Medicines Discovery Catapult:

A roadmap for the discovery of therapeutics in healthy ageing

Reshaping Discovery Together

CATAPULT Medicines Discovery

UK SPINE Knowledge Exchange

A ROADMAP FOR THE DISCOVERY OF **THERAPEUTICS IN HEALTHY AGEING**

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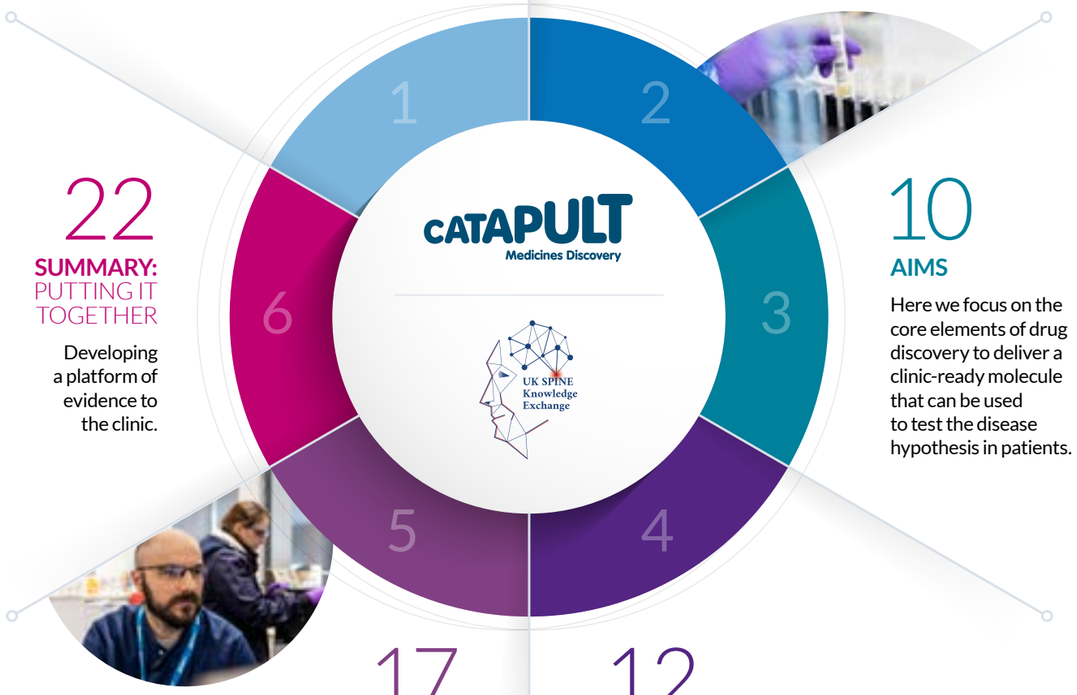

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This document, produced in collaboration with colleagues at the Medicines Discovery Catapult, a UK SPINE partner, is a guide to established best practice in drug discovery with a focus on interrogating aetiology of age-associated multimorbidity. Complementing the drug discovery roadmap, case studies drawn from recent clinical trials illustrate regulatory strategies for such interventions.

At the time of writing, drugs for mitigating deleterious ageing have yet to be approved explicitly for this purpose by a regulatory body. Therefore, strategies for the discovery of effective interventions and for facilitating their use via regulatory approval and clinical adoption are themselves works in progress. This guide aims to support researchers in this space by outlining strategies for de-risking the process of taking exploratory work forward into an innovative drug discovery programme.

Drug discovery strategies for interventions aiming to mitigate age-associated multimorbidity fall into two camps:

Treating age-associated disease. This strategy is described in detail in the body of this report and is the most common among existing clinical trial activities as it aligns with accepted regulatory frameworks. The extraordinary advantage of this approach is established methodology and infrastructure: the existing drug discovery ecosystem is heavily weighted toward treating a specific disease. In this framework, however, opportunities to develop drugs with potential to delay disease onset may be missed or not readily evaluated.

Delaying or preventing age-associated disease and functional decline. This strategy faces significantly greater challenges: there is no equally large body of knowledge to support methodology, nor is the infrastructure fully established, for interrogating age-associated multimorbidity, particularly in the clinic.

The overarching translational objective is to gain regulatory approval, and regulators require evidence of safety and efficacy. In this regard, the distinction between the two strategies hinges on availability and standardisation of metrics supporting such evidence (Fleming, *et al*, 2019). Age-associated diseases typically have established clinical biomarkers (alongside standardised collection methodology and interpretation of data) which support robust conclusions concerning efficacy. With respect to safety, acceptable levels of interventional risk are established in relation to the known risks associated with disease.

For prophylactic interventions targeting deleterious biological ageing (pre-disease), such metrics are a work in progress (Morsli and Bellantuono, 2021). Efficacy metrics may or may not overlap with biomarkers of disease, and composite measures of biological ageing (for example, complex panels of biomarkers or biological ageing clocks) may be required and considerable efforts are underway in this regard; see below for references representing the state of the art. Interventional risk would be measured against the likelihood of onset of age-associated diseases (broadly, or clustered by shared aetiology) weighted by the health risks of multimorbidity associated with their onset and progression. A robust and well-tested methodology to support this has not been established.

A trial for repositioning metformin (an approved drug for type II diabetes) (Barzilai, *et al*, 2016) is proceeding with a novel proposal for evaluating efficacy in mitigating multimorbidity, without reference to specific disease treatment, via changes in biomarkers (Justice, *et al*, 2018). As this and forthcoming proposals are scrutinised for potential to serve more broadly as standardised metrics of ageing, other similarly non-disease-specific prophylactic interventions will be worth revisiting. In this regard, the clinical histories of drugs now widely prescribed to moderate cholesterol levels (statins; Junod, 2007) and hypertension (ACE inhibitors; Borer, 2007), both of which have associations with multiple diseases, may be instructive.

Development, standardisation, and adoption of biomarkers of ageing suitable for assessing clinical impact are essential to progressing candidate drugs to clinical trials. Ultimately, a broad consensus of opinion will be sought by regulatory bodies to legitimise such representative measures of efficacy (Kinexum, 2020). Although regulatory authorities may be unlikely to publish specific opinion or guidance, FDA representatives have been engaging directly with the geroscience community, at workshops and conferences (Stanford, AIMI 2020; Kinexum, 2020), and also with individual research groups in regard to specific trials (Justice, *et al*, 2018).

It is recognised that innovations are rapidly evolving in this space, and the following are highlighted as of late 2020 and intended to serve as points of departure for further independent inquiry.

Clinical trials & biomarkers of ageing

- Metformin as a Tool to Target Aging (Barzilai, *et al*, 2016)
- A framework for selection of blood-based biomarkers for geroscience-guided clinical trials: report from the TAME Biomarkers Workgroup (Justice, *et al*, 2018)
- DNA Methylation Clocks in Aging: Categories, Causes, and Consequences (Field, *et al*, 2018)
- Deep Aging Clocks: The Emergence of AI-Based Biomarkers of Aging and Longevity (Zhavoronkov and Mamoshina, 2019)
- The Role of Biological Clocks and Other Biomarkers of Aging in Regulatory Development (Kinexum, 2020)

Preclinical models of ageing

- Animal and human models to understand ageing (Lees, *et al*, 2016)
- The dog aging project: translational geroscience in companion animals (Kaeberlein, *et al*, 2016)
- Mouse Models to Disentangle the Hallmarks of Human Aging (Folgueras, *et al*, 2018)
- Old and new models for the study of human ageing (Brunet, 2020)

Regulatory engagement

- A framework for selection of blood-based biomarkers for geroscience-guided clinical trials: report from the TAME Biomarkers Workgroup (Justice, *et al*, 2018)
- Regulatory considerations for AI in healthcare (Stanford AIMI, 2020)
- The Role of Biological Clocks and Other Biomarkers of Aging in Regulatory Development (Kinexum, 2020)

Machine learning and artificial intelligence in drug discovery for aging

- Artificial intelligence for aging and longevity research: Recent advances and perspectives (Zhavoronkov, *et al*, 2019)
- Will Artificial Intelligence for Drug Discovery Impact Clinical Pharmacology? (Zhavoronkov, *et al*, 2020)

Foreword references

Barzilai N, *et al* (2016). Metformin as a Tool to Target Aging. Cell., 23, 1060

Borer, JS. (2007). Angiotensin-converting enzyme inhibition: a landmark advance in treatment for cardiovascular diseases. European Heart Journal Supplements. 9; E2, https://doi.org/10.1093/eurheartj/sum037

Brunet A. Old and new models for the study of human ageing (2020). Nat. Rev. Mol. Cell Biol., 21; 491

Field AE, *et al* (2018). DNA Methylation Clocks in Aging: Categories, Causes, and Consequences. Mol. Cell., 71; 882

Fleming GA, *et al* (2019). A Regulatory Pathway for Medicines That Target Aging. Gerontol. Soc. of America Public Policy & Aging Report. 29; 128

Folgueras AR, *et al* (2018). Mouse Models to Disentangle the Hallmarks of Human Aging. Circ. Res., 123; 905

Junod SW. (2007). Statins: A success story involving FDA, academia, and industry. Available at: https://www.fda.gov/media/110452/download (Accessed: October 12, 2020)

Justice JN, *et al* (2018). A framework for selection of blood-based biomarkers for geroscience-guided clinical trials: report from the TAME Biomarkers Workgroup. GeroSci., 40; 419.

Kaeberlein M, *et al* (2016). The dog aging project: translational geroscience in companion animals. Mammal. Gen., 27; 279

Kinexum Services LLD, speaker: Robert Temple, Deputy Center Director, Clinical Science, CDER, US FDA (2020) The Role of Biological Clocks and Other Biomarkers of Aging in Regulatory Development. Available at https://youtu.be/eT5WvRoLelM?t=320 (uploaded 2020.09.14)

Lees H, *et al* (2016). Animal and human models to understand ageing. Maturitas., 93; 18

Morsli S, and Bellantuono I (2021). The use of geroprotectors to prevent multimorbidity: Opportunities and challenges. Mech. Age. Develop., 193; 111391.

Stanford AIMI, speaker: M. Khair Elzarrad, Deputy Director, Office of Medical Policy, CDER, US FDA (2020) Regulatory considerations for AI in healthcare. Available at https://youtu.be/5eKyJST8kpc?t=86 (uploaded 2020.08.12)

Zhavoronkov A, *et al* (2019). Artificial intelligence for aging and longevity research: Recent advances and perspectives. Age. Res. Rev., 49; 49

Zhavoronkov A, and Mamoshina P (2019). Deep Aging Clocks: The Emergence of AI-Based Biomarkers of Aging and Longevity. Trends Pharmacol.Sci., 40; P546

Zhavoronkov A, *et al* (2020). Will Artificial Intelligence for Drug Discovery Impact Clinical Pharmacology? Clin. Pharmacol. Therap., 107; 780

1 | The Landscape

Introduction

According to the World Health Organisation, 2015, "…every person – in every country in the world – should have the opportunity to live a long and healthy life…".

