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NEW HORIZONS

New horizons in life extension, healthspan extension and exceptional longevity

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Abstract

Many common chronic diseases and syndromes are ageing-related. This raises the prospect that therapeutic agents that target the biological changes of ageing will prevent or delay multiple diseases with a single therapy. Gerotherapeutic drugs are those that target pathways involved in ageing, with the aims of reducing the burden of ageing-related diseases and increasing lifespan and healthspan. The approach to discovering gerotherapeutic drugs is similar to that used to discover drugs for diseases. This includes screening for novel compounds that act on receptors or pathways that influence ageing or repurposing of drugs currently available for other indications. A novel approach involves studying populations with exceptional longevity, in order to identify genes variants linked with longer lifespan and could be targeted by drugs. Metformin, rapamycin and precursors of nicotinamide adenine dinucleotide are amongst the frontrunners of gerotherapeutics that are moving into human clinical trials to evaluate their effects on ageing. There are also increasing numbers of potential gerotherapeutic drugs in the pipeline or being studied in animal models. A key hurdle is designing clinical trials that are both feasible and can provide sufficient clinical evidence to support licencing and marketing of gerotherapeutic drugs.

Keywords: ageing, ageing biology, gerotherapeutic, exceptional longevity, metformin, rapamycin, nicotinamide adenine dinucleotide, older people

Key Points

- Gerotherapeutic drugs target ageing pathways to prevent ageing-related diseases and increase lifespan.
- Rapamycin, metformin and precursors of NAD are amongst many gerotherapeutic drugs entering the clinical trial phase of drug development.
- Licencing of gerotherapeutic drugs will depend on clinical trials that are both feasible and can provide evidence of a primary impact on ageing biology.

Introduction

The majority of people would like to live to the age of 120 years or more if their health remained good and nearly one half would like an unlimited lifespan [1]. About one-third of people would be prepared to take life extension or anti-ageing therapies now [1, 2]. The possibility that a pill might prevent ageing and increase lifespan is tantalising for most people. As a result, anti-ageing and life extension therapies are often the focus for media hype despite the absence of definitive human data [3].

In this review, the term 'gerotherapeutics' is used to refer to drugs that target ageing biology, and that have been developed using similar approaches to those used to develop drugs for diseases. A major scientific endeavour is underway to find biological switches that can manipulate ageing. This research aims to discover new gerotherapeutic drugs that

both reduce the burden of ageing-related diseases, and extend lifespan [4, 5]. There are many ageing-related diseases where the incidence increases exponentially throughout old age, including Alzheimer's disease, some cancers, ischaemic heart disease, ischemic stroke and chronic obstructive pulmonary disease [6]. The biological changes of ageing are a major risk factor these diseases [4, 5, 7]. The hope is that gerotherapeutic drugs might reduce the impact of these ageing-related diseases with a single therapy [4, 5].

Over the last two decades there has been a marked increase in the number of interventions reported to increase lifespan, and delay ageing and disease, in laboratory animals. However, the development of gerotherapeutic drugs is still in its infancy, and no gerotherapeutic drug has yet been shown to increase human lifespan or been licenced for an indication related to ageing.

'Anti-ageing' is a term mostly used to promote products that are not regulated or licenced. There are many drugs, supplements and other treatments that are marketed as anti-ageing and can be accessed direct-to-consumer from pharmacies or online. This global anti-ageing drugs market is estimated to be USD82 billion in 2020 [8]. None of these treatments can support their anti-ageing claims with high quality clinical trials equivalent to those that are required for the registration of drugs for the treatment of individual diseases.

There is very little information about how many people are taking anti-ageing therapies and gerotherapeutic drugs or what they are taking. It is likely that most doctors, including geriatricians, will have some or many patients using these treatments without supervision, so will need to have some knowledge about them.

This is the first review on this topic in Age and Ageing. It focuses on gerotherapeutics that have an established basic scientific foundation and/or where there is the possibility of widespread use in the community. It also provides a summary of how these drugs are being discovered, using traditional drug discovery approaches, repurposing, or by investigating populations with exceptional longevity.

Drug discovery and drug development in ageing

The overall process of drug discovery of gerotherapeutics has so far been similar to that used to discover drugs for the treatment of individual diseases. The foundation for discovering gerotherapeutic drugs is a detailed understanding of the biology of ageing. This knowledge is used to identify ageing pathways and proteins that can be manipulated by drugs [9]. The aim is to find novel compounds that can be protected by patents and then generate profits to offset the substantial costs involved in bringing any new drug to the market.

