Drugs That Modulate Aging: The Promising yet Difficult Path Ahead

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Abstract

Once a backwater in medical sciences, aging research has emerged and now threatens to take the forefront. This dramatic change of stature is driven from three major events. First and foremost, the world is rapidly getting old. Never before have we lived in a demographic environment like today and the trends will continue such that 20% percent of the global population of 9 billion will be over the age of 60 by 2050. Given current trends of sharply increasing chronic disease incidence, economic disaster from the impending silver tsunami may be ahead. A second major driver on the rise is the dramatic progress that aging research has made using invertebrate models such as worms, flies and yeast. Genetic approaches using these organisms have led to hundreds of aging genes and, perhaps surprisingly, strong evidence of evolutionary conservation among longevity pathways between disparate species, including mammals. Current studies suggest that this conservation may extend to humans. Finally, small molecules such as rapamycin and resveratrol have been identified that slow aging in model organisms, although only rapamycin to date impacts longevity in mice. The potential now exists to delay human aging, whether it is through known classes of small molecules or a plethora of emerging ones. But how can a drug that slows aging become approved and make it to market when aging is not defined as a disease. Here, we discuss the strategies to translate discoveries from aging research into drugs. Will aging research lead to novel therapies toward chronic disease, prevention of disease or be targeted directly at extending lifespan?

Introduction

While the quest for immortality goes back thousands of years, critical thinking about why we age begins, it can be argued, with Darwin and natural selection. If only the fittest survive, why would an organism age, lose functional capacity and die. Yet aging occurs in almost every species (1). Alfred Rüssel Wallace proposed an early version of group selection, where it would be beneficial for older individuals to be eliminated so that the reproducing younger individuals can have access to a larger allotment of available resources.

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The evidence for group selection with respect to aging is limited, but the question was right and the apparent answer at least in part comes from data on life expectancy. Essentially, average life expectancy among humans was under 25 and very few people died from age-related diseases (2). More prevalent causes of mortality were infectious disease, childbirth and malnutrition. There was no selective pressure to extend reproductive capacity or life expectancy since very few people lived long enough for it to matter. While beyond the scope of this review, evolutionary theories of aging have continued to evolve, with elegant hypotheses such as antagonistic pleiotropy and the disposable soma theory emerging (3, 4). Readers are encouraged to seek out the following reviews (5-7).

What is worth considering here is whether the aging process is fixed or malleable? All data collected from the wild and from experimental organisms indicates the latter: life expectancy and the intrinsic aging process are relatively easily altered. For instance, similar species in the wild can have widely divergent life expectancies based on requirements imposed by evolutionary life history traits and other environmental factors (8). Moreover, hundreds of genetic mutants have been identified with longer lifespan and often longer healthspan, the disease free and highly functional period of life (9).

Against this backdrop, a dramatic change in demography has occurred within the last two centuries. Never before have humans been so old. Life expectancy has surpassed 80 in many countries and, coupled with a declining birthrate in many of those same countries, the percentage of seniors is skyrocketing. In the near future, up to 40% of the Japanese and Korean populations will be over 65 and the rest of the developed world will not be far behind (http://www.who.int/ageing/publications/global_health.pdf). Using current projections, two of the nine billion people on the planet in 2050 will have lived at least six decades.

Older people offer experience and wisdom, but are also increasingly beset with chronic disease. Aging itself is the biggest risk factor for most of the leading causes of disease burden and mortality, including cardiovascular and neurodegenerative disease, metabolic syndromes and most forms of cancer. Add to that societal changes leading to over nutrition, lack of exercise and stress and the result is that most people over 65 in the US have 1-3 chronic diseases (http://www.who.int/ageing/publications/global_health.pdf). This reduces their productivity and dramatically escalates health care costs. In summary, the silver tsunami threatens to leave wrecked economies in its wake.

One partial solution is to keep people healthy longer and aging research may have much to offer. By delaying aging, it may be possible to prevent the onset of chronic diseases and increase healthspan. Healthy seniors could work longer at high rates of productivity and would certainly reduce the burden of healthcare. But aligning medical research on aging with prevention has its challenges. How do drugs that slow aging make it to market when aging is a slow process and not even recognized as a disease by the FDA. Prevention trials for chronic diseases are also slow and often expensive. Will drugs that slow aging be effective for treatment of chronic diseases? It is not obvious that a drug which slows aging will have any impact after an age-related disease is already creating havoc.

