9]. Edwards went on to discuss future work designed to investigate the mechanistic effect of bisphosphonates on target cell panels and their effects in vivo.

Eleanor Platt (Medicines Discovery Catapult (MDC)) presented preliminary data from a preclinical biomarker study of the potential mechanisms of these nonskeletal effects of bisphosphonates. Tissue samples were collected from three cohorts of mice; 22-month-old mice treated with either the bisphosphonate zoledronate or vehicle control, and young 2-month-old untreated mice. Whole transcriptome analysis was performed on each of the 216 samples collected, giving rise to over 10 million data points. Initial data from several tissues indicate that zoledronate-treated aged mice were more similar to the younger cohort on the transcriptome level.

The potential for repositioning the mTOR inhibitor rapamycin — a drug already shown to improve healthspan in experimental animals — was also discussed. Lynne Cox (University of Oxford) and Phil Atherton (University of Nottingham) described their collaboration to study the effects of low-dose rapamycin administration (1 mg day^{-1}, for 4 months)

in a placebo-controlled human clinical trial in older adults (NCT05414292). The study includes assessment of the effect of mTOR modulation on muscle parameters with and without exercise, as well the potential alleviation of immunosenescence, with a particular focus on restoration of DNA repair capacity in T cells.

In addition to repurposing approved medicines, the potential for using currently marketed supplements to help to alleviate age-related conditions was discussed: for example, the putative effects of spermidine to improve vaccination response. In studies from the Simon laboratory, exploring autophagy in immunosenescence, Ghada Alsaleh (University of Oxford) described the central role it has in both aging and memory T cell responses. In flu-infected mice, the memory T cell response to infection is less pronounced in old, as compared to young, animals. Drawing on the effect of spermidine to induce autophagy, spermidine was found to improve the memory $CD8^+$ T cell response to infection in aged mice. Examining this process in individuals undergoing vaccination, using blood samples from a respiratory syncytial virus trial, it was found that higher rates of autophagy correlated with a better response to vaccination — indicating spermidine may improve overall vaccine response. A clinical trial (NCT05421546) to improve COVID-19 vaccination in older adults, funded by UK SPINE, is underway.

Targets and biomarkers for multiple long-term conditions. A major theme explored within the conference was the challenges associated with producing therapeutics for age-related conditions. Several workshops and talks highlighted two key questions for the field: how to identify targets of intervention and how to develop translatable biomarkers.

In a workshop focused on selecting targets for multimorbidity in aging, Charlotte Green (University of Dundee), Andrew Leach (European Molecular Biology Laboratory–European Bioinformatics Institute (EMBL-EBI)), Ellen McDonagh (EMBL-EBI), Graeme Wilkinson (MDC) and Kirsty Winn (MDC) discussed the importance of model systems available to clearly define and test the multimorbidity potential of new targets: for example, using models of accelerated aging based on conditions such as Werner syndrome. Inflammatory mechanisms were highlighted as important drivers of aging pathology underpinning many pathways, which tend not to be included in comorbidity clusters. It was suggested that a multitarget approach to drug discovery may be more effective overall than targeting single points of intervention for treating comorbidities. There is the potential for using patient data to identify target association signals; however, this may be further complicated owing to polypharmacy of drug prescribing (and non-adherence) for comorbidities. Finally, there was some dialog around how best to stratify patients, in particular for less-treated conditions for which there are few treatment options (such as idiopathic pulmonary fibrosis, frailty and Alzheimer's disease), and the difficulty in positioning new treatments against existing standards of care.

In the workshop on translational biomarkers, Gayle Marshall (MDC) highlighted key challenges for translating geroscience targets and therapeutics into the clinic. Discussion topics included how innovative biomarkers can be used and additionally demonstrate the therapeutic hypothesis, alongside the challenges to their clinical implementation and the logistical issues faced in dealing with and interpreting the large amounts of data generated from such studies.