The WHO defines Healthy Ageing as "the process of developing and maintaining the functional ability that enables wellbeing in older age", with functional ability being made up of the intrinsic capacity of the individual, relevant environmental characteristics and the interaction between them. Intrinsic capacity comprises the mental and physical capacities that a person can draw on and includes such basic functions as the ability to walk, think, see, hear and remember. The level of intrinsic capacity is influenced by factors such as the presence of disease, injuries and importantly age-related changes. These in turn can be accelerated by intrinsic and extrinsic factors that can result in an increased risk of developing non-communicable diseases such as type-2 diabetes, arthritis, cardiovascular impairment and neurodegeneration. Thus, an individual's genetic background and the environment to which they are exposed may lead to the dysregulation of the ageing process providing a background for the development of several coexisting conditions. This combination of coexisting morbidities, so called multi-morbidities, further reduce overall health and wellbeing, leading to increased frailty in older age; in addition to producing an increasing burden on healthcare systems. Healthy ageing as a defence against these multi-morbidities, is thus important to individuals and to society, with the maintenance of functional ability, and thus independence, being paramount.

Ageing and the accumulation of multiple morbidities

Dysregulation of the ageing process has now been attributed to the accumulation of morbidity, and modulation of these fundamental ageing processes may be protective of or delay disease onset.

Although ageing itself is not, yet, described as a 'disease', efforts are underway to include it in the next scheduled international classification of disease (ICD) list (ICD-11, 2022). Age-related conditions and multi-morbidities are the leading cause of death worldwide. The Academy of Medical Sciences, 2015, has named multi-morbidities as a growing healthcare concern across the world with understanding and tackling the underlying biology being crucial to the development of novel interventions.

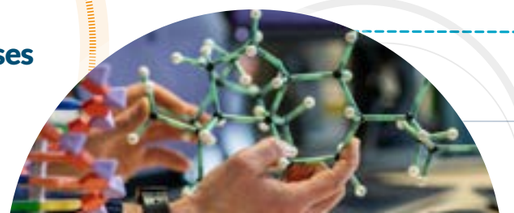
Reducing the rate of the ageing process could have a dramatic effect on overall health and from a health-economic perspective, lead to the development of new drugs to treat these conditions (Glossmann and Lutz, 2019; de Maghales *et al*, 2017). The costs of treating ageing and age-related conditions are significant; within the UK, the current cost of treatment in the over 60 age group consumes over 40% of the annual NHS budget (UK Gov. Country and regional analysis, 2015), totalling over £56Bn – with over £10Bn being spent on frail patients. The WHO projects that between 2000 and 2050 the total number of adults aged 60 years or over will more than triple, increasing from around 0.6 billion to 2 billion (WHO, 10 facts on Ageing, 2017), clearly these population dynamics and the associated costs will have major implications for healthcare.

Multi-morbidities are part of the natural history of disease progression (Hernandez *et al*, 2019) and typically manifest as a consequence of the ageing process. However, the underlying cause of many these phenotypes is not known, and with an increasing population over the age of 65, will place a growing burden on health and social care funding (Kingston *et al*, 2018). Additional increases in multimorbidity are also expected to be seen in younger populations due to the rise in diseases such as T2D and obesity (NHS digital statistics). In elder populations, ageing itself and the development of multi-morbidities are risk factors for frailty and a lack of physical resilience to external stressors, communicable disease and trauma.

The first generation of pharmaceutical interventions to mitigate biological drivers of ageing are beginning to graduate to clinical trials in humans. We are in the early stages of this transition and this document outlines strategies for proceeding, through currently accepted drug discovery processes, and also by recognising and leveraging an evolving understanding for discovery of potentially preventative interventions.

Data reflecting the mismatch between increased lifespan vs. a lesser increase in healthspan has been used to critique the fundamental value of interventions targeting the biological drivers of ageing: why increase longevity when increase in healthspan lags? This disparity, however, exists in an interventional environment focused on disease management, where the impacts of preventative interventions on the development of morbidity and multi-morbidity are not yet known. Indeed, the core motivation of shifting from a disease treatment focus to prevention is to eradicate this mismatch: by mitigating the deleterious effects of biological ageing, age-associated disease and comorbidities could be delayed or potentially avoided, and the quality of life vs chronological age curve will be better aligned.

Dysregulation of the ageing process has now been attributed to the accumulation of morbidity, and **modulation of these fundamental ageing processes may be protective of or delay disease onset.**



The purpose of this report is to indicate, in a straightforward manner, **a progression path for drug discovery programmes** which may be particularly useful for new entrants into this potentially fruitful area of pharmaceutical R&D.

Given the objective of delaying unhealthy ageing, the drug discovery process has an opportunity to ensure these interventions are suitably designed and tested. To date, drug discovery strategies have focused on disease management. Adjustments to intended use may enable potential solutions, for example, by demonstrating efficacy in treating a specific disease, an intervention may receive regulatory approval and then be used off-label to mitigate morbidity due to ageing-related biology. This approach enables commercialisation in the short term but, alone, is likely to fall short of having established a suitable evidence base to support a primary use case. As our understanding of the underlying biology evolves, a broader set of candidates for therapeutic use will emerge and best practices for establishing an evidence base to support their development and regulatory approval must emerge alongside (Fleming, 2019).

Targets associated with the ageing process have been the subject of intense preclinical research (e.g., see Partridge *et al*, 2020) and the way these might affect disease progression is being actively studied in the clinic. However, despite substantial progress in our understanding of these interplays and of the opportunities that might bring for clinical amelioration of disease, relatively few new R&D investments have been made (Ford *et al*, 2020).

The purpose of this report is to indicate, in a straightforward manner, a progression path for drug discovery programmes which may be particularly useful for new entrants into this potentially fruitful area of pharmaceutical R&D. This document seeks to provide a framework for drug discovery research in ageing, with the aim of helping innovators understand the current requirements for development of new therapeutics for use in an aged and multi-morbid population.

2 | Setting the Scene

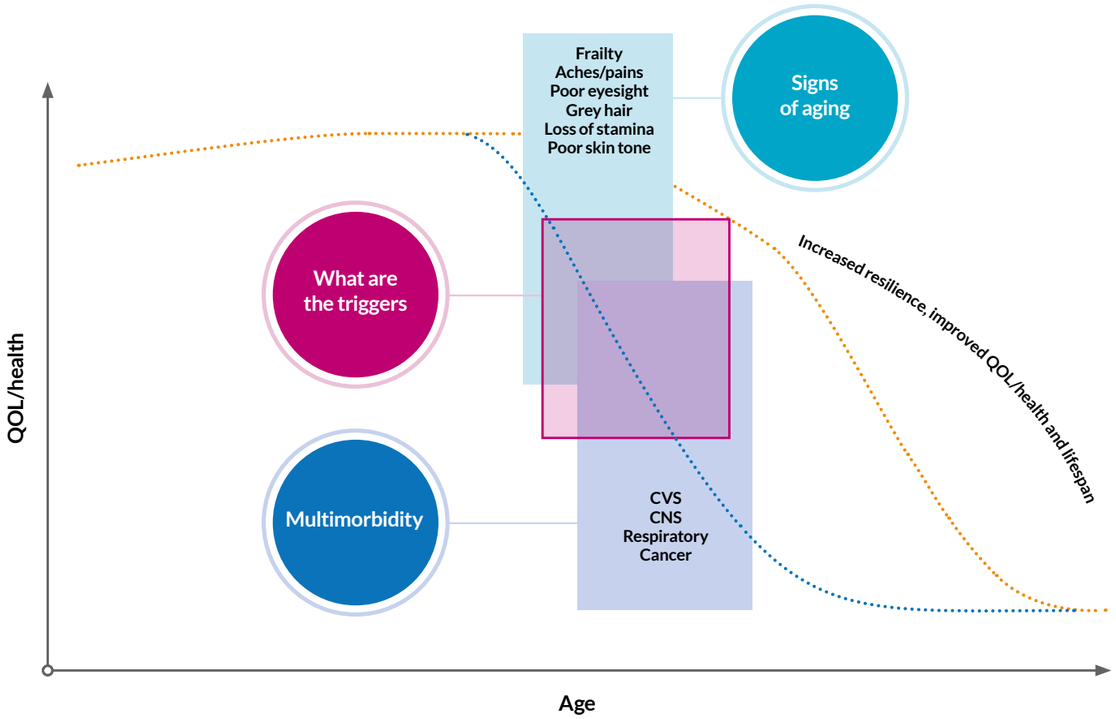


Figure 1.
A conceptual visualisation for focussing research and understanding of developing therapies for age-related multimorbidity; after Seals *et al* (2016). The normal ageing process leads to declines in physical performance and reduced resilience marked by outward signs such as a loss of stamina, gradual poor eyesight, etc. The rate of onset and progression can be mitigated by dietary and lifestyle factors but are also governed by genetic inheritance. Lifestyle and environmental factors may result in acute and chronic changes to the complex interplay of biological processes that underly normal ageing and result in morbidity and over time the accumulation of additional or multi-morbidities. Such multi-morbidity will more often necessitate prolonged medicalisation, reduce life expectancy impair overall quality of life.

Research Priorities

What constitutes a novel therapeutic for age-related and multi-morbid conditions? As illustrated in figure 1, during the normal ageing process there is a gradual loss of function in many organ systems, which can lead to a reduction in general health and quality of life. Individual genetic, epigenetic, environmental and lifestyle factors can also combine to accelerate certain of these leading to morbidity and, in many individuals, the accumulation of multiple morbidities (Campisi *et al*, 2019; Kingston *et al*, 2018). The focus of this road map is on the treatment of multi-morbid diseases by intervening therapeutically with cellular processes responsible for ageing and thus reducing the health burden on the individual and the economic burden on stretched healthcare systems.

The focus of this road map is on the treatment of co-occurring conditions and multi-morbid diseases by intervening therapeutically with cellular processes responsible for ageing and thus reducing the health burden on the individual and the economic burden on stretched healthcare systems. It also acknowledges innovative thinking and trial design which may enable the development or repurposing of drugs to prevent or rejuvenate the symptoms of ageing.

Reports such as those by the Academy of Medical Sciences (2018) clearly articulate the challenge of multimorbidity research, along with the subsequent formation of multidisciplinary working groups1 and associated funding streams2. However, these are largely focussed at academic researchers, clinicians, health professionals, patients, healthcare providers and non-government organisations (NGOs) to '…overcome the structural and cultural barriers facing multimorbidity research, and support the research needed to better understand the trends, clusters, mechanisms and causes, burden, prevention and management of multimorbidity…'.

The needs of drug discovery innovators, large and small, are thus separate and particularly for academic drug hunters and SMEs, knowledge of how to approach drug discovery in this setting is required.

1. (https://acmedsci.ac.uk/policy/policy-projects/multimorbidity-helpful-resources)
2. (https://mrc.ukri.org/funding/browse/tackling-multimorbidity/tackling-multimorbidity-at-scale-understanding-disease-clusters-determinants-biological-pathways/)

Target landscape

Modulation of the ageing process does not lack for potential targets and basic mechanisms, such as those within the so-called 'Hallmarks of Ageing' (Lopez-Otin *et al*, 2013).