In this review, we cover briefly the progress in studies on the genetics of aging and then turn to small molecules that modulate aging. The two best studied, rapamycin and resveratrol will be discussed in some detail. Finally, we return to the question of the potential utility of aging drugs, making the argument that they will be effective therapeutic agents for disease states, but maybe not for the reasons that are most obvious.

The Genetics of Aging

Before active pursuit of aging in invertebrates began in earnest, much of our understanding of the molecular and genetic events driving aging was based on correlative studies of young and old animals. However, starting in the 1960s, genetic studies of aging *Drosophila melanogaster* and *Caenorhabditis elegans*, simpler and cheaper model organisms, began to yield insights (10-14). Studies in yeast replicative aging, the number of times one mother cell can divide and produce a daughter (15, 16), date back to 1959 and turned to genetics as well (17, 18). Yeast chronological aging, the survival of yeast cells in a post-replicative environment (15, 19), has also proven highly informative. It was clear from these studies that extending lifespan was possible through methods such as mutagenesis and screening (10, 12, 20), or through selection, for instance, by isolating flies that maintain late reproductive capacity over many generations (13, 21).

The first longevity mutants began to be isolated in *C. elegans* and for yeast replicative aging in the 1990s and this field of research has gained steam in dramatic fashion ever since (11, 20). Worms and yeast have led the way in part because they are amenable to whole genome screening for longevity and hundreds of genes whose reduced expression lead to lifespan extension in both organisms have been identified (22-30). Critically, in many cases ortholog families have been identified that modulate aging across multiple species (31, 32). In addition, quantitative evidence has been generated that longevity pathways are conserved between *C. elegans* and yeast (replicative aging) (33). These results provide a demonstration that the aging process has significant overlap between disparate species, although there will certainly be unique features as well. By studying the conserved ones, it is likely possible to gain major insights into the human aging process.

Indeed research is starting to bear out this assertion. Four of the major pathways known to influence aging are insulin/IGF signaling (IIS) (11, 34-36), Target of Rapamycin (TOR) (22, 23, 37-40), the protein kinase A (PKA) pathway (41, 42) and the protein deacetylase *SIR2* (43-45). All four of these were defined first in invertebrates but evidence for the first three affecting aging has since followed in mice and even humans. The case for *SIR2* and its orthologs is more complex, but also promising (see below). Mice with reduced IIS, mTOR or PKA signaling all have extended lifespan and a majority of evidence suggests they are healthier and protected from many age-related diseases (46-51).

For humans, most evidence comes from genetic studies of centenarians. Mutations in the *FOXO3A* gene, encoding a transcription factor downstream of IIS signaling have been associated with enhanced longevity (52-57). Further linking the IIS pathway to human longevity, centenarians are more likely to have IGF receptor mutations (58). In this case, these mutations are known to be hypomorphic, IGF signaling is reduced when they are

introduced into cells in culture. With respect to the PKA pathway, Zhao et al. identified hypomorphic mutations in the β-adrenergic receptor, *ADRB2,* that are predicted to lead to reduced PKA signaling (59). All of these findings are consistent with the theory that longevity pathways are conserved among eukaryotes, implying that interventions to slow aging in animal models may have a similar effect in humans. In the next sections, we examine the two primary pharmacological interventions that affect aging and age-related disease in animal models.

Rapamycin and the Tor Pathway

The story of rapamycin starts with a wide-ranging scientific expedition by a group of Canadians to Easter Island in the 1960s and a soil sample that proved to have an activity capable of killing eukaryotic cells. That activity was later attributed to a small molecule, rapamycin, which was produced by bacteria (60). Since its discovery, rapamycin has been the focus of intense research both from academics and pharmaceutical companies. Clinical trials have been performed with rapamycin and derivatives (rapalogs) in a wide range of disease conditions and while side effects of treatment are significant, the class of drugs has been approved for several disease indications (61, 62).