Lorna Fitzpatrick (MDC) highlighted the potential for epigenetic targets in her presentation, which brought together two streams under the title 'Epigenetics and aging: can modulation increase lifespan?'. The roles of putative epigenetic modulators were assessed to investigate their potential to increase longevity in an in vitro human neuronal cell model, on the basis of their activity against a series of targets identified by previous research. Findings indicated clear evidence of target expression in the neuronal cell models, and there is a strong correlation of the data between genetic ablation and small molecule inhibition. Further research is now being undertaken by Adam Rolt (MDC) in collaboration with Nicholas Rattray (University of Strathclyde) comparing the effects of these modulators and their mechanisms on cell senescence markers between young and aged human dermal fibroblasts.

The innovation landscape of therapeutics for healthy aging. An important motivation of the conference was to look beyond the laboratory and into the wider ecosystem, to engage with stakeholders who are implicated in innovation in this field. This involved dialog with patients (to gather their perspectives on priority setting and challenges), industry representatives from across the sector (including the pharmaceutical industry, small-to-medium-sized enterprises (SMEs) and entrepreneurs), and regulatory bodies and others involved in the design and development of clinical trials.

Patients. The patient panel session, chaired by Janet Lord (University of Birmingham), began with a short video providing real-world feedback from patients and carers, who discussed their daily challenges in managing multiple long-term conditions and their hopes for the future. Two key themes emerged that would improve quality of life: (1) setting up integrated healthcare teams, with specialists working together to treat multiple conditions simultaneously; and (2) emphasizing the need for medication to be considered across their different conditions to clarify what was most effective and how different drugs might interact.

The subsequent panel discussion focused on the reality of supporting patients, many of whom experience multiple long-term conditions alongside the primary condition. Sarah Rudkin (Versus Arthritis) pointed out that although the majority of donations received by patient charities are for specific conditions, many recognize the importance of supporting patients with multiple long-term conditions, which cut across this necessarily narrow focus. Cathy Yelf (Macular Society) noted that maintaining functionality in old age should be a priority and that loss of sight affects the ability of patients to manage other conditions as well. Philip Bell (patient representative) discussed the value of patient and public involvement in driving the research agenda and the reality of the patient experience, against the backdrop of a healthcare system structured around siloed specialties. Clare Jonas (Stroke Association) acknowledged the challenge for many people with multiple long-term conditions of taking part in research, particularly in clinical trials, irrespective of their desire to do so; however, it was recognized that patients are very interested in and capable of shaping the discussion and articulating their priorities.

Building on the patient perspective and considering the public perception of geroscience and the language used to describe aging, a workshop facilitated by Harriet Teare (UK SPINE, University of Oxford) picked up on several points raised earlier in the conference. Workshop participants identified the language that they find most constructive: for example, they agreed that healthspan was a helpful concept. They also identified that the goal of achieving 'healthy aging' suggests a specific threshold. Using terms such as healthier or better suggests a spectrum of improvement, upon which everyone can

situate themselves. The audience were invited to explore the definition for 'health[ier] aging' and demonstrated the breadth of factors that might influence health, including (but not limited to) mental health, physiological aspects, mobility, a sense of purpose and value, and the ability to contribute.

Maximizing equitable health and wealth

A theme that arose several times during workshops and in discussions at the conference was the need to maximize health equality when considering advances in how we combat aging. In her keynote presentation, Tina Woods (Collider Health) addressed this directly and described the aim to provide a blueprint to maximize access to healthcare arising from advances in understanding aging biology and its effect on multimorbidity[10]. She asserted the need to close the gap in heathy life expectancy between the richest and poorest, which currently stands at an almost 20-year difference. She looked beyond new medicines to cover wider support systems for patients, including lifestyle factors, behavior and environment — the entire 'exposome' — that influence health and aging, reminding participants of the vast sums of money currently spent by the NHS on conditions that are largely preventable and potentially avoidable. One of the key points that Woods raised was the importance of hope; experts interviewed for Tina's book *Live Longer with AI* agreed that passion and purpose are central to healthier aging[11].