However, there is still a significant need for fundamental research linking these pathways to multi-morbid patients and hence allow drug discovery innovators to identify the value in investing in R&D programmes. The landscape for therapeutic intervention is wide, with, in addition to pharmacological therapeutic discovery, cell and gene therapies, organ transplant and other 'non-traditional' approaches being pursued (de Magalhaes *et al*, 2017). The latter including direct to consumer marketing of new and existing medications, herbal extracts and even research into parabiosis, whereby blood, plasma or constituents thereof, from young donors are given; Stanford University spin out Alkahest is developing plasma derived products for the treatment of Parkinson's Disease (ClinicalTrials.gov; NCT03713957).

Challenges and considerations

In addition to therapeutic discovery there are other considerations and challenges, amongst these there will be the need to:

1. Identify and validate mechanisms and targets that impact on the core cellular processes that underly ageing and demonstrate through their modulation that these can slow, reduce, or even reverse, the development of morbidity and the accumulation of additional morbidities in an already morbid individual.
2. Develop molecules that can be administered to a potentially already compromised, aged, or frail individual, who, for example, may have impaired renal, hepatic or immune function.
3. Demonstrate through the existing regulatory and clinical development routes in randomised, blinded and controlled trials, that not only individual diseases benefit but that other associated diseases are slowed or prevented from occurring; for example, conducting trials in individuals with a background of another significant morbidity.
4. Demonstrate a robust health economic case that is attractive to investors and payers.

Investing in research

Of the 9-Hallmarks of Ageing (Lopez-Otin *et al*, 2013), and including processes that lead to these hallmarks, those receiving the greatest attention in terms of fundamental and clinical research include; telomere shortening, cell senescence, NAD metabolism, mitochondrial dysfunction, sirtuin biology and antioxidant therapies (Campisi *et al*, 2019; de Magalhaes *et al*, 2017).

Some of the rationale for the attention on these pathways and mechanisms is related to their linkage to the processes of cell ageing as demonstrated in preclinical models. The AMPK – mTORC1 pathways has been studied intensively due to the ability of mTORC1 inhibition (with rapamycin) to delay further ageing in already aged mice (Kaeberlein and Kennedy, 2009). Subsequently analogues of rapamycin or other modulators of the pathway have been investigated in both mechanistic preclinical and clinical studies. Rapamycin increases longevity and may even reverse age-related diseases in a variety of preclinical species (Walters and Cox, 2018; Kaeberlein and Galvan, 2019) and has been suggested for clinical study in Alzheimer's disease. Importantly from the perspective of drug discovery, there is also clinical evidence, gathered through retrospective analysis of trials and prospective studies. For example, metformin, an anti-diabetic drug used in the treatment of type 2 diabetes acts upstream of mTOR and retrospective analysis of clinical data, both from randomized trials and observational post-market surveillance, has been linked to positive outcomes in age-related conditions such as cancer and cardiovascular disease (Bannister *et al*, 2014; Campbell *et al*, 2017). Metformin's mechanism of action in type 2 diabetes centres on its activation of AMPK in skeletal muscle and adipose tissue but has also been shown to have multiple effects on cell signalling and behaviour beyond these tissues, including effects on inflammatory cytokines (Rena *et al*, 2017).

In order to further understand the extent of clinical research being undertaken in ageing a search of trials registered in ClinTrials.gov was undertaken (updated 28th Feb 2020). Using the term 'aging' (US English) as the primary search criteria the following trials were identified:

- **1752** studies with aging as one study aim and of these **1357** that were interventional
- **441** were interventional with term 'drug' (agent, medications, medicine); which includes numerous studying dietary, 'app-based' or other non-drug interventions
- **156** of these interventional trials were in early clinical trials Ph1, Ph2 of which 29 were recruiting; there were **82** trials recruiting across all phases
- Of the **441** listed interventional trials, only a small proportion were studying the behaviour of drug-like molecules (registered or novel) on diseases with the fundamental aim being to understand the relationship of the ageing process on disease progression and of these **13** trials had been registered to study the behaviour of metformin.

Clearly this search methodology is not comprehensive, however, it does indicate the relative lack of clinical studies testing either fundamental processes or new targets. This may be due in part to the regulatory constraints and challenges in establishing new

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Despite significant fundamental clinical research efforts, investment in R&D from pharma and through start-ups and spin outs has been relatively modest. Notable exceptions have been the approaches taken by companies such as Boston-based Life Biosciences and UK-based Juvenescence, who have both raised significant funds that they are investing in a portfolio of diverse innovations (see 'Life Biosciences joins the longevity race,' Financial Times3, 2019; 'Venture Financing Deals on the Rise in the Longevity Space' (Global Data Report, 2019 GDHC2222EI)). Other significant investments are being made such as those by disruptive pharma entrants Alphabet (Google-parent) and their anti-ageing company Calico, who have committed to a $1bn deal with AbbVie for age-related disease, and individual company financing rounds such as that in Samumed who, despite having no assets on the market, recently raised $438m for their Wnt-signalling focused discovery platform. Major pharma companies have tended to enter this space via collaboration, through asset divestment or licensing, or the formation of spin outs; for instance, ResTOR Bio, was formed in 2017 by Boston based PureTech, a portfolio biotech, to progress Novartis' mTORC1 inhibitors into the clinic4 following the observation that mTOR inhibition can improve immune cell function in elderly patients (Mannick *et al*, 2013). However, as might be expected when investigating novel biology, not all areas have progressed in the same way; research into sirtuin biology, for example, has been controversial. It was initially hampered by a lack of effect preclinically (Miller *et al*, 2011) and by potential artefacts in assay science (Schmidt, 2010). More recent reviews, however, suggest that the original findings linking sirtuins to ageing have been successfully reproduced, again strengthening their link to the mechanisms of ageing (Imai & Guarente, 2016). A phase 3 study of ResTOR Bio's mTOR1 inhibitor RTB101 (NCT04139915) failed to meet its primary end point of prevention of illness associated with respiratory tract infections (defined as clinically symptomatic respiratory illness) in adults ≥65 years of age. However, the company continues to investigate the mechanism in combination with other drugs in settings such as Parkinson's Disease. It also continues to pursue the goal of applying its gereoscience hypothesis in the clinic.

The economic challenge

The economic burden of multimorbidity on society is considerable and increasing (Wang *et al*, 2018; Pico *et al*, 2016; Zulman *et al*, 2015). Several studies have looked at the effectiveness of a variety of interventions and strategies designed to improve outcomes in patients with multimorbidity in primary care and community settings (Smith *et al*, 2012). NICE have published a Guideline seeking to optimise UK NHS care for adults with multimorbidity by reducing treatment burden (polypharmacy and multiple appointments) and unplanned care. However, the economic value of strategies for multimorbidity are generally not well quantified and remain conceptual.

To be persuasive with reimbursement agencies, the 'value proposition' for a new Product (a new therapeutic intervention for multimorbidity and diseases related to aging processes) will need to identify, measure and value all relevant cost and benefit parameters compared to the current polypharmacy standard-of-care treatment (SoC) options, for example quantifying changes in:

1. The 'performance gap', i.e., the difference between randomised controlled trial (RCT) evidence and real-world outcomes: Single indication RCTs generally exclude patients with co-morbidities, so treatment effects are formally less well-characterised for multimorbidity patients in routine clinical practice.
2. Polypharmacy (patients taking 10 to 20 medications) is common and may increase the risk of adverse events and tolerability issues resulting in sub-maximal doses, poor compliance or non-adherence, leading to sub-optimal real-world effectiveness.
3. Healthcare resource use related to multimorbidity and its treatment, such as the need for multiple appointments, the consequences of a change in risk of falls and accidents, and mitigation and management of treatment-related adverse events.
4. The role of primary and secondary prevention treatment effects: will the target population be different vs. SoC today? Will starting (& stopping) rules be developed? Where the product is initiated based on one morbidity can it leverage primary prevention value for other morbidities?
5. The overall healthcare budget impact: numbers of patients indicated for treatment, the expected duration of treatment and (net) prices as well as cost-offsets (healthcare resource use avoided).

Finally, development of the product must include a Global Pricing & Market Access (PMA) strategy that considers the different access channels and the fundamental evidence needs across the broad payer archetypes in different health care systems, such as comparative effectiveness, budget-impact and cost-effectiveness. The UK NICE process of health technology assessment is commonly used as a template for the development of these data sets as this allows adaptation to other territories. Commercial sales forecasts must be calibrated for the potential in each market, which is typically assessed through payer research and validation.

Clearly, a broad understanding of the economic opportunity and payer benefits in the appropriate territory must be performed before any new R&D programme is undertaken.

The economic burden of multimorbidity on society is **considerable and increasing.**

3. (https://www.ft.com/content/47c21416-15d0-11e9-a581-4ff78404524e)
4. (https://www.labiotech.eu/medical/novartis-puretech-anti-aging/)

3 | Aims

Drug discovery requires the interplay of technical and scientific disciplines and the alignment of these with clinical, commercial and regulatory considerations.

Here we focus on the core elements of drug discovery to deliver a clinic-ready molecule that can be used to test the disease hypothesis in patients.

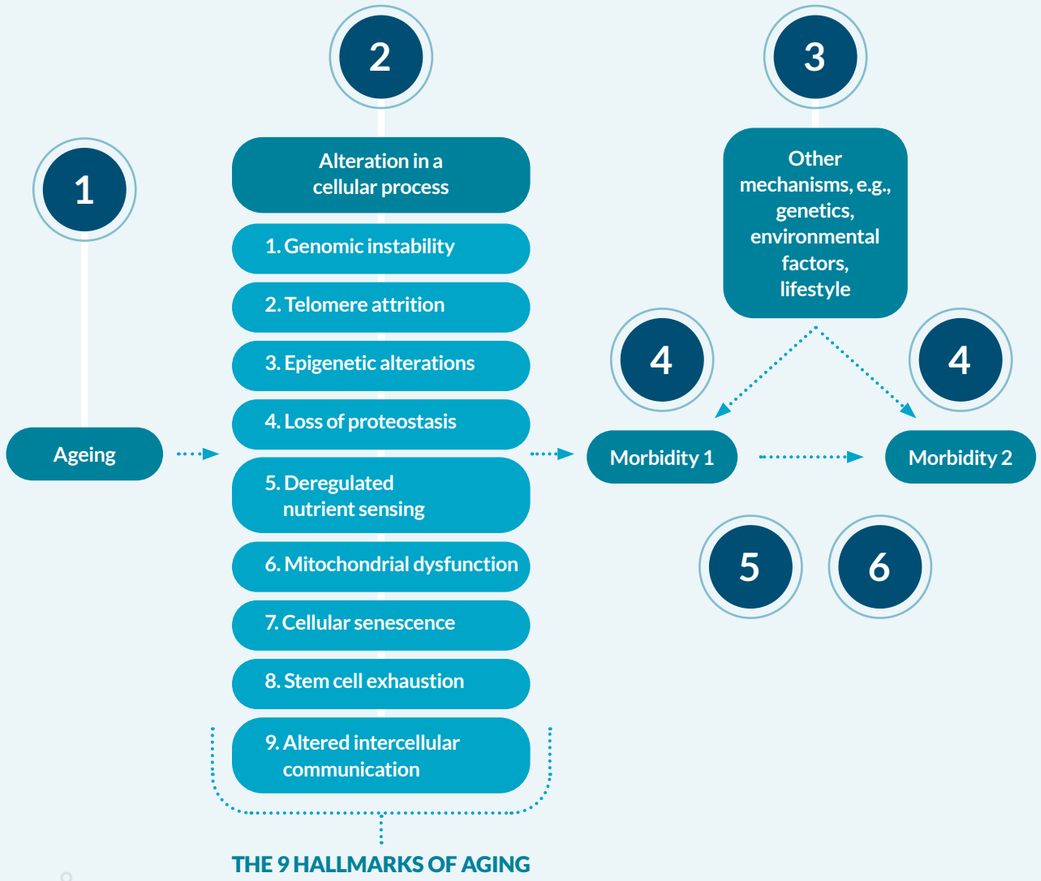


Figure 2.
The natural ageing process governed by the "9-Hallmarks of ageing" (Lopez-Otin *et al*, 2013) and its interplay with other mechanisms and environmental factors determines the development of morbidity and the chances of developing subsequent or multiple morbidity. Once an individual has developed a single disease or morbidity, an understanding of the drivers of these changes may allow for prediction of ensuing morbidity and hence lead to targeted interventions that might be able to prevent this.