The biological processes of ageing that are potential targets for gerotherapeutics have been classified into nine groups called the Hallmarks of Ageing. These are currently considered to be the fundamental processes of ageing, or at least reflect the current major domains of research in ageing biology. The Hallmarks are interconnected and integrated. This means that a drug that acts on just one Hallmark can potentially influence the other Hallmarks, and hence the entire ageing process. The Hallmarks of Ageing are a useful platform for grouping gerotherapeutics on the basis of their major mechanisms [9].

Repurposing provides another pathway for drug development. Here, drugs that are already registered for unrelated diseases and have established safety, are tested for additional indications [9]. In the case of gerotherapeutics, an innovative process involving detailed analysis of clinical and preclinical effects on lifespan, healthspan and ageing biology found nine drugs that could potentially be repurposed for their ageing or 'gerotherapeutic' effects. These were: sodium-glucose cotransporter-2 (SGLT2) inhibitors, metformin, acarbose, rapamycin/rapalogs, methylene blue, ACEi/ARB, dasatinib (and quercetin), aspirin and *N*-acetyl cysteine [10]. Metformin, rapamycin and the combination of dasatinib and quercetin have already been extensively studied for their effects on ageing.

As with all drugs, the pivotal step for any gerotherapeutic will be undertaking high quality clinical trials that prove clinical efficacy and acceptable safety, and comply with international regulatory guidelines. The detailed format for clinical trials of gerotherapeutics has not yet been formalised. The primary outcomes should ideally include lifespan, healthspan and ageing-related diseases. In the past the main aim of life extension therapy has been, by definition, to increase life span.

More recently, the value of increasing healthspan, which is the duration of healthy life before the onset of disease or disability, has been emphasised. Recent studies of gerotherapeutics in laboratory animals have been more like to report increases in healthspan measured by latelife health, than increases in lifespan [11, 12].

Although ageing-related diseases are poorly defined [6], it is believed that therapies targeting ageing might delay or prevent multiple ageing-related diseases. This will be preferable to the current medical approach of treating each disease individually, with the associated risks of polypharmacy and overmedicalisation [5]. However, due to funding and duration constraints, human clinical trials of gerotherapeutics with the primary outcomes of lifespan and healthspan are unlikely to be feasible. Instead there has been an attempt to develop biomarkers of ageing that reflect ageing biology and can act as surrogate markers for these outcomes in clinical research [13].

Nutrient sensing pathways

Many strains and species of animals, when given significantly less food than they would eat if food was freely available, have longer lifespans, reduced cancers and delayed onset of ageing changes. This is called caloric restriction. Conversely, overeating and obesity can be potentially considered to be

accelerated ageing and is associated with accumulation of all the Hallmarks of Ageing [14].

The Hallmarks of Ageing include deregulated nutrient sensing pathways that link food intake with ageing and lifespan. These pathways have been extensively studied on the assumption that drugs acting on these pathways might generate the beneficial effects of caloric restriction [15]. Some of these pathways are regulated by two older drugs, metformin and rapamycin, now repurposed as gerotherapeutics. Rapamycin and metformin remain amongst the frontrunners in the quest to find drugs that impact on ageing in humans. Recently, nicotinamide adenine dinucleotide (NAD), which along with its metabolites is influenced by nutrition [16], has become a focus of ageing research. NAD precursor formulations are marketed widely as anti-ageing nutraceutical supplements.

Metformin

It may be surprising to many clinicians that metformin, the common anti-diabetic drug that was first available in 1957, is also widely lauded as for its potential effects on ageing.

It was initially proposed that metformin might be a CR-mimetic, a drug that replicates the ageing benefits of caloric restriction without any need to alter diet [17]. Rather than being simply a CR-mimetic, metformin has now been found to have effects on all the Hallmarks of Ageing. Amongst its actions, metformin interacts with mitochondrial complex 1 and activates the AMP-activated protein kinase (AMPK) pathway. This leads to increased insulin sensitivity and decreased mTOR signalling, oxidative stress, genetic instability and inflammation [18].

As reviewed elsewhere [19] human clinical trials have shown the metformin has many effects apart from managing hyperglycaemia in type 2 diabetes. These include two pivotal clinical trials related to the use of metformin in diabetes: the Diabetes Prevention (DPP) study, which found that metformin prevented type 2 diabetes in non-diabetics; and the UK Prospective Diabetes Study (UKPDS), which found that it reduced cardiovascular outcomes and diabetes related deaths in people with type 2 diabetes. There are many (>250) other studies and systematic reviews concluding that metformin can also reduce mortality, cancers, cardiovascular events, dementia and cognitive impairment [19].