A major discovery that advanced the field involved the identification of the Target Of Rapamycin (TOR) kinase and the vast biology that emerged from this line of investigation. Here we will not cover TOR signaling in depth and readers are directed to several recent reviews (63, 64). The finding that reduced TOR signaling enhanced longevity in yeast, worms and flies suggested that reduced TOR signaling might have a similar effect in mammals (22, 23, 37-40). The NIA Intervention Testing Program tested the small molecule during mouse aging and rapamycin turned out to be the first robust hit, extending lifespan by 15% in females and 10% in males, even when administered relatively late in the lifespan of a mouse (20 months) (47). Rapamycin has also been reported to extend lifespan in another mouse strain (48), as has deletion of the downstream TOR target, S6 kinase 1 (S6K1) (65). Moreover, in physiological aging studies, rapamycin is reported to delay a subset of age-associated pathologies, including neurodegenerative diseases, age-related cardiac hypertrophy and others (66-71). It is not a panacea for chronic disease, however as chronic administration does not affect phenotypes including kyphosis and may accelerate others such as cataracts (66, 70).

There are two TOR complexes, and the majority of evidence indicates that it is reduced TORC1, and not TORC2, activity that promotes longevity (61, 63). Rapamycin primarily inhibits TORC1 but upon chronic administration can inhibit TORC2 signaling as well (72). TORC1 is ideally suited to modulate aging processes. Among upstream regulatory pathways that control TORC1 activation are extracellular nutrient levels including carbohydrates (mediated through the IIS pathway) and amino acids (63, 64, 73). High nutrients and activated TORC1 translates to rapid cell growth and proliferation. A rapamycin-mediated reduction in TORC1 signaling may thus phenocopy dietary restriction, known to enhance longevity in a wide range of organisms for many decades. The jury remains out on this hypothesis and perhaps the best interpretation of current data is that dietary restriction and rapamycin-mediated TORC1 inhibition extend lifespan through overlapping but non-

identical effects (74, 75). Other inputs controlling TORC1 activation include stress sensors such as MAP kinase and AMP kinase signaling (76, 77).

Downstream of TORC1 are a range of pathways that permit control of cell growth and proliferation, as well as stress response pathways. For instance, activated TORC1 leads to enhanced protein translation and cell cycle entry, whereas reduced TORC1 activity instead enhances autophagy and proteasome-mediated turnover (63, 64, 73). Thus, TORC1 is poised to integrate environmental signals and modulate downstream responses accordingly. Although likely something of an oversimplification, high TORC1 equates to rapid growth, reproduction and aging whereas reduced TORC1 signaling delays growth and enhances cellular stress response pathways leading to enhanced longevity.

Rapamycin and derivatives have been and continue to be tested in a wide range of clinical trials for numerous chronic disease indications, and the drugs have already been approved for uses in cancers including renal carcinomas and to inhibit restenosis after implantation of stents during angioplasty (61). It is also used to prevent organ transplant rejection in combination with other potent immunosuppressants such as cyclosporine A (78). In addition, chronic rapalog administration results in a range of side effects such as hyperglycemia and dyslipidemia. Interestingly, at least some of the side effects appear to be through inhibition of hepatic TORC2 (79),. Whether rapalogs prove effective to slow aging in humans remains to be determined, but the results establish proof-in-principle that it is possible to slow aging and, when achieved, delay the onset or progression of at least a subset of age-related chronic diseases.

Resveratrol, Stacs and Sirtuins

Overexpression of *SIR2* enhances replicative lifespan in yeast (43). Sir2 is the founding member of a class of protein deacetylases termed Sirtuins. Eukaryotic species have multiple Sirtuins (80), but it is *SIR2* orthologs that have been linked to aging in worms and flies, albeit controversially. Some studies report that overexpression of *Sir.2-1* extends lifespan in *C. elegans,* but others have failed to replicate this finding (45, 81, 82). Similar findings have been reported with *Sir2* in flies (81, 83, 84). The reasons for these discrepancies remain to be fully elucidated. In mice, the closest ortholog by sequence homology is *SIRT1,* however constitutive expression failed to extend lifespan in mice (85). Recently, it was reported that overexpression of SIRT1 in the brain enhances longevity likely through enhanced hypothalamic function with age (86). Overexpression of another Sirtuin, *SIRT6,* also extends lifespan, but only in male mice (87).