Figure 2 attempts to describe how the accumulation of disease burden (single and then multiple morbidity) are a consequence of the interplay between the natural ageing process and intrinsic and extrinsic factors. Ageing is a fact of life and the nine-hall marks of ageing will proceed in an individual at rates governed by their genetic makeup and exposure to external circumstances. Such external factors may result in epigenetic and other adaptive or maladaptive changes, with the propensity for development of morbid conditions and susceptibility to reductions in physical capacity that can accelerate the accumulation of further morbidity; modulating the ageing process may slow or prevent the development of morbidity.

However, prophylactic treatment to slow ageing poses an economic and ethical issue for payers and patients, respectively (point 1). Ageing is not a disease but a natural process and designing a molecule to slow ageing could see patients taking medication for tens of years without clear clinical benefit. Research to date does not demonstrate a clear mechanistic and translatable link between the cellular processes of ageing and developing multimorbidity that could provide a testable hypothesis and demonstrate clinical benefit over current treatments for individual morbidities (point 2). As has been described, morbidities manifest due to alterations in other cellular and physiological processes (point 3) which poses a challenge to research as a clear differentiation between the impact of altering one of the hallmarks of ageing versus the well-established disease triggers needs to be demonstrated. When testing the hypothesis in the clinic (point 4) the identification of patient population is crucial. There are not currently any clinically validated biomarkers for the natural signs of ageing and patient stratification plans will need to be defined for the mechanism of focus. This has added complexity posed by that highlighted in 3. The identification of biomarkers of the ageing process and how these enable identification of at-risk patients and manifest as multimorbidities is clearly of great importance. Given the diversity in morbidities that occur in the aged population, designing the clinical trial and defining the clinical measure(s) of success requires a clear understanding of the mechanistic link between target, cellular process and disease biology (point 5); requiring points 2 and 3 to be addressed. There are however studies ongoing which characterise associated morbidities by clustering age-related diseases co-occurring at a higher rate than random chance.
There is some consensus that multimorbidities can fall into three main clusters: musculoskeletal, neuropsychiatric and cardiometabolic (Prados-Torres et. al, 2014). Validation of this consensus could support a future mechanism for stratifying patients for clinical trials measuring time to second morbidity. The time to onset of morbidity-1 and subsequent development of morbidity-2 can vary considerably, which impacts the design of the clinical trial (point 6). Lengthy clinical trials will require a high number of participants for statistical power and ultimately be very costly. Early biomarkers of success could reduce this, requiring points 2 and 4 to be addressed. A proposed list of biomarkers for geroscience-informed trials (Justice *et al*, 2018) include C-reactive protein (CRP) and IL-6 for inflammation; GDF15 for mitochondrial stress; IGF-1 and fasting insulin for nutrient signalling; cytostatin C for kidney function; NT-proBNP for cardiovascular health; and glycated HbA1c for metabolic ageing. Validation of these markers in a clinical setting could provide earlier indications of efficacy in anti-ageing trials.

The opportunities for developing successful therapeutic interventions to slow or halt the progression of multiple morbidities will, need to focus research on addressing challenges 2, 3 and 4. This will allow clear testable hypotheses that enable a focussed drug project screening strategy aligned to a clinical trial design that demonstrates patient benefit in a timely and cost-effective manner.

4 | The Roadmap

For the purposes of this report, we will focus on the theme of cellular senescence, as an example to illustrate the principals involved and as there has been considerable interest in the ablation of senescent cells as potential target mechanisms in the treatment of age-related diseases and multi-morbidities (Serrano, 2017).

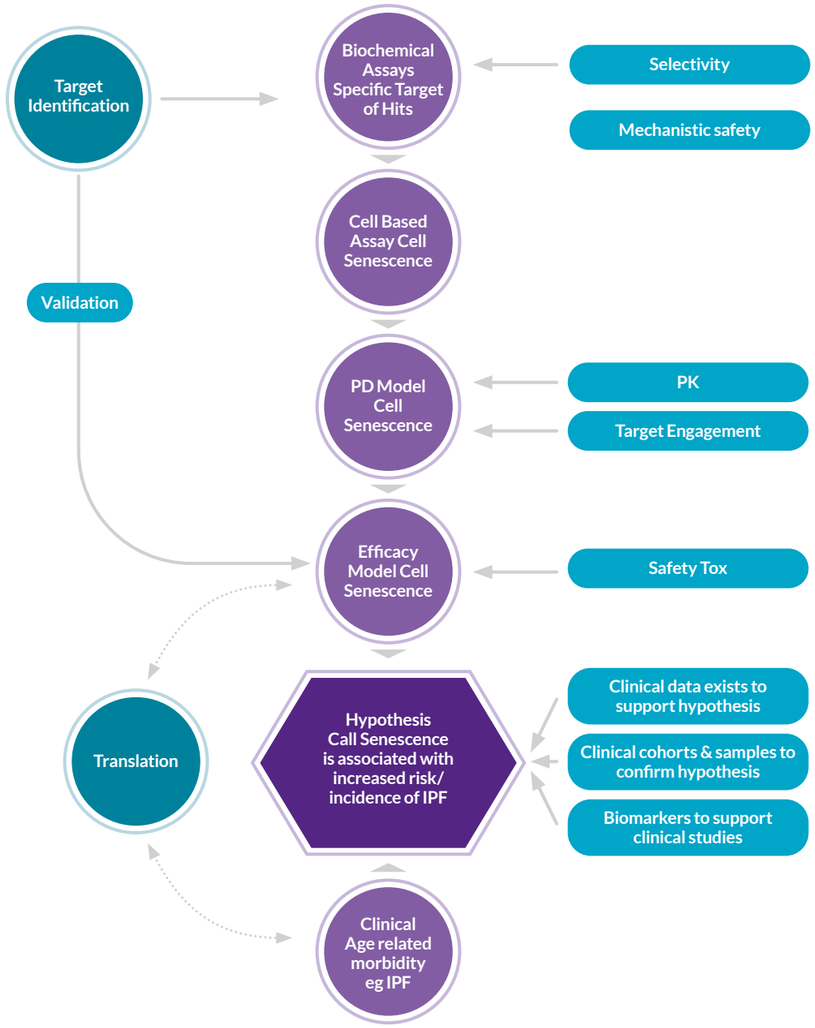


Figure 3.
A preclinical cascade detailing a preclinical drug discovery programme. Age related cell senescence is used as an example highlighting the risks in translation from the preclinical programme to the clinical Proof of Concept studies.

Somatic mammalian cells have a finite propensity for cell division, after which they enter an irreversible growth arrest termed cellular senescence. Cellular senescence is a state of stable replicative arrest induced by telomere attrition, oxidative stress, DNA damage and proteome instability.

A typical drug discovery programme (as shown above in fig 3), is discussed in the sections below and the report uses cell senescence, in the context of recent studies in IPF (Justice *et al*, 2019), to illustrate an example of drug discovery in an age-related disease in a series of Case Studies.

Following initial target validation implicating a target or mechanism to the process of cell senescence, a drug discovery programme can be initiated resulting in the generation of optimised molecules with drug-like properties. Assays and models are available to test compounds modulating cell senescence, however, in the example of IPF, preclinical models of the disease driven by mechanisms of cell senescence have not proven translation to the clinic. There is therefore a risk that compounds showing efficacy preclinically may not demonstrate a PoC when tested in patients with IPF. These risks can be mitigated where clinical data exists to support the hypothesis, clinical cohorts and samples are available to confirm the hypothesis and a clear biomarker strategy is in place to monitor effects of the drug in line with the hypothesis.

The Target

While multiple mechanisms of ageing have been proposed a single target, which has the means of modulating such mechanisms will need to be identified and validated for a drug discovery programme to commence.

The majority of Phase II clinical trials fail due to efficacy, where, in most cases the project teams have been unable to demonstrate a clear linkage of the target to the disease. Therefore, the importance of selecting the right target is paramount (Cook *et al*; 2014).

Traditional pharmacological targeting of the ageing process does not lack a plethora of potential targets and basic mechanisms within the so-called 'Hallmarks of Ageing' (Lopez-Otin *et al*, 2013), however, there is still a significant need for fundamental research linking such pathways to multi-morbid patients and conditions to allow drug discovery innovators to identify the value in investing in R&D programmes.

Target Identification

Link to Disease

A clear understanding of the relationship of the target and mechanism of ageing being intervened with and how this relates to disease and the subsequently results in multiple morbidities is crucial, in essence demonstrating the strength of the linkage between the underlying pathology of ageing and the target of interest.

Target expression

Is the target (including ligands, modulators or substrates of the target) expressed in the tissue of interest and importantly localised in areas of disease pathology?

In some instances, the levels of target may be differentially expressed in diseased tissue relative to healthy tissue, but this may not always be the case. Bioinformatics approaches which focus on pathway analysis may be able to highlight multiple members of a pathway differentially expressed in diseased tissue suggesting that pathways involvement.

The relevant tissue for the target patient population will need to be defined. In the context of ageing, senescent cells accumulate in tissues and are localised at sites of pathogenesis in many age-related diseases (Kirkland, 2017). Markers of cell senescence such as p16, p21 and SA-b-gal have been observed in multiple tissues and also accumulate in an age dependent manner. However, a better understanding of which tissues or cell types that become senescent in the multiple age-related pathologies is required. Senescence biomarkers colocalised with cell-type specific markers ensure that the drug target and mechanism is active in the cell types relevant to the appropriate ageing pathology and / or the intended age-related disease or diseases, or, in the case of the ideal preventative aims, drivers of unsuccessful ageing.

Such correlations do not prove "cause" or "effect"; modulation of cell senescence and its effects in a series of target validation experiments will be required to confirm the hypothesis and build confidence.

Genetic linkage

Do human gene mutations link the target to a disease phenotype? In a review of AstraZeneca projects, drug targets showing genetic linkage to the disease were less likely to fail in the clinic due to lack of efficacy (Cook *et al*, 2014).

To provide evidence of a genetic linkage of target and disease in an ageing population we need to consider that the genetics of lifespan are highly population specific and genetic risk factors can be age specific, but certainly there is evidence of a close correlation between genetics of longevity and genetics of age-related diseases (Giuliani *et al*, 2018).