Industry. The industry panel chaired by Graeme Wilkinson (MDC) included David Weinkove (Magnitude Biosciences), Malcolm Skingle (GlaxoSmithKline), Jens Kiechbusch (AstraZeneca), Mark Ramondt (MultiplAI) and William Bains (Five Alarm Bio). A key challenge facing engagement with industry is that current R&D processes and strategy in the pharmaceutical industry are based on clearly defined patient populations that can be addressed with defined targets (ideally genetically validated) and tested in the clinic through registerable endpoints. These do not yet exist for the treatment of multimorbidity, making it difficult to align with existing portfolios and priorities. Start-ups and SMEs can be more agile and disruptive, but often have issues in accessing early-stage funding to progress their programs. Networks, and in particular the UK's innovation ecosystem (in the form of accelerator programs, academic collaborations and access to funders and universities), were highlighted as particularly beneficial to start-ups and SMEs working in this space.

Other challenges identified included the development of animal models that allow rapid and iterative testing of potential molecules. Furthermore, there is an issue of the lack of availability of datasets representing diverse human populations. Ascertaining and guaranteeing safety (and in particular long-term safety) was also raised as an issue. Differences between the UK and USA in terms of appetite for failure and risk-taking were suggested as reasons underlining the disparity in funding for aging research, and therefore the larger market for aging companies in the USA. The need for clarity in messaging was again recognized as vital, to articulate the intentions of SMEs when interacting with potential investors. A major opportunity for UK SPINE was identified in helping to bridge the gap between industry stakeholders.

In the workshop on start-ups in the healthy aging space, Paul Mercer (The Francis Crick Institute), Caroline Cake (Oxford Science Enterprises), David Weinkove (Magnitude Biosciences) and Mark Ramondt (MultipleAI) provided their perspectives on how the SME community can play a key part in healthy aging research. The conversation began with reflections on the stimulus for starting a company, ranging from entrepreneurial drive to the convergence of career experiences and an awareness that there are options to have both an academic career and follow an entrepreneurial path through a start-up. Schemes such as accelerators were highlighted as having an important role in the landscape, and it was suggested that the key to a successful start-up is to identify the challenge or problem and then identify a solution (rather than starting with a solution).

Knowledge exchange and cross-sector collaboration. Stuart Wilkinson (University of Oxford) and Jennie Shorley (Manchester Metropolitan University) explored what is meant by knowledge exchange, from the perspectives of different stakeholders, and provided workshop participants with the opportunity to reflect on the role of knowledge exchange in tackling healthy aging. Participants were invited to consider one of four perspectives — novel research, clinical application, unmet patient needs and commercial gains — and to reflect on the skills and experience each group could bring to improving healthspan. Interestingly, most participants could not limit their association to only one of the groupings. A recurring theme was the importance of communication and feedback loops between different stages of the process, each of which involves multiple disciplines.

Michael Hopkins (University of Sussex) presented his research looking at challenges and opportunities for collaborations that span organizations and sectors by necessity. Boundary spanning was conceptualized as a critical process in biomedical innovation involving the exchange of knowledge across physical, organizational and technical boundaries that separate the individuals involved. Obstacles to these interactions included divergences of technical language, accepted practices and norms, culture, systems and values. Increasing the porosity of boundaries was considered possible through building familiarity, understanding, trust and agreement, and using shared standards.

The role of knowledge exchange was emphasized as an avenue to facilitate this process, which is increasingly being acknowledged by funders (for example, Research England) and universities. The role of knowledge exchange professionals in these increasingly complex collaborations is to help to shape research proposals, administer funding competitions, forge connections internally and externally, support collaborative projects, organize events and develop strategy.

Regulation and clinical trial design. A critical challenge is the current structure of regulatory approval systems and clinical trial design, which generally follow a condition-specific framework. In addition, clinical trials largely exclude the involvement of older people and those suffering with multiple long-term conditions. The challenges for influencing and developing regulatory frameworks in this space were discussed in a series of workshops at the conference.

In a workshop facilitated by Jennifer Harris and Hannah Chance (Association of the British Pharmaceutical Industry (ABPI)), Yasmin Allen (Academy of Medical Sciences (AMS)), Dawn Beaumont-Jewell (National Institute for Health and Care Research (NIHR)) and Janet Lord (University of Birmingham), the aim was to develop thinking around policy interventions in the design and delivery of clinical trials.