The functions of Sirtuins linked to enhanced longevity remain to be elucidated. In yeast, enhanced Sir2 activity suppresses rDNA recombination (43), reducing the number of extrachromosomal rDNA circles, which accelerate aging through still poorly defined mechanisms (88). However, there are other functions of yeast Sir2 that have been linked to longevity, including possible effects on gene expression near telomeres and on replication at ARS elements in rDNA repeats (89, 90). In worms, *Sir.2-1* overexpression may lead to enhanced function of the FOXO ortholog, DAF-16, possibly linking the Sirtuin pathway to

IIS signaling (45). In flies, the mechanisms also remain poorly defined but involve interaction with another deacteylase, Rpd3 (44).

In mice, the mechanisms underlying the longevity effects of SIRT1 overexpression in the brain likely involve enhanced hypothalamic neural activity, which protects and maintains mitochondrial function in aging skeletal muscle (86). It also remains possible that tissue-specific *SIRT1* overexpression may affect aging directly. Also of note, deletion of *SIR2* orthologs have pronounced metabolic effects and may be required for lifespan extension by dietary restriction, depending on the DR regimen that is chosen and other unidentified factors (91, 92).

In a screen for SIRT1 activators, the molecule resveratrol was identified to enhance the SIRT1 activity in an in vitro assay using acetylated non-native substrates (93). The substrate was engineered for high throughput screening and involved the release of a fluorescent moiety triggered by the deacetylase reaction. A series of other molecules, named Sirtuin Activating Compounds (STACs), were also identified that could activate SIRT1. These molecules have triggered a wave of studies reporting potentially beneficial effects in chronic disease assays, and several clinical trials have been initiated. See recent reviews for a more complete description of these studies (80, 94).

The activity of resveratrol and STACs toward SIRT1 has also been the subject of great controversy, starting with the discovery that these molecules generally fail to activate SIRT1 toward native peptides in vitro (95, 96). Follow up studies suggested that in the original screen, the non-native fluorescent moiety interfered with SIRT1 deacetylation and that resveratrol and STACs alleviate that interference. In vivo, however, these same molecules could promote deacetylation of SIRT1 substrates and their physiologic properties were often, but not always, found to be SIRT1-dependent (97). A recent report may have resolved this controversy, finding that a subset of native substrates have amino acids that act similarly to the fluorescent moiety in the screen (98). Therefore, resveratrol and STACs appear to demonstrate selective SIRT1 activation.

To date, resveratrol and STACs have been reported not to extend mouse lifespan (99), with data in non-vertebrate organisms conflicting (100). Specifically, a large study by the NIA Intervention Testing Program was unable to detect enhanced longevity in mice (99, 101). Given the recent report that brain-specific *SIRT1* expression extends mouse lifespan, it is possible that other STACs will have a longevity effect, but further studies will be needed to address this question in detail. Interestingly, resveratrol does extend lifespan in one fish model, the annual fish *Nothobranchius* (102, 103).Regardless of their impact on lifespan, the Sirtuin activating compounds represent another intriguing class of small molecules derived from aging studies that may have significant clinical applications.

Other Drugs Linked to Aging

Within the next few years, several more drugs likely will be reported to extend mouse lifespan. However, two already widely used drugs are worth discussing. One, metformin, has recently been reported to increase male mouse median and maximum lifespan by approximately 5% (104). This is the latest and most definitive of several studies examining

the effects of metformin on lifespan, with a variety of results observed (105). It is particularly relevant since metformin is a widely used drugs for type II diabetes and relatively safe for human administration. Also consistent with the possibility that metformin modulates aging, it has been reported to be beneficial in more than one age-related disease. Reports from clinical studies indicate that the drug also reduces risk of cardiovascular disease and cancer (106, 107). Although other activities have been reported, metformin is primarily thought of as an activator of AMP kinase, which responds to cellular energy deficits to mediate starvation responses in the cell (108). Therefore, as proposed for both rapamycin and resveratrol, metformin can be considered a dietary restriction mimetic.