Identification of genetic risk factors, associated with polymorphisms or mutations in the target gene, is challenging in aged populations where somatic mutations may be implicated. Somatic mutations that occur over a lifespan may have functional consequences in certain cells and tissues of the body, but the tools that link each genomic mutation to a possible functional consequence are not there yet (Zhang *et al*, 2018).

Is there clinical precedent (PoC in man) for the target or mechanism?

For drug discovery programmes aiming for a Best in Class therapy, it may be possible to benefit from pre-existing clinical Proof of Concept studies to support the hypothesis; consequently, risks resulting from a lack of efficacy are minimised.

But for programmes aimed at novel mechanisms, evidence from published clinical Proof of Concept studies is unlikely. However, in some cases evidence can be gained from modulation of the mechanism or even the target and the serendipitous observations in patients caused by drugs for alternative diseases. For example, meta-analyses of the effects of the anti-diabetic drug metformin, have resulted in significant clinical and preclinical work to understand its mechanism of action in ageing and role in preventing multimorbidity (see Glossmann and Lutz, 2019, for review). Bisphosphonates prescribed to elderly patients with osteoporosis have also been associated with increased longevity in this population (Lyles *et al*, 2007). There has however been conflicting data in this area and a recent opinion is that the data linking these drugs to longevity is confounding (Bergman *et al*, 2019)

While processes and mechanisms have been identified in the clinic which are associated with ageing, it is not certain whether their pharmacological modulation in a patient population will positively impact the ageing processes, subsequent health span and age-related morbidities.

Drugs such as dasatinib, an inhibitor of BCR/Abl and src-family tyrosine kinases used to treat chronic or acute myeloid leukaemia and quercetin, a plant-derived flavanol with antioxidant properties, have been shown to have senolytic properties when tested preclinically. When the combination was tested in patients with IPF (Justice *et al*, 2019), although beneficial effects in clinical scores were seen, exploratory measures taken to determine the impact on cell senescence were inconclusive, hence the role of senescent cell ablation in a patient setting remains to be fully demonstrated (see box below).

CASE STUDY

There is an elevated abundance of senescence biomarkers, p16, p21 and senescence-associated β-galactosidase activity (SA-β-gal), observed in human IPF lung tissue with p16 expression increasing with disease severity (Lomas *et al*, 2012; Schafer *et al*, 2017).

To date there are no PoC studies in patients for senolytics positively impacting IPF disease progression. However pilot studies with dasatinib plus quercetin suggest improvement in functional endpoints (6-minute walk test; chair stands time), but pulmonary function and reported health measures were unchanged. Exploratory measures of circulating SASP were inconclusive.

This was a small pilot study where the optimal human dose was undetermined, the numbers of patients (n=14) was not sufficiently powered and the duration of the study (21 days) was of insufficient length to determine functional changes resulting from effects on cell senescence, if indeed changes in cell senescence had been achieved (Justice *et al*, 2019).

Target Validation

A hypothesis built around target linkage to human disease or an ageing pathology needs to be confirmed through a series of experiments which build confidence that modulation of the target will lead to efficacy in the clinic.

Ultimately target validation will be carried out with the candidate compound but in the initial stages, tools which can be used to modulate the target pathway provide evidence to support the drug discovery programme (Fig 3).

Knockouts, knockdowns and the impact on ageing of a single pathway.

Gene knockout or knockdown of a single target can provide evidence of target role in a particular pathway or mechanism. It is important, wherever feasible, to carry out the experiments in the relevant cell type for the intended disease indication as pathways and mechanisms may not behave similarly in model systems.

Indeed, siRNA targeting Bcl-xl reduces the viability of senescent endothelial cells but is not senolytic in primary preadipocytes (Zhu *et al*, 2015), suggesting different mechanisms may be involved in cell senescence between these cell types.

It should be noted that target validation using a gene knockout or knockdown approach is based on target ablation rather than target blockade and findings should therefore be confirmed with the compound as soon as a molecule is available.

Redundancy from multiple mechanisms involved in cell senescence may be an issue where a single target is modulated. Together with the potential multiple mechanisms involved in ageing cf., the nine hallmarks of ageing (Lopez-Otin *et al*, 2013), then redundancy could be expected to be a significant issue. Human genetic data and animal gene knockout data can increase confidence in a single target, for example individual mechanisms are able to artificially age experimental animals. However, to be clinically relevant a thorough understanding of the role of the various pathways and targets will be required; will multiple pathways need to be inhibited to prevent unhealthy ageing, or do patients only present with one or two?

A number of putative target mechanisms implicated in senescence have been proposed. For some senescent cell types, candidate senolytic agents that act on multiple pro survival targets could be more effective than agents that act through a single target; the particular combination of target proteins that drugs act on is critical (Zhu *et al*, 2015).

However, modulating multiple targets or using combinations of drugs may be required to avoid redundancy, which adds significant complexity to drug discovery and development due to the need for parallel safety and efficacy studies for each drug as well as the combination.

Tractability

The majority of successful marketed drugs target a relatively conserved group of targets classes, such as kinases, membrane proteins and ion channels. This is typically achieved with small molecules that have advantages of scalability and minimal cost of goods; the latter being important for medications that may be taken frequently and for prolonged periods.

Although small molecules are often typically preferred for these reasons, it may not always be possible depending on the target and its accessibility; non-small molecules such as antibodies may be feasible however, patient compliance and cost of goods may negatively impact the use of injected or parenteral drugs. Under such circumstances, alternative, possibly more addressable targets within the pathway or mechanism may be sought.

Crossover to animal species for the mechanism as well as the molecular target, is crucial as preclinical efficacy and toxicity testing will typically be carried out in rodent and non-rodent species, it is therefore essential to understand the degree of cross over, homology or conservation of function of the target between man and preclinical species. In the first instance it is possible to confirm existence of orthologues using gene/ protein sequence data. However, structural information will be required to predict sequence identity at drug binding sites or, alternatively, activity of the compounds in biochemical assays against target protein from rodent species will tested as preclinical cell based assays can be useful to confirm target engagement and target/pathway activation prior to going *in vivo*.

The feasibility of drug discovery is dependent on the availability of assays for screening and access to molecules or reagents which can be used as tools for investigating the hypothesis.

Typical compound generation strategies can involve high throughput screens requiring biochemical assays or cell lines expressing the recombinant target. Selectivity is addressed with assays developed for target family members particularly where there is a safety implication for non-selective compounds.

Cell-based assays particularly those involving primary or complex cell models can be designed to screen for compounds that modulate the mechanisms of ageing. These reagents should reflect the appropriate cellular environment of the target observed in the disease pathology. Examples in cell senescence include:

- Human WI-38 fibroblasts, are a cell line which has been used to study replicative and stress-induced premature senescence in culture, associated with accumulation of p53 and $p16^{INK4a}$ (Serrano *et al*, 1997; Chang *et al*, 2016)
- Human primary cells relevant to the target disease, as this will provide evidence where mechanisms of senescence may be cell specific
- The use of techniques such as radiation, or high oxygen tension (20%) to cause a senescent phenotype
- The ability to measure effects on SASP factor expression, SA-β-gal activity by Flow Cytometry.

Disease Models

In order to translate to man, it is vital that models selected to test efficacy should resemble the human pathology as closely as possible and also ensure the disease state is driven by the mechanism being tested.

Models exist for complex diseases such as osteo-arthritis, cardiovascular disease, diabetes and some CNS disorders, but often the drivers of the disease pathology do not stem from an ageing process. Indeed, preclinical injury-induced arthritis or chemically induced liver and lung disease reflect human disease pathology in certain respects but would be inappropriate in this context. Models for age related diseases are in existence, with varying degrees of success in their ability to predict efficacy in the clinic (Koks *et al*, 2016). Where there are disease models resulting from relevant ageing processes, do these animals develop additional pathologies as a consequence of the initial insult or will therapies aimed at multi morbidities need to be tested in multiple disease models?

Cell senescence has been implicated in the pathogenesis of disease endpoints in various models of age-related diseases. Approaches which delay senescent cell accumulation have delayed the onset or alleviated conditions resulting from ageing in animal models. For example, in BubR1 progeroid mice, which exhibit many of the features of accelerated ageing, targeted removal of $p16^{Ink4a}$-expressing senescent cells delayed the accumulation of age-related phenotypes, such as sarcopenia, and improved exercise duration, compared to untreated animals (Baker *et al*, 2012).

Similarly, clearance of $p16^{InK4a}$-positive cells in normal-ageing mice extended their median lifespan, delayed tumorigenesis, improved health span indices such as heart and kidney function and delayed age-related decline in exploratory behaviour (Baker *et al*, 2016).

However, mice develop only some pathologies resembling human ageing. Models developed with transgenic or genome-editing approaches are suitable for certain diseases or possibly ageing pathologies, but many chronic disease states in humans are multifactorial. To model these diseases, animals with single gene mutations may acquire superficially similar syndromes, but the mechanisms which lead to this may not reflect the drivers of disease in man (Mitchell *et al*, 2015).

Relating study endpoints in the clinic to those that can be measured in disease and ageing models are clearly pivotal to successful translation (see case study).

CASE STUDY

Cell senescence is implicated in the pathogenesis of IPF.

However, the question of whether there is any role for cell senescence in the development of the disease in a preclinical model of IPF and whether there is a suitable efficacy model to screen compounds targeting cell senescence remains.

The standard model for IPF is the bleomycin-driven rodent model of pulmonary fibrosis. Bleomycin lung injury induces a molecular signature of senescence similar to human IPF (Schafer *et al*, 2017; Aoshiba *et al*, 2013). Targeted removal of senescent cells in a bleomycin induced pulmonary fibrosis model improves lung function but does not affect fibrosis. These benefits are replicated with the combination of senolytic drugs dasatinib and quercetin (Schafer *et al*, 2017).

Hence a target which modulates cell senescence preclinically may be expected to affect bleomycin induced lung function, but additional data is required to show whether drugs modulating cell senescence are able to modulate the fibrotic endpoints. Confounding its translatability, the bleomycin model of pulmonary fibrosis involves an inflammatory drive which is not associated with IPF in patients, and cells which express markers of senescence are also characterised by upregulation of cytokines and markers of inflammation.

The lack of effect on lung fibrosis, the proposed linkage of senescence with inflammatory cell types and the previous poor track record of the bleomycin induced pulmonary fibrosis model, suggest a high risk in translating efficacy seen preclinically to a Proof of Concept in the clinic.

There is therefore a lack of a well characterised efficacy model for targets which modulate cell senescence in IPF, in summary:

- There is just one model, bleomycin-induced pulmonary fibrosis, which does not have a strong track record in translation to the clinic
- Cell senescence is associated with inflammatory cell types in the rodent model with conflicting evidence of their involvement in human disease pathogenesis
- Endpoint measures of fibrosis have not been achieved and so development of alternative measures and biomarkers which translate to the clinic should be considered.

Finally, regulatory bodies, such as the FDA and EMA, have requirements for the use of certain animal models that cover the quality and safety of chemical compounds, pharmaceuticals, and biological products. While these agencies offer specific recommendations for the design of preclinical safety studies, there are no regulatory guidelines offering standards for the design and reporting of preclinical efficacy studies, hence comparison between models may be difficult.

