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From Fruit Flies to the Frontline: Slow Science in a Demanding Medical Climate

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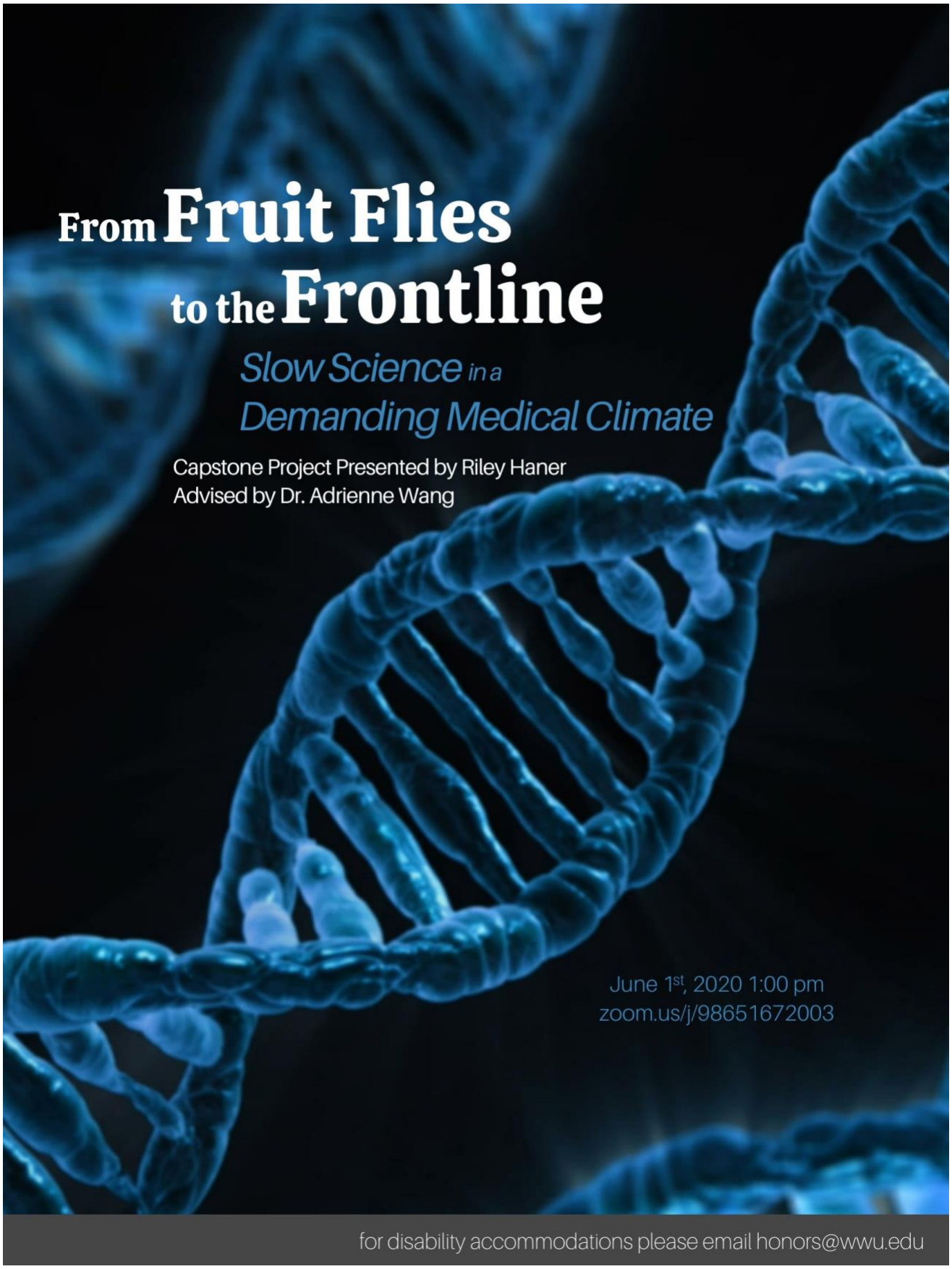
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Slow Science in a
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Capstone Project Presented by Riley Haner
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From Fruit Flies to the Frontline: *Slow Science in a Demanding Medical Climate*
Capstone Project by Riley Haner

At the beginning of the 19th century, very few countries had a life expectancy over 25 years. Extreme poverty and little medical knowledge meant many people expected an early death. In the last 150 years however, health statistics around the world improved tremendously. High risks of early death and mid-life mortality meant few people lived long enough to die from chronic diseases of aging; the aging process was simply not seen as a risk to public health. Breakthroughs in laboratory sciences however, led by **Koch** and **Pasteur**, ushered in strategies aimed at understanding and treating the acute diseases that were prominent among a young population (Marvasti & Stafford 2012). These led to advances in **sanitation**, **vaccination**, antibiotics, **publicly funded healthcare**, and specific medical interventions such as in the treatment of chronic diseases like **cancer** and diabetes or infectious diseases like **malaria** and influenza that have been crucial in enhancing both the quantity (lifespan) and quality (**healthspan**) of people's lives.

For many countries, life expectancy has since more than doubled, surpassing 65 years for men and 70 for women (Riley 2001). In Norway, Sweden, Australia, and Japan female life expectancy has risen for 160 years at a steady pace of nearly 3 months per year (Oeppen & Vaupel 2002).

