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Longevity Pharmacology Comes of Age

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Teaser:

Imagine preventing multiple age-related diseases with a single drug, extending not only lifespan but also the healthy years of life. This is the prospect offered by the emerging area of longevity pharmacology. In animal models longevity drugs can retard aging, now the challenge is to translate these promising pre-clinical findings to humans.

Abstract:

With the global aging population, longevity is becoming the most promising market for the biotech industry. In animals, aging can be retarded and longevity extended, which if translated to humans would result in huge health benefits of remarkable commercial value. The potential to slow down human aging has led to a race to discover the most promising longevity drugs in animals and ultimately translate them to humans. Indeed, in recent years there is an exponential growth in longevity drugs discovered in animal models. Investment in longevity biotech is also booming, and a number of clinical trials will soon shed light on which drugs extent healthy lives. The longevity pharmacology field promises to revolutionize the healthcare of a growing aging population.

Main text:

Advances in our understanding and manipulation of aging have been remarkable in the past three decades [1]. We now know that aging is surprisingly plastic and can be substantially retarded in animal models *via* genetic manipulations, diet and drugs. Impressively, single gene manipulations can extend longevity by as much as 50% in rodents and up to 10-fold in invertebrates [2]. A number of pathways and mechanisms have also been associated with aging and longevity [3,4]. Manipulating these longevity pathways in animals has been shown to retard aging and result in an extension of life and health as well as disease resistance. Retarding human aging would result in huge health benefits of remarkable commercial value [1]. It is not surprising then that the field of anti-aging science has exploded with various companies now trying to develop longevity therapies, in particular drugs. I call this emerging field "longevity pharmacology" and the challenge now is to translate longevity drugs to the clinic.

It is remarkable that, using recent data from our benchmark databases of genes and drugs associated with longevity [2], the growth in the number of known compounds that increase longevity in model organisms is now exponential (Figure 1A). Such growth in candidate longevity drugs is even more noteworthy when we see that the growth in longevity associated genes in model organisms appears to have reached a plateau (Figure 1B). There are possible explanations for these trends, including a loss of appetite by scientists for conducting large-scale screens for genes associated with longevity, given that these often identify similar, known pathways [5]. Although no doubt many genes remain to be discovered associated with longevity, it seems that single gene manipulations modulating longevity tend to converge on common mechanisms and pathways. Perhaps the discovery of new longevity-associated genes has lost some of its novelty. By contrast, there is a greater focus now in translating results from the basic biology of aging to the clinic, and pharmacological approaches are the primary means by which clinical translation can be achieved. It is thus not surprising that there has been a significant growth in the number of longevity drugs discovered in model organisms.

The growth in longevity drugs is driven both by academics wishing to become more translational and a growing number of companies hoping to capitalize on an expanding knowledge of longevity manipulations. Indeed, while the definition of "anti-aging company" is subjective, there has clearly been a growth in recent years in the number of companies focused on longevity: from roughly 20 companies in 2002 and 2014 to over 50 companies at present (source: WhosAge database [2,6]). Investment and funding are now flowing to longevity biotechnology, led by Calico, a Google-backed biotech that is arguably one of the reasons for the recent excitement in the field (Figure 2).

Aging research has finally become mainstream, an established area of scientific research. Such excitement is a vindication for a field that has historically a poor reputation.

Drug developers in longevity often focus on a set of proteins, pathways and processes previously associated with aging in model organisms [3], including the so-called hallmarks of aging [4] that have become widely-adopted in anti-aging biotech. Aging processes popular among anti-aging biotech companies include oxidative stress and mitochondria, which have for long been studied and targeted with antioxidant compounds. Senescent cells have also long been thought to be a mechanism of aging [7], and efforts to target key players in senescence like telomeres and telomerase date back over 20 years. Even though conclusive evidence is still lacking for a causative role of cell senescence in human aging [7], recent experiments in mice support a role for senescent cells in age-related degeneration of some tissues [1,7]. In turn, these experiments in mice led to several recent attempts to develop senolytic drugs (i.e., drugs that kill senescent cells) [7,8]. Significant efforts to slow aging pharmacologically have also focused on pathways thought to play a role in dietary restriction and other dietary manipulations of aging [9]. Various pathways and molecules, such as TOR (target of rapamycin) and NAD+, have been suggested as mediators of the beneficial actions of dietary restriction and are thus exciting pharmacological targets in the context of longevity [1,8,9]. However, one concern that I have is that longevity pharmacology is too narrowly focused on a relatively small set of pathways and mechanisms. We need to be more creative.

Discovery of longevity drugs is being conducted primarily in pre-clinical models, in particular using traditional biomedical model organisms like worms and flies (>75% of longevity-associated drugs come from studies in invertebrates), yeast, mice and rats (Figures 1C and 1D). One limitation of longevity experiments in animal models is that they often employ strains of limited genetic diversity which may not always translate to clinical applications in the much more diverse human population [10]. Nonetheless, in addition to pre-clinical drug discovery, the field of aging research is also now embarking on a growing number of clinical trials. One initial placebo-controlled clinical trial in 264 elderly subjects by Novartis showed that low-dose mTOR inhibition improves immune function and reduces infections [11]. This study added to the excitement surrounding mTOR inhibition with rapamycin. The discovery in 2009 that mice fed rapamycin late in life live longer [12], arguably a watershed moment in longevity pharmacology, put the spotlight on rapamycin and its analogs (rapalogs) [1], and the Novartis results in turn led to further trials. Of note, in 2019 ResTORbio did a Phase 3 clinical trial of RTB101, an inhibitor of TORC1, in lung disease, which was a failure (NCT04139915) [13]. In spite of ResTORbio's promise to continue another trial for RTB101 to