The case for statins as an aging drug can also be proposed. Statins inhibit HMG-CoA reductase, leading to reduced levels of low density lipoprotein (LDL) associated cholesterol and are widely used with efficacy in cardiovascular disease states (109, 110). Statins may also prevent cellular senescence, possibly through reducing levels of reactive oxygen species and/or stabilizing telomere structures (111). Although the NIA Intervention Testing Program was unable to detect any longevity benefit with simvastatin (99), statins have been reported in human clinical trials to protect in some cases against other age-related diseases including dementias and forms of cancer. It has also been suggested that these drugs should be administered in a widespread fashion to individuals above 50. However, there are several notes of caution (109, 110). First, there are significant although manageable side effects associated with statins in a subset of patients. In addition, the protective effects of statins against diseases other than CVD are not always seen in clinical studies and finally, it has been debated whether statins are beneficial for CVD in individuals over the age of 80 (109). While further studies are certainly warranted, it seems premature to classify statins as anti-aging drugs at this juncture.

How Does Aging Research Translate to Clinical Applications?

The last two decades of research have led to the following hypotheses: (1) aging can be delayed in animal models (including mammals) with genetic interventions and small molecules; (2) the pathways modulating aging are at least partially conserved in eukaryotes; and (3) aging is a common cause of many if not most chronic diseases that are the leading contributors to morbidity and mortality. The latter assertion is based on findings that interventions delaying aging in animal models protect against chronic diseases. Put this together and the potential is obvious: develop interventions to slow human aging as a means of preventing disease and extending healthspan. This approach could improve quality-of-life while simultaneously lowering healthcare costs. Whether aging drugs will also serve as treatment for diseases is another issue, addressed below.

But this approach does not blend well with current drug development strategies, which are primarily aimed at treatment strategies. Many of these treatments are accompanied by high costs and some fail to significantly improve quality-of-life. In fact, approval of drugs aimed at chronic diseases has occurred at a slow pace. Approval of drugs aimed at prevention is feasible, but these studies are often shunned to extended trial times and high costs. Finally, even if a drug existed that extended lifespan without side effects, it would be hard to get it approved as aging is not a disease indication. Thus the conundrum - there is a disconnect

between the likely benefits of drugs that slow aging and likely strategies that would get them approved for human use (Figure 2).

This has led the small number of researchers focused on aging to take hits and direct them at treatment of chronic diseases. But why should this work? Aging may indeed enable disease, but why should the specific molecular pathology that accompanies chronic diseases be mitigated by methodologies slowing aging. Early evidence, however, suggests that this strategy might work. In this section, we lay out a hypothesis for why drugs that slow aging may be viable treatment options for chronic diseases and it comes with a twist - it may not be the diseases of aging for which small molecules extending lifespan show the most efficacy.

As an example, we describe a recent study we reported examining a mouse model of Emery-Dreifuss Muscular Dystrophy (EDMD2/3) and Dilated Cardiomyopathy (CDM1A) (112). These diseases are caused by mis-sense mutations in the *LMNA* gene, which encodes the nuclear intermediate filaments A-type lamins (113, 114). Interestingly, there are over a dozen diseases associated with mutations in *LMNA,* including multiple progeroid syndromes such as Hutchinson-Gilford Progeria Syndrome (HGPS). The motivation for the study was to test rapamycin in a mouse progeria model, reasoning that a drug that affects normal aging may be highly efficacious in progeria. As a control, with the intent of showing specificity for rapamycin toward HGPS, we also tested the $Lmna^{-/-}$ mice (115), which succumb to conduction defects due to the dilated cardiomyopathy after 6-8 weeks (116). The surprise, rapamycin was ineffective in the progeria model (unpublished observation), but highly effective in extending survival as well as improving cardiac function in the $Lmna^{-/-}$ mice (112, 117). Why should rapamycin work for this disease, which is not associated with aging? The likely answer, the TORC1 pathway is aberrantly upregulated in the $Lmna^{-/-}$ mice (112), and in another *Lmna* mutant mouse model as well as tissue from human patients (117). The connection between A-type lamin and TORC1 is still being elucidated, but the reason rapamycin works is readily apparent - it suppresses elevated TORC1 activity in pathologic tissues.