This combination of human clinical studies and preclinical data on the ageing effects of metformin, together with its established safety record led to metformin becoming one of the first drugs to be considered for human ageing trials. Led by Nir Barzilai, 'Targeting Ageing with Metformin' (TAME) is a 6-year, double blind, randomised, placebo-controlled diet evaluating metformin in 3,000 non-diabetic participants aged 65–80 years of age. Outcomes include age-related diseases and biomarkers of ageing. Although there are already convincing studies of metformin and cardiovascular disease, cancer and cognition [19], the purpose of TAME is to use metformin as a tool that will tie those outcomes in a cluster that will give a green light to study ageing outcomes for other gerotherapeutics in the pipeline.

Rapamycin

Rapamycin, in high doses is an immunosuppressant used in organ transplantation. However, its main physiological main action is to inhibit its eponymous receptor, Mechanistic Target of Rapamycin (MTOR). The MTOR pathway is a nutrient sensing pathway that responds to increased levels of amino acids by increasing protein synthesis via activation of transcription. Inhibition of MTOR by rapamycin leads to a reduction protein synthesis. Rapamycin, like metformin was initially thought to be a CR-mimetic [20] but since has been shown to have effects that are distinct from caloric restriction [21] and influences other Hallmarks of Ageing such as autophagy and stem cells.

Rapamycin increases the lifespan of mice, even when commenced in mid-life and late life. Studies undertaken at the National Institute of Ageing Interventions Testing Program showed that lifespan of mice commenced on rapamycin at the old age of 20 months increased by 9% in females and 14% in males [22], and by 18% in females and 10% in males when started at 9 months [23]. This was associated with lower rates of diseases and age-related pathology [24].

A small clinical trial in healthy older people aged 70–95 years found that rapamycin was safe over 8 weeks [25]. A trial of two rapamycin-like drugs ('rapalogs') in 264 participants 65 years and older found that they were associated with a reduction in infections, improved influenza vaccination responses and antiviral immunity [26]. In an novel twist, the effect of rapamycin on ageing is also being trialled in companion dogs [27]. Clinicaltrials.gov shows several clinical trials in humans underway or completed of rapamycin for ageing-related outcomes.

NAD precursors

NAD is a ubiquitous metabolite involved in many fundamental cellular pathways including those maintaining redox status, DNA repair and bioenergetics. Ageing is associated with reduced levels of NAD in many tissues, and depletion of NAD influence many ageing hallmarks [28, 29].

Because NAD is a naturally occurring metabolite, there has been considerable interest in establishing the effects of NAD supplementation on ageing. Most studies have used NAD precursors (nicotinamide mononucleotide, NMN; nicotinamide riboside NR and nicotinamide NAM) because of their greater intracellular bioavailability. *In vitro* and animal experiments have shown that NAD supplementation can prevent or reverse a wide range of age-related pathologies and Hallmarks [30, 31].

Lifespan studies have been undertaken in mice. One study reported an increase in lifespan of 5% when old mice were administered NR in food for 6 weeks [30], whereas another reported that 62 weeks of supplementation with NAM commenced in midlife did not increase lifespan [31].

Recently the Interventions Testing Program confirmed that NR commenced in midlife or old age had no effect on lifespan [32].

There are >30 human clinical trials of NR and NMN registered in clinicaltrials.org [28]. To date, published studies of NR have mostly evaluated its bioavailability [33], whereas there have been some recent studies of NMN that have evaluated clinical outcomes in older adults. A 12-week period of treatment with NMN reduced drowsiness and improved leg function in older people [34]. A randomised clinical trial in 25 obese postmenopausal women found that 10 weeks of NMN compared to placebo was associated with improved insulin sensitivity in muscle but not liver or adipose tissue [35]. It should be noted that these are all very small studies where multiple outcomes were evaluated.

Other gerotherapeutics in the pipeline

There are many biotech companies that are developing drugs that have been designed to act on ageing pathways [36]. However the majority of these have nominated a specific age-related disease, rather than ageing, as the therapeutic target. This likely reflects the current regulatory environment where ageing has not yet been established to be a licensable indication, and the higher costs and lower feasibility of undertaking clinical trials where ageing is the outcome, compared with those where an age-related disease or syndrome is the outcome [9].