5 | The Drug

An effective and successful drug requires a number of essential properties. Primarily, the drug must be efficacious and drive a significant positive therapeutic benefit for the patient. However, this needs to be balanced with low adverse side effects to enable the drug to be tolerated and not pose risk to human health and well-being.

The drug must be relatively easy to administer or have a simple dosing regimen as this, along with low side effects, increases the chances of patient compliance and ensures the efficacy is maintained and providing maximal benefit to the patient. Finally, the drug must be relatively easy to manufacture at a reasonable cost and provide significant benefit over standard of care to enable a clear market position.

Target Engagement

The importance of confirming that the drug engages with the target. Failures of efficacy may not necessarily be due to a failure of target disease linkage but indeed that the compound has not penetrated the target cell or engaged with the target molecule.

With respect to therapies proposed for cell senescence, Zhu *et al* (2015) reported that imatinib is not senolytic in certain cell types despite resembling dasatinib structurally, targeting many of the same tyrosine kinases, and having similar clinical indications. Ensuring target engagement in the cell types important for disease pathogenesis will be essential for onward translation.

The Patient and unmet need

Successful drug discovery campaigns require a clear benefit for the intended patient population over and above the current standard of care and a strong scientific rationale for involvement of the targeted mechanism in patients, which is the context of targeting age related multimorbid conditions or individual diseases in a multi morbid patient.

In the future, this may extend to the individual hallmarks of disease, which exist prior to patients presenting with multi morbid conditions, using a targeted biomarker strategy. Current standards of care include therapies targeting age related diseases such as CV disease, arthritis and diabetes, but there are no therapies which target ageing per se, and the therapeutic environment indicates a lack of clinical studies testing the fundamental processes of ageing (ClinicalTrials.gov). This may change as the regulatory landscape evolves or validated early biomarkers are uncovered.

As has been described above, in selecting the disease indication and patient populations based on unmet need and commercial value, it is important that the scientific rationale and target linkage to disease are not compromised.

Patient Stratification

Selection of specific patient populations for both clinical trials and eventual treatment is key to first testing the clinical hypothesis and for successful drug development.

The hallmarks of ageing manifest during normal ageing, so stratified biomarkers to identify individuals with an increased risk of developing multi morbidities and their associated mechanisms will need to be addressed (Lara *et al*, 2015). Where multiple mechanisms are implicated in the ageing process, it will be essential to identify those patients where the mechanism being tested is driving the disease or ageing pathology. Mixed patient populations with uncertain background pathologies will significantly reduce the chances of demonstrating efficacy, or a positive signal will be lost within the noise of the total population due to inadequate powering of the trial ultimately leading to failed therapeutic response in the clinic.

To overcome this and aid the right choice of patient, a biomarker strategy must be included in the drug discovery programme which should ideally be initiated at an early stage.

Stratified biomarkers to identify individuals with an increased risk of developing multi morbidities and their associated mechanisms will need to be addressed

Clinical trial feasibility

New drug candidates must pass through clinical trials to gain regulatory approval with the current regulatory framework largely addressing disease treatment and corresponding efficacy and safety data being demonstrated in the patient group prior to regulatory approval (Fleming, 2020).

Targeting the ageing process itself however, although it may prevent disease arising will undoubtedly require adjustments to this regulatory landscape. For therapies aimed at an aged population, patients may present with age-related morbidities and recruitment will be under the care of a clinician. However, for therapeutics aimed at the fundamental processes of ageing, methods of recruiting subjects will need to be considered. Clinical trial outcomes need to be achievable and measurable in a reasonable timeframe and in a multimorbid patient may pose challenges that may result in lengthy studies that are expensive to run and have consequences for retention of subjects.

Clinical efficacy is traditionally evaluated in relation to a specific disease; however, it is possible that future medicines may delay or prevent the onset of morbidity unrelated to any specific disease, and new strategies for evaluating efficacy will undoubtedly be required (Fleming, 2019). The validation of alternatives to traditional clinical trial design is an area of active concern. For example, the TAME trial in the US has primary endpoints which reflect the rate of progression to secondary/new morbidities in contrast to direct impact on specific disease states (Barzilai, *et al*, 2016); while the current COVID-19 pandemic has demonstrated that interventions targeting the processes of ageing, for instance the removal of senescent cells from the lung may be of benefit and immune-supportive, (Akbar and Gilroy, 2020); the urgent need for solutions may result in regulatory shifts.

As noted, patient stratification strategies for ageing-specific clinical trials, may have outcomes not directly linked to a specific disease, and will rely on biomarker approaches to monitoring changes in ageing biology, such as those recently reviewed (Ferrucci *et al*, 2020). These same biomarkers impact clinical trial design, so the continued refinement of meaningful, accurate ageing metrics will support both innovative trial design and the identification and monitoring of trial cohorts.

Ageing is not currently designated as a disease and brings unique challenges in presenting appropriate clinical endpoints for candidate interventions. To date, most clinical studies of ageing-biology have monitored a disease-specific endpoint; notable examples including the study of dasatinib and quercetin in IPF (Justice *et al*, 2018) and the resTORbio trial for RTB101, an mTOR inhibitor (study NCT02874989 (ClinicalTrials.gov)). This approach has allowed studies to proceed within the current clinical trial framework, potentially enabling off label use, while alternative frameworks, measuring health span (delayed multimorbidity and functional decline) or resilience (response to or recovery from an acute health stress) are being considered (Barzilai *et al*, 2016; Konopka and Miller, 2019). Innovative developments also short (3-6 month) clinical trials evaluating response to adverse events, such as those being designed and evaluated at the University of Sheffield's Healthy Lifespan Institute (Longevity.Tech, 2020).

CASE STUDY

Patient stratification is required for successful clinical trial and treatment strategies. For instance, stratification based on biomarkers to identify those patients where the mechanism being tested is driving the disease e.g., cell senescence. Senescent cells have elevated levels of senescence-associated β-galactosidase (SA-β-gal) activity, which remains the gold standard to identify senescent cells in culture and tissue samples (Dimri *et al*, 1995; Debacq-Chainiaux *et al*, 2009). However, this requires active enzymatic SA-β-gal activity and hence is limited in some tissue samples. As senescent cells are terminally growth arrested, cell cycle regulators such as p16INK4a, p21CIP1 and p53 are commonly employed to detect senescent cells. p16 and γH2AX are markers of cellular senescence and DNA-damage, respectively. They have been used to identify senescent cells in vitro, in tissues in vivo (Dungan *et al*, 2017) and elevated levels in IPF lung, with p16 expression increasing with disease severity.

In a pilot study of senolytics in IPF patients, a lack of effect on a biomarker, SASP, was reported. Were the patients selected for inclusion in the trial based on biomarkers of cell senescence?

ADME & pharmacokinetics

Ageing has a significant effect on the responses to pharmacological interventions. Age-related changes in hepatic and renal functions significantly affect the absorption, distribution, metabolism, and excretion (ADME) of drugs and changes in bioavailability may be secondary to changes in absorption or gut wall and hepatic metabolism.

Ageing is associated with slowing of gastric emptying, decreased peristalsis, and reduced colonic transit which influence important pharmacokinetic parameters such as the time to achieve the maximal blood concentration and the concentration itself, T_{max} and C_{max}, respectively. Other age-related changes include impairment of the active transport of some nutrients and reductions in gastrointestinal blood flow which adversely affects drug absorption. Decreases in serum albumin may increases the unbound concentrations of many drugs, while changes such as an increase in body fat and a decrease in body water may influence volumes of distribution of drugs. Such changes in body composition can lead to an increased concentration of water-soluble drugs and a prolonged elimination of lipid soluble drugs (McLean and Le Couteur, 2004)

Any new orally dosed drug molecule must overcome many challenges within the body before it reaches the target of interest to initiate therapeutic action, which may be compounded by some of the changes in physiology associated with ageing noted. A clear understanding of the ADME features required to achieve drug-like properties in the desired, aged or multi-morbid patient population is therefore vital. These govern the pharmacokinetic profile, i.e., the measure of the drug concentration, usually within the blood, of a molecule over time in relation to dose and ensuring the right amount of drug is present to retain efficacy while balancing potential adverse events and safety.

Two critical pharmacokinetic differences between younger and older patients have been established and relate to (1) impairment of excretory (renal or hepatic) function and (2) drug-drug interactions. Specific regulatory guidance, such as ICHE7, have been developed to support use of new drugs that will have significant use in elderly patients, either because the disease is typically found in older individuals (e.g. Alzheimer's) or due to the population to be treated to include a substantial number of geriatric patients (e.g. hypertension). The main components of this guideline focus on the importance of assessing age-related pharmacokinetic profiles to influence dose adjustments and suggests generating data in the elderly and in patients with functional excretory impairment. This guideline therefore is key to refer to for researchers developing therapies within this population as it will influence their clinical trial design.

The elderly are more likely to be using concomitant medications. This poses a significant risk of drug-drug interactions, whereby one drug can alter the pharmacokinetics of another, or the drugs could either compete and reduce the effectiveness or combine to accentuate properties leading to alterations in effect and the potential for increased adverse events. It has been estimated that over a third of elderly patients regularly use 5+ medications (Hajjar *et al*, 2007), increasing the risk of significant drug-drug interactions.

There are well established assays and models to evaluate drug metabolism and excretion mechanisms of new chemical entities, which include Cytochrome P450 (CYP450) induction, CYP450 inhibition, metabolite profiling in hepatocytes, hepatic and renal transporter substrate inhibition and phase II metabolism; data generated across these models aids an understanding of the risk of drug-drug-interactions and renal/hepatic toxicity. In addition to conducting these studies, it would be advised to evaluate the potential for renal excretion and avoid this in new chemical entities for this patient population.

Safety and Regulatory

Prior to a molecule being tested in man, it must be assessed to understand if it has the potential for causing serious harm and adverse events; this is of particular importance if the drug is intended to be taken for long periods of time or in at risk patient groups such as those with multiple morbidities of the elderly.

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), have developed a set of guidelines to standardise across the industry the scientific requirements and study designs required for the data necessary for the registration of new drugs for human use. These guidelines are accepted and adhered to by regulatory authorities (e.g. FDA, EMEA) and pharmaceutical companies worldwide. From a safety perspective there are 12 guidelines that cover the pre-clinical and clinical requirements for assessing the risk of a new drug for human use; an overview of these guidelines and more detail can be found at https://www.ich.org/page/safety-guidelines

Overall, in the aged, aged single morbidity or aged multimorbid population, any novel therapies need to have an acceptable safety profile. The following section we will draw out some of the key points from a safety perspective that need to be considered during the discovery and development phase which can influence the requirements of the preclinical safety package and study design.

Mechanistic Safety Evaluation

At the very early stages of target selection, a key factor in the decision making, along with promising efficacy, is an in-depth evaluation of the other roles of the target, which could give rise to potentially unintended adverse consequences.

Ideally this is conducted at project initiation as it will enable the development of a risk evaluation and mitigation strategy, allow front loading of investigative studies to characterize the toxicities in a timely manner, supporting the overall decision making for success and progression of the project. Identified target-mediated toxicities can be addressed using bespoke assays depending on the risk in question, or by including observations and readouts in efficacy studies and early in vivo safety studies.

