

# A roadmap for the discovery of therapeutics in healthy ageing

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## Introduction

Normal ageing leads to reduced physical performance and impaired resilience; the rate of onset and progression of which can be mitigated by diet and lifestyle plus underlying genetic inheritance. Lifestyle, environment and genetics then influence acute and chronic changes to the biological processes underlying normal ageing, which can result in morbidity and, over time, the accumulation of additional or multi-morbidities. Multi-morbidity often necessitates prolonged medicalisation, reduces life expectancy and impairs overall quality of life (figure 1).

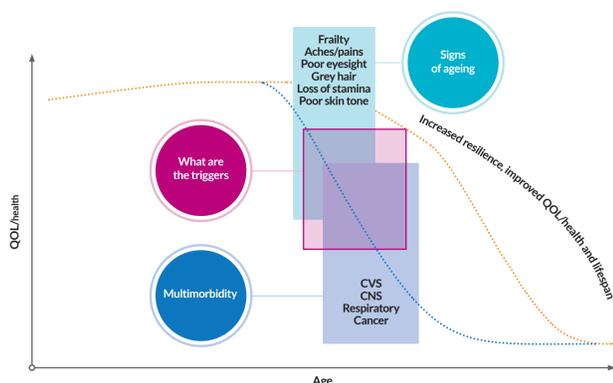


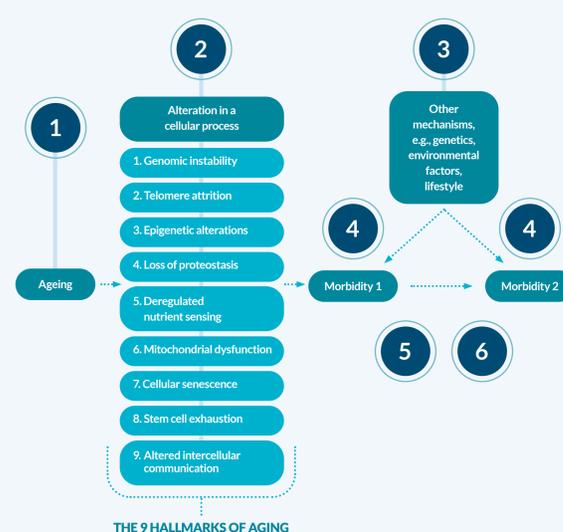
Figure 1: Life expectancy and the impact of intrinsic and extrinsic factors.

## Ageing and Multimorbidity

Alterations in cellular processes during ageing can lead to disease (figure 2), and are influenced by environmental factors. 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. Disease burden as a consequence of the natural ageing process and intrinsic and extrinsic factors.

1. Slowing ageing could see patients taking medication for many years, requiring clear clinical benefit
2. Morbidity arises from alterations in cellular and biochemical processes (López-Otín et al., 2013)
3. A clear rationale to target individual ageing processes versus the well established disease triggers needs to be demonstrated
4. Testing the hypothesis requires
  - Clinically validated biomarkers for the signs of ageing. It is a challenge to tie biomarkers and clinical benefit to disease when the aim of intervention is prevention
  - Patient stratification plans for the mechanism of focus
  - Understanding of the mechanistic link between target, cellular process and disease biology
5. Multi-morbidities can fall into three main clusters: musculoskeletal, neuropsychiatric and cardiometabolic (Prados-Torres et al., 2014)
6. Time to onset of morbidity-1 and development of morbidity-2 can vary considerably: impacting the design of clinical trials



## The Challenge for Drug Discovery



Figure 3. Challenges facing SMEs in geroscience research.

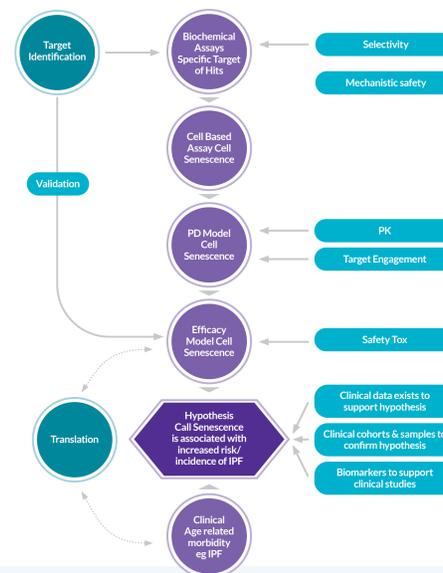
Challenge	Description
1	Identify and validate mechanisms and targets that impact on the core cellular processes that underlie ageing and demonstrate through their modulation that these can slow, reduce, or even reverse, the development of morbidity and the accumulation of additional morbidities in an 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

Table 1. Challenges facing SMEs in geroscience research.