One group of drugs receiving considerable attention currently, are the senolytics. Senescence cells are cells that have stopped dividing. These cells often produce an inflammatory cocktail called the 'senescence associated secretory phenotype' (SASP) that contributes to age-related inflammation [37]. Senolytic drugs target and destroy senescent cells. Front runners amongst the senolytics are the combination of dasatinib, which is a tyrosine kinase inhibitor used in leukaemia, with quercetin which is a naturally occurring flavonoid antioxidant [38]. Two early phase clinical small trials have reported that treatment with dasatinib and quercetin is associated with clinical improvement in pulmonary fibrosis [39] and decreased numbers of senescent cells and SASP levels [40].

In the recent past, resveratrol and the Sirtuin Activating Compounds (STACs) had a very high profile in the media. Studies in laboratory animal models had identified the sirtuins, in particular SIRT1, as important regulators of ageing. Initial studies were undertaken with resveratrol, a naturally occurring SIRT1 agonist, and later a range of other compounds (STACs) that increase SIRT1 activity. Resveratrol and STACs delayed ageing and increased lifespan in some animal models [41, 42]. After many trials in humans did not find major effectiveness of these drugs for a range of indications, further clinical development was shelved.

A natural product similar to resveratrol, called pterostilbene has been combined with NR in a fixed dose combination oral capsule. It is claimed that this combination of drugs will both replenish NAD and increase the activity of sirtuins, providing a multipronged approach to delay ageing. Human trial data proving efficacy in any aspect of ageing has not yet been published. However a small placebo controlled trial in 32 participants with amyotrophic lateral sclerosis reported clinical improvement after 4 months of treatment with pterostilbene and NR [43]. Social media marketing of this drug combination emphasises the basic ageing science supporting these claims, and endorsement by high profile scientists. The product has been available online and likely has substantial international market penetration.

There are many other gerotherapeutics in the drug development pipeline and many more available direct-to-consumer [8, 36]. Only a small fraction of these are discussed in this review. The basic science and animal lifespan data underlying gerotherapeutics often can be exciting and compelling. However, as in all other areas of medicine, the use of drug therapies in people must be supported by clinical trial evidence proving that there is both efficacy and acceptable safety. This is even more important for treatments that are claimed to delay ageing, where healthy people without disease may want to take these drugs, potentially for many decades.

Populations with exceptional longevity

Studies of the unique biological and lifestyle characteristics of populations with exceptional longevity may uncover novel targets for gerotherapeutics and other interventions to delay ageing [44]. The National Institute of Ageing has collected several studies of people with exceptional longevity in order to generate multi-omics databases that can be harnessed for drug discovery. These include the Long Life Family Study, the Longevity Consortium, Longevity Genomics, the Integrative Longevity Omics and the Longevity Genes Study/-LonGenity. This 'translational genomic' approach has been fruitful in cancer and some cardiovascular diseases. While most studies to date indicate that exceptional longevity is polygenic a new approach suggested that centenarians are enriched with rare genotypes for some of the major ageing pathways including the insulin-like growth factor-1 (IGF-1)/insulin signalling pathway, MTOR and mitogen-activated protein kinase (MAPK) [45]. In the past, two cardiovascular drugs were developed based in part on genetic data in centenarians: an inhibitor of the cholesteryl ester transfer protein (CETP) anacetrapid; and an apolipoprotein C3 (APOC3) inhibitor, olezarsen. A British biotech startup is now targeting SIRT6 variants found in centenarians to delay ageing [46].

Another approach is to study discrete populations in particular geographic areas that have longer average lifespans. Famously labelled 'the Blue Zones' by the National Geographic, the five areas with the longest lifespans are Loma Linda, California, USA; Nicoya, Costa Rica; Sardinia, Italy; Ikaria, Greece and Okinawa, Japan. To date studies of the Blue Zone populations have focussed mostly on environmental and lifestyle factors [47] rather than identifying potential drug targets.

Conclusions

The discovery of gerotherapeutics has been facilitated by the increased understanding of the biological mechanisms for ageing. This has shown that there are a wide range of cellular pathways that can manipulated by drugs to delay ageing and ageing-related diseases. Such drugs have often led to remarkable outcomes in laboratory animal models. However, there has not been any convincing evidence from high quality clinical trials in humans that any gerotherapeutic drug should be made available to delay ageing, but for the example of metformin. However, in order to define the therapy as gerotherapeutics it has to be tested for effects of a cluster of seemingly unrelated diseases whose major risk is ageing. Even so, ongoing research is motivated by the enormous potential benefits of gerotherapeutics, especially the possibility of delaying multiple ageing-related diseases with a single therapy.

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