Interestingly, TORC1 activity may also be upregulated in a variety of aging cells and tissues, including the mouse liver, hematopoietic stem cells and others (48, 118). In the initial NIA Intervention Testing Program study, rapamycin was only administered at 20 months of age (47), leading many to predict even bigger benefits associated with earlier administration. Yet this proved largely incorrect. Rapamycin administration starting at 9 months only led to lifespans slightly longer than when given at 20 months (99). From these findings, it may be that the benefits of rapamycin come not from reduced steady-state TORC1 signaling in young animals, but rather from suppression of age-associated aberrant upregulation. While more studies are needed to confirm this hypothesis, it presents an intriguing picture of the genetic pathways identified to modulate aging.

While TORC1 becomes elevated at least in a subset of aging tissues, Sirtuin activity declines. For instance, Sir2 degradation is enhanced during yeast replicative aging, leading to reduced activity and accompanying phenotypes (89). Similarly, SIRT1 function declines with age in at least a subset of mouse tissues (119, 120). Interestingly, while it has been

relatively easy to identify conserved longevity pathways, determining why they affect aging and how they interface with mechanistic hypothesis of aging such as oxidative damage, altered proteostasis, telomere shortening etc. has been very challenging. One possibility is that Sirtuin and TOR dysfunction are not the primary events that drive aging but rather the secondary responses to those events. In other words, these are the pathways that go wrong when things go wrong, and moreover, that once aberrantly regulated they further contribute to the pathology of aging. Suppressing this dysfunction therefore enhances lifespan and healthspan.

If this is the case, there may be significant overlap between aging and disease states - the same pathways may be mis-regulated. This may be the case at least with both TOR and Sirtuins, whose altered function has been linked to pathology in a wide range of disease conditions. Of course, the concept will require testing with other longevity pathways as they emerge, but if true, it leads to a reasonable explanation of why small molecules that slow aging will be effective therapeutic agents, as well as a path to approval. Moreover, it suggests that screening for delayed aging may yield a wide range of new pathways and chemical classes for chronic diseases. Finally, it implies that the molecules slowing aging may be as likely to have efficacy for non-aging diseases as ones associated with aging.

Ultimately, the focus has to turn to healthspan, either tested directly or through disease prevention studies. Avoiding disease rather than slowing progression is an economic and a quality-of-life winning ticket. This will require a change of thinking in drug development, including an increased tolerance for prevention trials and acceptance of new parameters of aging, such as frailty and altered biomarkers, as disease indications. This latter issue remains a major challenge for aging and longevity specifically. While many efforts involving both unbiased large-scale and targeted hypothesis-driven studies have been performed, there remains a dearth of solid biomarkers that are predictive of longevity in mice or humans. Studies of miRNA levels in serum may prove to be a useful approach to generate these critically needed biomarkers. In hand, it would be feasible to examine whether anti-aging drugs reduce biomarkers of aging in human trials.

Aging research has unique features. Not only does it touch upon the major chronic disease states that are currently plaguing humanity, but it offers the potential of aligning medical research with disease prevention. After all, at least in the cases studied to date, slowing aging is coupled with extending healthspan. The best way to treat a major debilitating disease is to not get it in the first place and aging research has the potential to help achieve that goal. With new small molecule interventions that slow aging emerging, the opportunity is there for aging research to revolutionize medicine. Rapamycin derivatives and STACs may or may not be appropriate to extend healthspan in humans, but as more and more candidates emerge, the likelihood dramatically increases that one will work in humans.

Methods

This paper conforms to the relevant ethical guidelines for animal research.

