# 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).

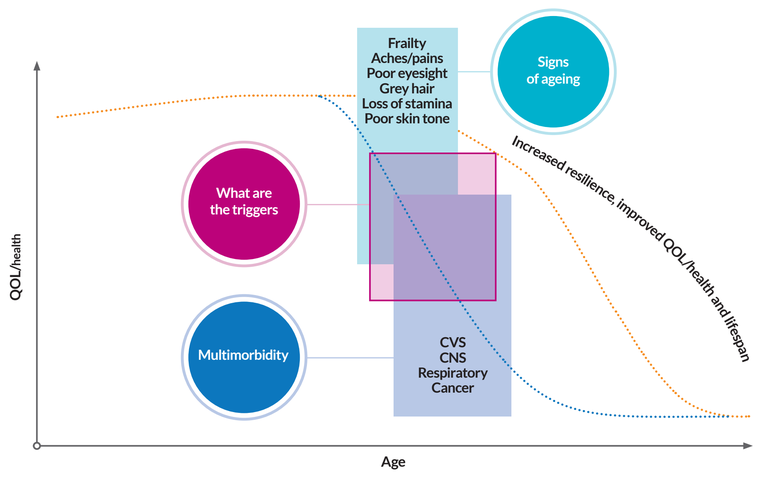


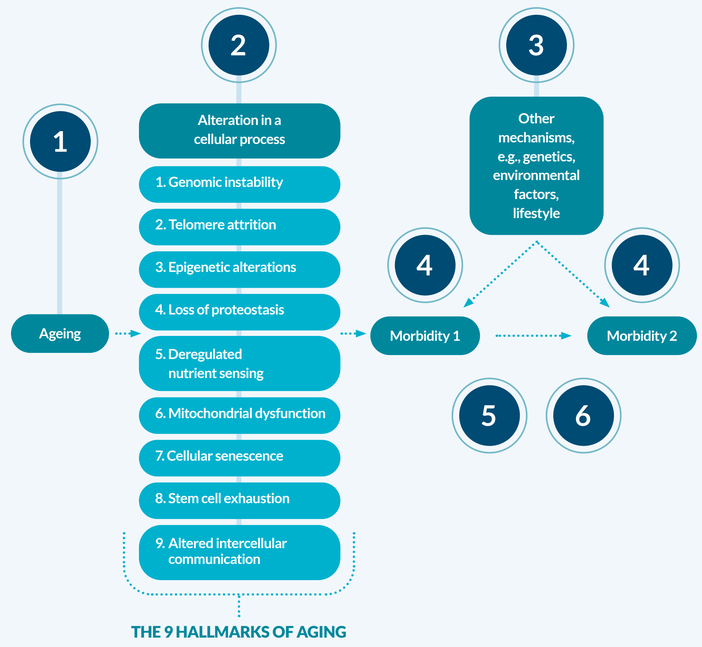

**Figure 1:** Life expectancy and the impact of intrinsic and extrinsic factors.

## 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.

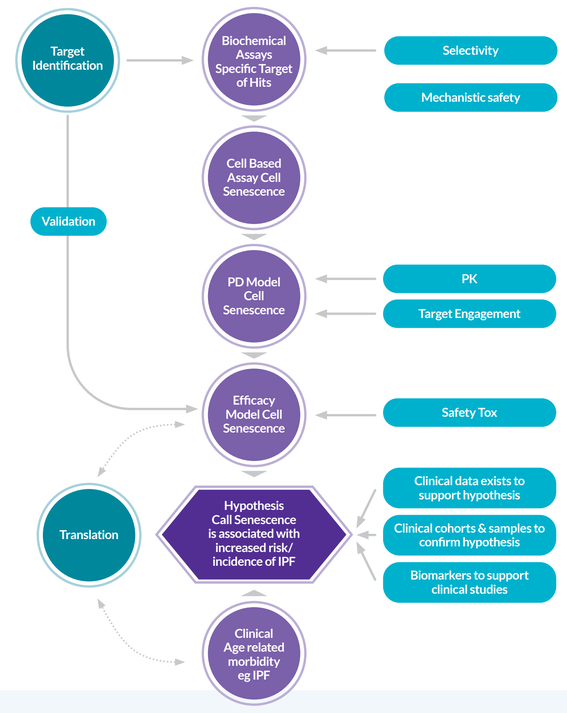
| | |
|---|---|
| 1 | Identify and validate mechanisms and targets that impact on the core cellular processes that underly ageing and demonstrate through their modulation that these can slow, reduce, or even reverse, the development of morbidity and the accumulation of additional morbidities in an already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

**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.

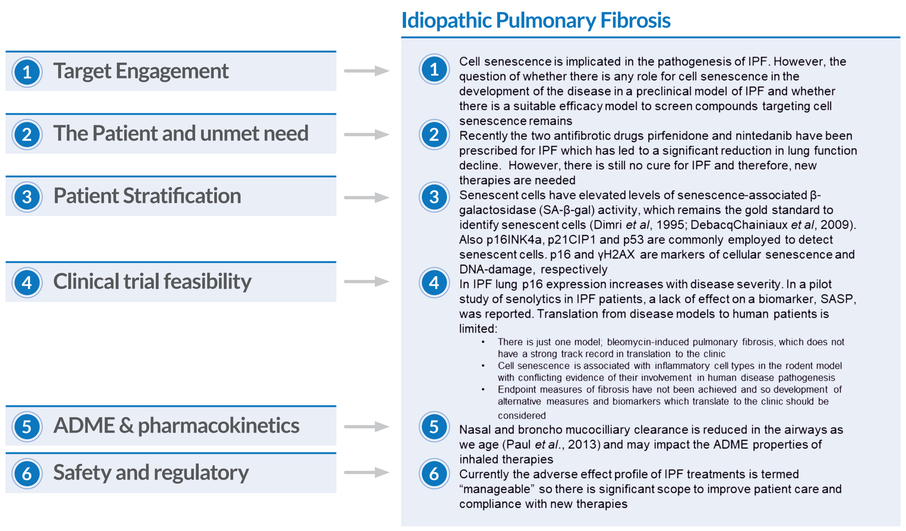



**Figure 5.** Factors to be considered in the discovery of new therapeutics for diseases of ageing; IPF is used as a case study.

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

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

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