Toxicology studies

Preclinical safety toxicology studies are generally conducted in two different species and must provide details on dose and toxicity levels to define a therapeutic margin between expected efficacy and the safety finding.

Integrating data from each of the preclinical safety study types will influence the drugs acceptability to be tested in man. Data may influence inclusion/exclusion criteria, capping the doses levels that can be used clinically, or influence monitoring of specific endpoints if there is a risk that, although not deemed a clear no-go decision, they may require wider monitoring for patient safety, compliance or interference with efficacy.

The primary goal of repeated dose toxicity studies is to characterise the toxicological profile of the test compound following repeated administration. This includes identification of potential target organs of toxicity and exposure/response relationships, as well as the potential reversibility of toxic effects. The information generated should be part of the safety assessment to support the conduct of clinical trials and the eventual approval of a marketing authorisation.

Repeat dose toxicity studies are required to be evaluated in two different species, which will normally include a rodent and non-rodent animal. Three important factors that can influence the selection of the species and must be taken into consideration in light of the project knowledge are:

1. Response to primary pharmacodynamic measurement. To ensure any toxicities related to primary pharmacodynamics are assessed, the species of choice must express the orthologue of the primary target of interest. Any differences in target structure, biology or expression need to be understood to influence the species selection and provide confidence that data can be translated to man.

2. Pharmacokinetics similar to those in man. Differences in drug absorption, distribution, metabolism and extraction are clearly understood and studies are designed to ensure drug exposure is equal and higher to that expected in man, and through a similar route of administration. If drug exposure or desired dosing route cannot be achieved, then an alternative species may be needed, or specific bridging studies conducted to address the gaps in order to de-risk for the clinic.

3. Biotransformation similar to that in man. Exposure to the main human metabolite(s) should be ensured and if this cannot be achieved in toxicity studies with the parent compound, studies with the metabolite(s) should be considered. When the product is administered as a pro-drug, its conversion to the active substance should be demonstrated in the species under study.

The length of the dosing period of repeat dose toxicity studies is related to the duration, therapeutic indication and scope of the clinical trial proposed. In general, the duration of the animal toxicity studies should be equal to or exceed the duration of the human clinical trial up to the maximum duration recommended. For clinical studies up to 6 months, the preclinical study would match the duration of the trial, for studies >6 months the maximal preclinical studies would be 6 months in rodent and 9 months in non-rodent species as a starting point. In specific circumstances where significant therapeutic gain has been shown, trials can be extended beyond the duration of supportive repeated-dose toxicity studies on a case-by-case basis dependent on regulatory approval. Given many of proposed therapies may need to be taken for a long period of time in the aged and multimorbid population, this could add to lengthy preclinical studies with associated costs.

Immunotoxicology studies

It is well established that a consequence of ageing is a decline in immune function. Elderly individuals tend to have reduced B-cell and T-cell production within the bone marrow and thymus, along with decreased function of lymphocytes.

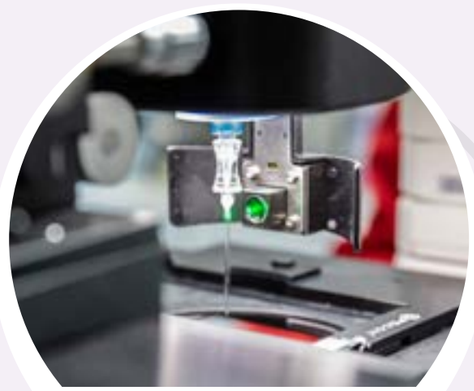
Although the elderly are not immunodeficient per se, immune changes mean they do not respond as efficiently or strongly when challenged and are much more vulnerable (Wilson *et al*, 2019; Yao *et al*, 2011). In addition, as described above, this patient population are likely to be taking a number of concomitant medications, some of which may directly or indirectly affect the immune system.

A key consideration for development of drugs in this space is therefore to ensure any target or pathway modulated, where possible, avoids deleterious action on components of the immune system. The ICHS8 guidelines provide guidance on study design and additional in vitro assays that can be used to evaluate effects on the immune system. It may be advantageous to front load much earlier in the discovery process, assessments of the effects of new modalities on immune function.

Safety Pharmacology Studies

Many of the morbidities seen in later life affect the function of vital organs such as the heart, lungs and brain.

A clear understanding of any drug-induced detriment to these organ functions by an investigational drug is essential and required for any new pharmaceutical but is even more critical if targeting an elderly, multimorbid population where these systems may be already compromised; ICHS7A/B guidelines, provide guidance on the battery of models and assays that can be applied to evaluate effects on each system. There are numerous assays that can be used to monitor critical effects, and which can enable very early screening options to flag risks to these systems in emerging chemistry. Many of the *in vivo* safety pharmacology endpoints can be utilised alongside in an investigative capacity either in efficacy studies, whereby the investigation will also take into account the underlying physiological deficiencies or combined in toxicological studies. Given the importance of identifying risks early, as for other risk mitigating studies, it would be advantageous to front appropriate safety pharmacology assessments.



Genotoxicity Studies

A number of approaches which prevent the accumulation of senescent cells in ageing tissues are associated with reduced age related diseases and multimorbidities, however, strategies to achieve this that involve blocking $p16^{INK4a}$ and p53, or activating telomerase to extend the proliferative capacity of cells, may inevitably lead to an increased cancer risk.

These targeted mechanisms, along with those that work in similar pathways altering cell cycle progression, effecting DNA damage response and chromosomal separation have a higher propensity to drive a positive genotoxic response in the assays used for safety detection, which would ultimately be inherent within a chemical series due to the primary target. Data from genotoxicity assays requires careful interpretation to balance risk with benefit, particularly in a more chronic dose setting. Safer approaches may be to selectively eliminate senescent cells from tissues or modulate their function, particularly via the SASP (Wang *et al*, 2018).

Considerations for clinical trial design

Senescent cells, like cancer cells, are resistant to apoptosis. Many of the senolytics cited in the literature are anti-apoptotic therapies used for oncology; in order to consider them or drugs targeting the same mechanisms for repurposing for chronic diseases in ageing, a clear understanding of the toxicities associated with these drugs is required.

In the example of dasatinib and quercetin that are being explored as senolytic treatments, dasatinib is currently used in the clinic for the treatment of chronic myeloid leukaemia, and at its standard oral dose (100mg/day) there a number of adverse events that would be problematic in an elderly population, such as anaemia, neutropenia, increased infection risk, cardiovascular dysfunction and changes in electrolyte balance (dasatinib BNF; Keskin *et al*, 2016). Quercetin, a natural product flavonoid used for its antioxidant and anti-inflammatory properties, has reported adverse events such as nausea and vomiting, with some reports of it accentuating kidney damage at high doses (Andres *et al*, 2018).

In the recent study in IPF patients, previously referred to in this report, Justice *et al* (2019) used a combination of dasatinib and quercetin to investigate its potential as a senolytic. This open-label, single arm study, conducted in 14 patients, utilised doses of 100mg/day dasatinib plus 1250mg/day quercetin but importantly, given the noted concerns for adverse events, drugs were given as an intermittent schedule with 3 consecutive days, followed by 4 days off, over a total of 3 weeks. The known safety liabilities of these drugs, in particular those for Dasatininb (safety data for Dasatinib / Sprycell are available from the FDA website; https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/021986s7s8lbl.pdf) some of which were mentioned above, were used to determine the inclusion/exclusion criteria outlined in Appendix 2 and the intermittent dosing strategy used. Reported adverse events of this trial were generally acceptable and largely consistent with placebo participants of randomized controlled trials in IPF, although it is difficult to conclude given this was a single arm study. Events of oedema, pleural effusion and dyspnoea were reported, and careful monitoring would be required in future trials. Consideration also needs to be given in regard to the longer duration of treatment which may be required for this aged, multimorbid population and which could significantly impact the access to a patient cohort in a multimorbid population.

6 | Summary: putting it together:
developing a platform of evidence to the clinic

Drug discovery projects are informed by a precise understanding of the needs of the patient and the market opportunity and balanced by the challenge and expense of developing a solution to those needs; these are guided by a target product profile and the evidence base that will be required to fulfil it.

The platform of evidence is the critical path, or line of sight, from the target biology to clinical application, which outlines the key decision-making data required.

Stage	Main studies required	Reason data required
Discovery	• Target validation: established platform of evidence for target • Lead molecule identification and Optimisation • Define biomarkers	• Strong link between target and disease • Generate lead matter • Biomarker discovery
Pre-clin	• Develop platform of evidence for target relevance, differentiation and target safety • Preclinical safety & toxicology; ADMET • Define biomarkers for clinic; dose-to-man-prediction	• Strong link between target and disease • Differentiating efficacy • Available and predictive biomarkers
FTIM	• Formal PK studies; dose escalation; safety endpoints • Biomarkers possibly used to define evidence of target engagement	• Bioavailability and tissue exposure • PK/PD
Ph2 PoP	• Exploratory study to demonstrate evidence of biological activity in targeted patients • Evidence of target engagement confirmed	• Clear understanding of safety risks • Safety biomarkers • Evidence in lead indication
Ph3 PoC	• Confirmatory study demonstrating biological activity in large targeted patient group	• Risk/benefit in lead indication • Personalised health strategy
Launch	• Additional patient groups	• Differentiated market position vs current and future SoC • Market access; payers ect...

Figure 4. Drug discovery and development phases

Figure 4, illustrates the typical drug discovery and development path, the key studies required at each stage and the reason the data is collected; the ensuing data builds the platform of evidence, ultimately delivering the data package that substantiates the assignment of a licence by a regulatory agency. In the context of the example of cell senescence used throughout this document we have developed a target product profile for the use of senolytic agents in IPF which in turn informs the criteria required for a candidate drug molecule that can test the hypothesis in the clinic (Appendix 1). A drug discovery path for a novel molecule targeting an ageing pathway such as senescence would not substantially deviate from this. The biological target would still need to be elucidated and its relevance to the process of ageing validated. There would also be the additional challenges of identifying clinically validated biomarkers and appropriate patient populations / timelines discussed previously.

In summary, unlocking the biology of the ageing process and applying this to the development of therapeutics for preventing age-related and multiple morbid conditions may lead to the generation of new interventions capable of alleviating symptoms and underlying causes of many chronic and debilitating diseases. As we have described, targeting these basic mechanisms of biology and intervening in the ageing process, although the focus of much fundamental and applied research, needs to be balanced with the potential risks associated with the patient population, whether that is due to age- or morbidity-related alterations in physiology or the long term treatment for younger single morbidity populations or prophylaxis. The development of biomarkers with clearly translatable endpoints and clinical trial and dosing strategies, informed by the target profile, and which can mitigate these issues, will be required and help meet these challenges.