Acknowledgments

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Abbreviations

FDA	Food and Drug Administration
IGF	Insulin-like Growth Factor
SIR2	Silent Information Regulator Two
IIS	Insulin/IGF Signaling
PKA	Protein Kinase A
mTOR	Mammalian Target Of Rapamycin
TORC1	Target of Rapamycin Complex 1
TORC2	Target of Rapamycin Complex 2
ADRB2	Beta-Adrenergic Receptor
NIA	National Institute on Aging
S6K1	S6 Kinase 1
MAP Kinase	Mitogen-activated Protein Kinase

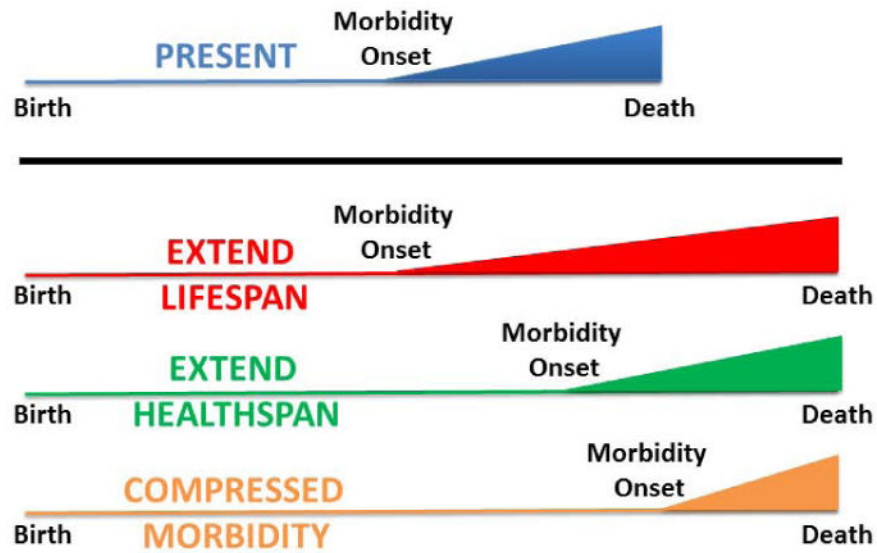| **AMP Kinase** | 5′ Adenosine Monophosphate-activated Protein kinase |
STACs	Sirtuin Activating Compounds
DR	Dietary Restriction
LMNA	Lamin A/C
HGPA	Hutchinson-Gilford Progeria Syndrome