The approach built on the AMS 2021 report on cross-sector opportunities for developing new interventions for patients with multiple long-term conditions, and the work of the ABPI–Birmingham Health Partners Memorandum of Understanding and the ABPI's Multimorbidity Project Team.

The workshop also highlighted the importance of patient engagement in multimorbidity trial design, and particularly where barriers to clinical trial participation need to be overcome to include those with multimorbidities, such as a dedicated resource that is committed to facilitating and communicating opportunities for participation.

The need for clear guidelines to develop methodologies for multimorbidity trial design, including learning from existing trial data and determining the 'gold standard' comparator for trials specifically targeting multimorbidities, was seen as crucial to building confidence in outcomes.

A workshop facilitated by Glenn Wells and Marc Bailey from the Medicines and Healthcare Products Regulatory Agency (MHRA) introduced the revised strategy for the UK's regulatory agency, before leading a conversation about the need to consider regulation for clinical studies in aging and the regulatory challenge of multimorbidity treatments.

Trial endpoints were highlighted, as well as the outcome measures that will be needed to determine whether a treatment has been effective. Crucially, regulators such as the MHRA need to anticipate future topics of relevance for them, with the caveat that they are driven by what is safe, useful and needed. The opportunities for medicines to prevent disease by better understanding aging biology, and therefore developing treatments that might be used to avoid progressing into ill health, raise interesting challenges for regulators and will therefore need to be considered carefully. Focusing on diseases associated with aging is more in line with current health system structures and therefore provides a more familiar route for appraisal.

One approach to the design of healthy aging trials is through the development of outcome measures. Muslim Abbas Syed, Eliot Marston and Melanie Calvert (University of Birmingham) discussed the initial findings of a review undertaken by the Birmingham Health Partners Centre for Regulatory Science & Innovation that focused on the roles of stakeholders, the outcomes considered most important, the challenges associated with measuring outcomes, strategies for consensus, and the development of a core outcomes set for healthy aging trials to test drug and device interventions. Outcomes identified as important in healthy aging trials for drugs and devices included mobility, autonomy, quality of life measures, diagnostics (laboratory tests and biomarkers) and assessment of physiological indicators of responses to intervention.

BOX 1

Key themes and challenges of translating aging research and developing new medicines

Discovery and use of biomarkers to aid target validation and clinical trial design
Relevant target discovery and moving away from single target to multiple target activity
Relevant and predictive aging models
Patient involvement in the design and implementation of clinical trials
Industry participation in drug discovery and development (both in Big Pharma systems and approaches, and in funding and support for the SME community)
Challenges of existing regulatory systems

Strategies for recruitment and the challenges of statistically powering studies were also considered. The discussion emphasized the need for 'subject matter experts' (stakeholders with relevant and substantial experience in healthy aging trials) to be included in defining these strategies but also that future design should be informed by wide consultation, particularly with individuals and/or communities who should be involved and represented in trial outcomes.

Conclusions

The UK SPINE annual conference brought together multidisciplinary and multisector stakeholders to examine the future needs for aging research and its translation for the development of new medicines to combat multimorbidity. It highlighted the need to support patients with multiple long-term conditions and to address disparities in healthspan. It emphasized the considerable progress that has been made in recognizing the link between fundamental biology of aging and age-related conditions, and the opportunity to develop novel therapeutics. Key challenges of translating aging research and developing new medicines were identified as needing further thought and discussion (Box 1).

The language and terminology used to describe and discuss aging research was a thread throughout the program, and raised by a variety of stakeholders — clarity and consistency were considered essential for ensuring engagement with the public, supporting cross-disciplinary collaboration and pitching to investors. Participants agreed that to secure public trust and support the geroscience community should develop clear messaging and communication regarding the current and anticipated benefits that are likely to arise from geroscience research to patients and the public. Likewise, the geroscience community should develop a clear narrative for engagement with potential investors.

The UK SPINE conference provided a timely opportunity for interaction and networking, and for showcasing the work undertaken and the progress made in the two years since the last face-to-face meeting. Many of the conversations initiated will now be continued, sharing outputs and leading to further meetings and connections to ensure that UK SPINE can continue to support and shape the aging research agenda.

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Competing interests
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