## The Roadmap

There has been considerable interest in the ablation of senescent cells as a potential target mechanism in the treatment of age-related diseases and multi-morbidities (Serrano, 2017). Figure 4 illustrates a proposed pre-clinical cascade for this mechanism in idiopathic pulmonary fibrosis (IPF).

Figure 4. A proposed drug discovery roadmap illustrating the decision making assays and associated milestones to translate to the clinic for age associated cell senescence in IPF.



## Case Study (IPF)

Target linkage to disease needs to be confirmed to build confidence that modulation of the target will lead to efficacy in the clinic. Figure 5 illustrates IPF which is influenced by senescent cells in the lung.

Factor	Considerations
1 Target Engagement	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
2 The Patient and unmet need	Recently the two antifibrotic drugs pirfenidone and nintedanib have been prescribed for IPF which has led to a significant reduction in lung function decline. However, there is still no cure for IPF and therefore, new therapies are needed
3 Patient Stratification	Senescent cells have elevated levels of senescence-associated β-galactosidase (SA-β-gal) activity, which remains the gold standard to identify senescent cells (Dimri et al., 1995; Debacq-Chainiaux et al., 2009). Also p16INK4a, p21CIP1 and p53 are commonly employed to detect senescent cells. p16 and γH2AX are markers of cellular senescence and DNA-damage, respectively
4 Clinical trial feasibility	In IPF lung p16 expression increases with disease severity. In a pilot study of senolytics in IPF patients, a lack of effect on a biomarker, SASP, was reported. Translation from disease models to human patients is limited: <ul style="list-style-type: none"> <li>• There is just one model, bleomycin-induced pulmonary fibrosis, which does not have a strong track record in translation to the clinic</li> <li>• Cell senescence is associated with inflammatory cell types in the rodent model with conflicting evidence of their involvement in human disease pathogenesis</li> <li>• Endpoint measures of fibrosis have not been achieved and so development of alternative measures and biomarkers which translate to the clinic should be considered</li> </ul>
5 ADME & pharmacokinetics	Nasal and broncho mucociliary clearance is reduced in the airways as we age (Paul et al., 2013) and may impact the ADME properties of inhaled therapies
6 Safety and regulatory	Currently the adverse effect profile of IPF treatments is termed 'manageable' so there is significant scope to improve patient care and compliance with new therapies

Figure 5. Factors to be considered in the discovery of new therapeutics for diseases of ageing; IPF is used as a case study.

## Summary

Drug discovery projects link unmet patient need to the market opportunity. The platform of evidence is the critical path from the target biology to clinical application, and defines the decision-making data. Figure 6 illustrates the drug discovery and development path with key studies required to build the platform of evidence required by a regulatory agency.

Stage	Main studies required	Reason data required
Discovery	<ul style="list-style-type: none"> <li>• Target validation: established platform of evidence for target</li> <li>• Lead molecule identification and Optimisation</li> <li>• Define biomarkers</li> </ul>	<ul style="list-style-type: none"> <li>• Strong link between target and disease</li> <li>• Generate lead matter</li> <li>• Biomarker discovery</li> </ul>
Pre-clin	<ul style="list-style-type: none"> <li>• Develop platform of evidence for target relevance, differentiation and target safety</li> <li>• Preclinical safety &amp; toxicology; ADMET</li> <li>• Define biomarkers for clinic; dose-to-man-prediction</li> </ul>	<ul style="list-style-type: none"> <li>• Strong link between target and disease</li> <li>• Differentiating efficacy</li> <li>• Available and predictive biomarkers</li> </ul>
FTIM	<ul style="list-style-type: none"> <li>• Formal PK studies; dose escalation; safety endpoints</li> <li>• Biomarkers possibly used to define evidence of target engagement</li> </ul>	<ul style="list-style-type: none"> <li>• Bioavailability and tissue exposure</li> <li>• PK/PD</li> </ul>
Ph2 PoP	<ul style="list-style-type: none"> <li>• Exploratory study to demonstrate evidence of biological activity in targeted patients</li> <li>• Evidence of target engagement confirmed</li> </ul>	<ul style="list-style-type: none"> <li>• Clear understanding of safety risks</li> <li>• Safety biomarkers</li> <li>• Evidence in lead indication</li> </ul>
Ph3 PoC	<ul style="list-style-type: none"> <li>• Confirmatory study demonstrating biological activity in large targeted patient group</li> </ul>	<ul style="list-style-type: none"> <li>• Risk/benefit in lead indication</li> <li>• Personalised health strategy</li> </ul>
Launch	<ul style="list-style-type: none"> <li>• Additional patient groups</li> </ul>	<ul style="list-style-type: none"> <li>• Differentiated market position vs current and future SOC</li> <li>• Market access; payers etc...</li> </ul>

Figure 6. Development of a platform of evidence for regulatory approval.

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