Figure 1. Possibilities for lifespan extension

In the diagram (Blue - normal lifespan, the total lifespan is depicted as the length of the line, whereas morbidity onset associated with chronic diseases occurs at the inflection point. There are three ways in which lifespan might theoretically be extended. In red, lifespan extended with no alteration in the onset of morbidity. This is the most non-preferable option since it creates a prolonged period of high healthcare costs and low quality of life. In green, lifespan extension is accompanied by a coordinate delay in the onset of morbidity. Thus, healthspan is enhanced relative to morbidity. Many animal models of enhanced longevity appear to fit this paradigm. Finally, in orange, lifespan is extended with a reduction in the period of chronic disease, a condition termed compressed morbidity. While the most preferable, this result has not been consistently achieved in animal models to date.
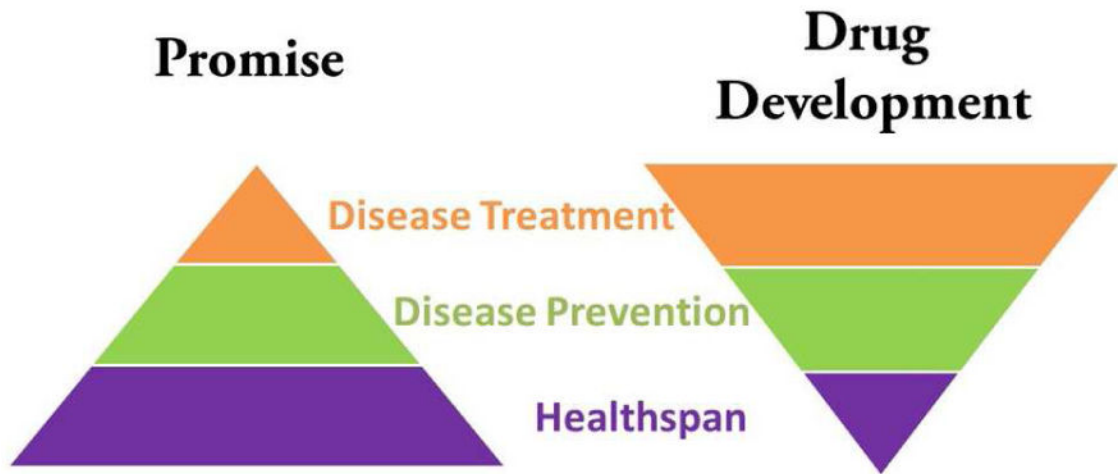
Figure 2. The translational promise of aging research is mis-aligned with current approaches to drug development
By manipulating the pathways that underlie and promote aging, researchers hope to extend healthspan, the disease free and highly functional period of life (purple). This approach will likely lead to interventions that prevent the onset of age-associated diseases (green). Less clear is whether treatments for disease will be generated (orange). However, most drug development is focused on disease treatment, with a smaller emphasis on prevention in part due to the high cost of often lengthy trials. The concept of providing drugs to healthy people to keep them healthy longer has yet to emerge as a mainstream approach.
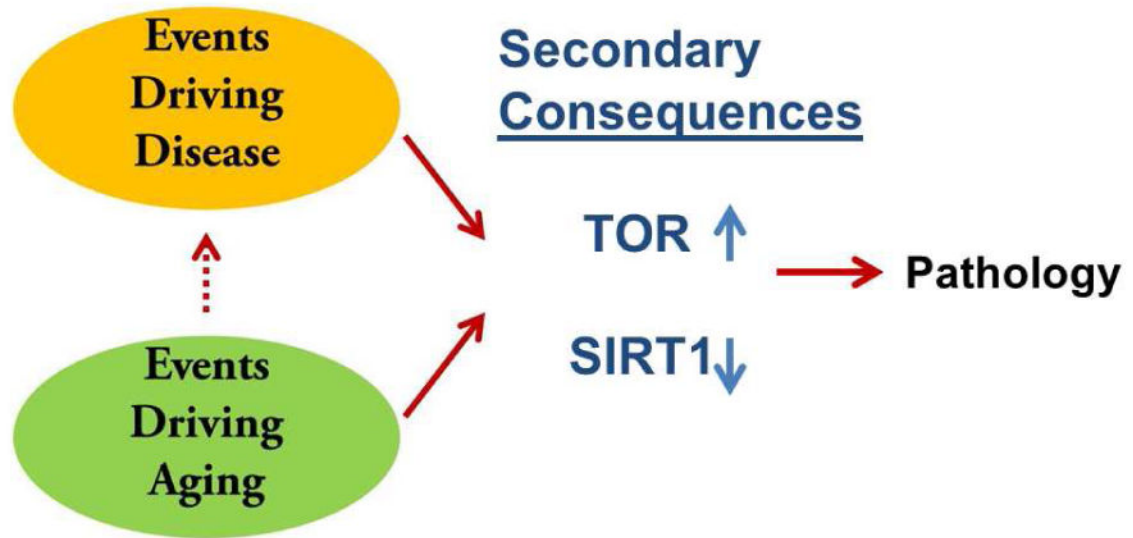
Figure 3. What goes wrong when things go wrong
From recent studies, we put forward the hypothesis that major aging pathways that have been discovered, TOR signaling and SIRT1-dependent protein deacetylation, may be linked not only to normal aging processes but also over-represented in disease states. With mammalian aging, it is emerging that TOR signaling is elevated aberrantly and SIRT1 activity is reduced. These may occur in response to the primary molecular events that underlie aging, but appear not to be beneficial compensations. Restoring SIRT1 activity of suppressing elevated TOR signaling suppresses aging pathology, extends lifespan or both. Primary aging molecular events almost certainly promote many disease states as well. Interestingly, however, aberrant TOR and SIRT1 function may be an enriched occurrence in a range of diseases, even ones not associated with aging. If true and if the trend continues, it suggests that a new approach to therapy may be possible. Aging pathways may emerge as targets for a wide range of disease indications, not all of which age-related. Thus it may be possible to identify small molecules that target aging pathways, such as rapamycin and resveratrol, and then use them to probe disease indications for efficacious outcomes. If so, aging research will yield therapeutic strategies, but not in the way expected.