treat Parkinson's disease [14], the company recently merged with Adicet Bio [15], who are performing trials using RTB101 aimed at COVID19 (NCT04584710 and NCT04409327). In addition to ResTORbio, Unity Biotechnology's clinical trial (NCT04349956) for its senolytic drug UBX0101 to treat osteoarthritis also failed [16], and Unity are now focused on ophthalmologic and neurologic diseases with one ongoing trial at the time of writing for diabetic macular edema (NCT04537884). Various academic institutions are also conducting clinical trials for senolytics for frailty and inflammation (NCT03675724), skeletal health in older subjects (NCT04313634) and Alzheimer's disease (NCT04063124). While no doubt many (likely most) of these trials will fail, because the global aging population crisis will only get worse a focus on longevity will not abate.

Several other companies are currently conducting clinical trials for drugs that are hypothesized to retard the process of aging or at least target mechanisms of aging. Alkahest is targeting chronokines, proteins that increase or decrease with age, with several clinical trials for neurodegenerative diseases (e.g., NCT03713957 and NCT03765762). In 2021 plasma-based specialist Grifols will acquire the remaining Alkahest stock for a reported $146 million [17]. BioAge, a company using data-driven approaches to identify drug targets for treating aging diseases, is doing a phase 2 trial for COVID19 using an inhibitor of prostaglandin D2 (NCT04705597). The focus by some anti-aging biotech companies on COVID19 is not surprising due to the strong age-related patterns of this disease. Perhaps, by shedding light on the most vulnerable elderly population, COVID19 will accelerate the growth of the longevity industry. Many other trials are currently being planned in the context of aging and longevity. Noteworthy is the Targeting Aging with Metformin (TAME) clinical trial which is hoped to serve as a proof of concept for an FDA clinical trial focused on aging [8,18]. The fact the FDA is allowing the TAME study is in itself a key turning point in developing a regulatory framework for testing drugs targeting aging. Moreover, because aging itself is not yet a suitable endpoint for clinical trials, TAME aims to define a set of readouts that can be used in subsequent clinical trials for aging. Indeed, in spite of advances in identifying biomarkers of aging [19], one major obstacle of translating findings in aging is designing suitable clinical endpoints for obtaining regulatory approval [1]. Besides, even if a given longevity drug may have clinical benefits towards various diseases, determining the best one for successful clinical trials remains a challenge. Off-label prescriptions and classification as nutritional supplements are alternative avenues to commercialization [9].

Given the large number of longevity drugs that have shown positive effects in animal models, and the costs and difficulties in performing clinical trials, another emerging area of research in longevity

pharmacology is the use of computer-based methods to predict the best longevity drugs for clinical indications [9]. An in-depth discussion of such methods is beyond the scope of this article, yet coupled with vast publicly available datasets, various bioinformatics and machine learning/AI methods have been developed for deriving biomarkers, predicting longevity genes and prioritizing compounds in the context of longevity. Because manipulations of longevity pathways and genes can have side effects, for example rapamycin is also an immunosuppressor [9], one promising area involves drug repositioning in the context of longevity. In other words, discover new clinical indications for existing drugs for which some information (e.g., side-effects) and studies exist already. In the future, information on the anti-aging properties of existing drugs might even be used to inform prescribing decisions. Another unexplored area is the use of drugs/compound combinations in the context of longevity. Again, *in silico* methods can help prioritize synergistic drug combinations. Lastly, another challenge is personalized medicine, can we predict which drug (or drug/compound combination) at which dosage is ideal for each patient?

In conclusion, there is an exponential growth in the number of longevity drugs being discovered in pre-clinical animal models, which showcases the dynamism and excitement in the emerging field of longevity pharmacology. A longevity industry is starting to emerge and investment in longevity pharmacology is on the rise. Questions remain regarding whether longevity drugs in animals will have therapeutic benefits in humans with minimal side-effects [1,8], and computational methods can help guide experiments and clinical trials. Importantly, a growing number of clinical trials are now being conducted to test various drugs targeting aging mechanisms as therapies for age-related diseases. These trials will shed light in the coming years on which drugs extent healthy lives. As people worldwide are living longer than ever, longevity pharmacology promises to revolutionize the healthcare of a growing aging population.

Conflict of interest

I am CSO of Centaura, a company that aims to prevent and reverse aging, an advisor for the Longevity Vision Fund and the founder of Magellan Science Ltd, a company providing consulting services in longevity science.

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Figure Legends

Figure 1: A: number of life-extending compounds per year according to the DrugAge database [2]; B: number of longevity-associated genes per year according to the GenAge database [2]; C: longevity-associated drugs and compounds in DrugAge per species; D: histogram of lifespan effects, as measured for average lifespan changes, for entries in DrugAge for worms (*Caenorhabditis elegans*), flies (*Drosophila melanogaster*), mice (*Mus musculus*), rats (*Rattus norvegicus*) and yeast (*Saccharomyces cerevisiae*).

Figure 2: Top 15 longevity companies, defined as companies listed in the WhosAge database [2,6], ranked by investment; data from Crunchbase and the websites/press releases of the featured companies.