Unlocking the biology of the ageing process and applying this to the development of therapeutics for preventing age-related and multiple morbid conditions may lead to **the generation of new interventions capable of alleviating symptoms and underlying causes of many chronic and debilitating diseases.**

7 | References

Akbar and Gilroy (2020). Science, 369; 256.
Andres *et al* (2018). Mol. Nutr. Food Res., 62; 1700447. doi: 10.1002/mnfr.201700447.
Aoshiba *et al* (2013). Exp. Toxicol. Pathol., 65; 1053.
Baker *et al* (2012). Nature, 479; 232.
Baker *et al* (2016). Nature, 530, 184.
Bannister *et al* (2014). Diabetes Obes. Metab., 16; 1165.
Barzilai *et al* (2016). Cell, 23; 1060
Bergman *et al* (2019). Osteoporos. Int., 30; 1973.
Campbell *et al* (2017). Ageing Res. Rev., 40; 31.
Campisi *et al* (2019). Nature, 571; 183.
Chang *et al* (2016). Nat. Med., 22; 78.
Cook *et al* (2014). Nat. Rev. Drug Discov., 13; 419.
Debacq-Chainiaux *et al* (2009). Nat. Protoc., 4, 1798.
de Maghales *et al* (2017). Trends Biotech., 35; 1062.
Dimri *et al* (1995). Proc. Natl. Acad. Sci. U.S.A., 92; 9363.
Dungan *et al* (2017). FASEBJ., Abstract 713.9
Ferrucci *et al* (2020). Aging Cell, 19; e13080.
Fleming *et al* (2019). Public Policy & Aging Report, 29; 128.
Ford *et al* (2020). J. Gerontol. A Biol. Sci. Med. Sci., 1; 87.
Giuliani *et al* (2018). Circ. Res., 123; 745.
Global Data Report (2019). GDHC2222EI.
Glossmann and Lutz (2019). Gerontol., 65; 581.
Hajjar *et al* (2007). Am. J. Geriatr. Pharmacother., 5; 345.
Hernández *et al* (2019). Sci. Rep. 9; 14567.
Justice *et al* (2018). Gerosci., 40; 419.
Justice *et al* (2019). EBio. Med., 40; 554.
Kaeberlein and Kennedy (2009). Nature, 460; 331
Kaeberlein and Galvan (2019). Sci. Trans. Med., 11; e4289.
Keskin *et al* (2016). Drug Des. Devel. Ther., 10; 3355.
Kingston *et al* (2018). Age and Ageing. 47; 374.
Kirkland (2016). Cold Spring Harb. Perspect. Med., 1; 6.
Koks S *et al* (2016). Mech. Age. and Dev., 160; 41.
Konopka and Miller (2019). Gerosci., 41, 101.
Lara *et al* (2015). BMC Med., 13; 222
Lomas *et al* (2012). Int. J. Clin. Exp. Pathol., 5; 58.
Lopez-Otin *et al* (2013). Cell, 153; 1194.
Lyles *et al* (2007). New Eng. J. Med., 357; 1799.
McLean and Le Couteur (2004). Pharmacol. Rev., 56, 163.
Mannick *et al*, (2014). Sci. Trans. Med., 6, 268.
Miller *et al* (2011). J. Gerontol. A. Biol. Sci. Med Sci. 62; 191.
Mitchell *et al* (2015). Annu. Rev. Anim. Biosci., 3; 283.
Partridge *et al* (2020). Nat. Rev. Drug Disc., 19; 513.
Picco *et al* (2016). BMC Health Serv. Res., 10; 16.
Prados-Torres *et al* (2014). J. Clin. Epidemiol., 67; 254.
Rena *et al* (2017). Diabetologia. 60; 1577.
Schafer *et al* (2017). Nat. Commun., 8; 14532.
Schmidt (2010). Nat. Biotech., 28; 185.
Seals *et al* (2016). J. Physiol., 594; 2001.
Serrano *et al* (1997). Cell, 88; 593.
Serrano (2017). Nature, 545; 294.
Smith *et al* (2012). Brit. Med. J., 3; e5205.
Walters and Cox (2018). Int. J. Mol. Sci., 19; 2325
Wang *et al* (2018). Appl. Health Econ. Health Policy, 16;15.
Wang *et al* (2018). Front. Genet., 9; 247.
Wilson *et al* (2017). Aging Res. Rev., 36; 1.
Yao X. *et al* (2011). Clin. Geriatr. Med., 27; 79.
Zhang *et al* (2018). Annu. Rev. Genet., 52; 397.
Zhu *et al* (2015). Aging Cell, 15; 428.
Zulman *et al* (2015). BMJ Open, 16; e007771.

8 | Abbreviations

PoC	Proof of Concept
SA-β-gal	senescence-associated β-galactosidase
SASP	senescence-associated secretory phenotype

9 | Appendix 1.

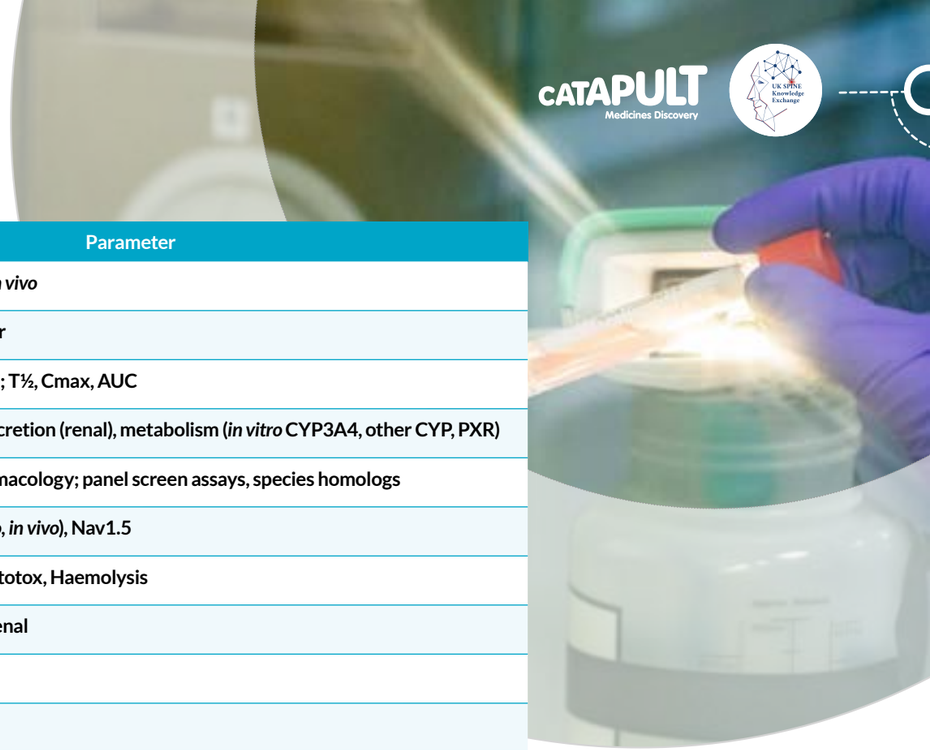
Proposed target product profile (TPP) for the use of a combination of dasatinib and quercetin to slow the progression of loss of lung function and associated breathlessness and reduction in distance able to walk, in patients with chronic idiopathic pulmonary fibrosis.

[1]Nice guidelines for the diagnosis and management of IPF:

(https://www.nice.org.uk/guidance/cg163/chapter/1-recommendations)

Product specification	Product profile	Minimum case	Best case
Primary indication	Treatment of the signs and symptoms of IPF in patients with stable disease.	Chronic treatment of the signs and symptoms of IPF manifesting as breathlessness, walking distance (etc…), in patients with stable moderate and severe IPF disease.	Chronic treatment of the signs and symptoms of IPF manifesting as breathlessness, walking distance (etc…), in patients with stable mild, moderate and severe IPF disease.
Patient population(s)	Patients with IPF confirmed according to published consensus guidelines1 based on historical high-resolution computed tomography (HRCT) and/ or surgical lung biopsy showing usual interstitial pneumonia (UIP), on stable (3 months) therapy with current SoC (nintedanib or pirfenidone) or no therapy, and free of lung transplant, pulmonary hypertension or cor pulmonale.	-	-
Treatment goal	Reduction in episodes of breathlessness; increased stamina as measured by the distance covered in a standard 6minute walking test. Improved patient reported outcomes.	A reduction in episodes and severity of breathlessness. Increased in unaided walking time and distance. Improved QoL.	-
Efficacy	1. Equal to or superior to current anti-fibrotic therapies licenced for use in managing IPF 2. Equal to or superior treatment duration to current treatments [baseline for SoC].	1. A reduction in occurrence of episodes of breathlessness 2. Sustained efficacy for the duration of dosing 3. Time to respond within 2 weeks.	1. Breathlessness episodes halted following acute dosing 2. Sustained efficacy for chronic use 3. Time to respond less than 24 hours.
Adverse effects	No additional adverse effects in mortality or morbidity. Low drug-drug interactions requiring dose adjustments for other common concomitant medications in IPF patients. Suitable for combination therapy with SoC.	-	-
Administration and treatment regimen		Must be suitable for patients with swallowing difficulty. Viable options include; • Oral tablet or liquid (preferred)	

Candidate drug target profile (CDTP). Essential requirements for entering pre-clinical development will be determined by the patient setting, ensuring compound bioavailability and target engagement, while mitigating likely risks.



Parameter
Efficacy in vitro, ex vivo and *in vivo*
Target engagement biomarker
Pharmacokinetics (IV, SC, PO); T½, Cmax, AUC
ADME; tissue distribution, excretion (renal), metabolism (*in vitro* CYP3A4, other CYP, PXR)
Selectivity & secondary pharmacology; panel screen assays, species homologs
Cardiac liability; hERG (*in vitro*, *in vivo*), Nav1.5
Toxicity; Genotox (AMES), Cytotox, Haemolysis
Safety panel; CNS, CV, liver, renal
Safety biomarker
IP strategy
Chemical feasibility and pharmaceutical development
Commercial and patient strategy

10 | Appendix 2.

Inclusion and exclusion criteria for a phase 2 proof-of-concept study for the ability of dasatinib and quercetin to improve functional outcomes in patients with IPF (taken from Justice *et al* (2019) and study NCT02874989 (ClinicalTrials.gov).

Dosing Regimen/ Patient	Inclusion criteria	Side effects
Dasatinib 100mg/ day + Quercertin 1250mg/day given as 3 day dosing + 4 days interval, for 3 week duration N=14 patients with table IPF.	Eligible participants were free of: • Lung transplant, pulmonary hypertension or cor pulmonale confirmed by echocardiography • Heart catheterization, myocardial infarction, angina, hospitalization for cardiac etiology, stroke or transient ischemic attack in the past 6 months, chronic heart failure • Current or chronic history of liver disease • Neurologic condition, drug or alcohol abuse in previous 5 years • QTc prolongation • Low CBC, Glomerular Filtration Rate (GFR) <30 (mL/min/1.73 m^2), or ALT >2xULN and bilirubin >1.5xULN. Participants were not taking anti-arrhythmic medications known to cause QTc prolongation or Coumadin or other anti-platele or anti-coagulant medication. Participant h d no current use of quinolon antibiotics or drug metabolized by the same liver enzymes as D or Q.	Respiratory symptoms (n = 14 reports); cough, shortness of breath, rhinorrhea). Skin irritation and bruising from study procedure (n = 14 reports; 11 related to biopsy or adhesives), Gastrointestinal discomfort or heartburn (n = 12 reports). One serious adverse event (possible bacterial multifocal pneumonia and pulmonary edema superimposed on IPF), which resulted in temporary hospitalization with subsequent complete resolution.

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