Experts have, multiple times, had a hard time imagining the rising lifespan estimated to rise much further. An ultimate limit to life expectancy has been suggested many times. For example, in 1928, Dr. Louis Dublin used current US census tables to estimate a hypothetical maximum of 64.76 years for both men and women (Dublin 1928). At the time, US life expectancy was 57 years. Without access to the non-Maori life table of 1921, however, Dublin did not know that female life expectancy in New Zealand had already reached 65.93 years (Oeppen & Vaupel 2002). Similar conclusions were made by Olshansky et al. in 1990, where they asserted life expectancy was "highly unlikely to exceed 35 years at the age of 50, unless major breakthroughs occur in controlling the fundamental rate of aging" (Olshansky 1990). That cap was surpassed by Japanese females in 1996, alluding to a pattern of estimated of lifespan limits that are broken about 5 years after publication (Oeppen & Vaupel 2002).

Because these lifespan estimates have increased by 2.5 years per decade for over 150 years, it would not seem unreasonable to envision this trend continuing into the coming decades (Oeppen & Vaupel 2002). This estimate would predict life expectancy to reach 100 before 2100 and would imply

future centenarians may be commonplace within today's populations. Although these modest increments in life expectancy may plateau far below reaching true immortality – which is especially likely when accounting for factors like **homicide, suicide, war, unavoidable accidents**, unprecedented **environmental collapse**, **antibiotic resistance**, or **future pandemic events** – they have fueled enormous increases in overall population size, economic output, and **self-reported satisfaction** for life.

These life-extending moves that come about by changes in many social aspects are often targeted at reducing rates of individual mortality. For populations of similarly low overall mortality – i.e. **fewer rates of death** – most individuals naturally survive to similar ages, implying a focus on reducing mortality in individual cases was critical in improving the lifespan for a greater population. For instance, before 1950, aiming to reduce death rates at younger ages primarily increased life expectancy. On the other hand, in the second half of the 20th century, it was a focus on survival *after the age of 65* drove life expectancy (Oeppen & Vaupel 2002).

With fewer young people – attributed to a decreasing **fertility rate** – and a lower mortality rate, there has been a particularly dramatic boom in the relative number of the elderly. This makes those over 80 the fastest growing population around the world (Nass & Thorner 2004). Currently, 600 million persons worldwide are age 60 or older. The **World Health Organization** estimates that number will reach 2 billion people by 2050 (WHO 2016).

The process of aging is generally characterized by a progressive decline in physiological stability that leads to an increased risk of death (López-Otín 2013). This deterioration is the primary risk factor for many major human pathologies, including neurodegenerative disease, immunosenescence, and somatic diseases like cancer, diabetes mellitus, osteoporosis, arthritis, and cardiovascular disease (Jaul 2017). As a specific example, the risk for developing Alzheimer's disease, an age-associated neurodegenerative **disorder** in which there are currently no treatments that effectively delay *or prevent* its onset, has been shown to double about every five years after the age of 65 (Alzheimer's Society 2020, Kaeberlein 2013).

The generally *healthiest* age group, on the other hand, is the group of people younger than 40 years of age that have the fewest cases of chronic disease. It has been well established that the majority of patients *with* a chronic ailment are over the age 65. While 80% of this age group has one chronic disease, about 50% of this group have at least two (Prasad 2013). The widespread accumulation of these conditions is alarming for today's aging population.

The economic burden of chronic disease has accelerated; increases in the prevalence of chronic disease are "outstripping reductions in acute infectious diseases" (Marvasti & Stafford 2012). For a person with one or more chronic conditions, healthcare costs are an estimated five times higher than a person without a chronic disease (Dukes 2019**)**. The most common chronic ailments, causing 70% of US deaths, are cardiovascular disease, cancer, and diabetes (Marvasti & Stafford 2012). They account for nearly 75% of the nation's $3.3 trillion in annual healthcare expenditures (Healthy People 2020**,** Marvasti & Stafford 2012).

Although chronic disease is often referred to as all non-communicable disease, there have been **several studies** that outline many socially transmittable components of these conditions. When considering conventional **infectious diseases**, however, the elderly are one of the most susceptible groups. Seasonal influenza deaths by age have historically been **U-shaped**; deadliest for the very young and the very old. In 2018, 83% of influenza-related deaths occurred among people age 65 and older (Fox 2020).

"One of the most striking features of the COVID-19 pandemic is this disproportionate impact on the elderly," Says **Dr. Matt Kaeberlein**, "Nearly 80% of the over 100,000 deaths in the United States have been age 65 and older" (CDC 2020, Kaeberlein 2020). The shocking statistic is also seen in the relative **age and mortality distribution** of both the **seasonal flu** and **the 2009 H1N1 influenza epidemic**.

The **1918 H1N1 influenza pandemic**, on the other hand, is unique amongst influenza outbreaks. In the United States, this pandemic caused 500,000-700,000 deaths; nearly half were otherwise healthy, young adults (CDC 2019). The age-specific influenza deaths for the 1918 pandemic exhibits a distinct **W-shaped** pattern with the addition of a middle peak of deaths in young adults between the ages of 15 and 35. It is the first pandemic in which the absolute risk of influenza risk was higher in those younger than 65 than in those older than 65. Although the cause of this phenomenon has remained largely unexplained, it has been hypothesized that the elder populations could have been exposed to a related influenza strain during the **1889 H3N8 pandemic**, from which they developed a partial immunity to the 1918 virus (Taubenberger & Morens 2006).

There are several explanations for why the COVID-19 virus preferentially **targets the elderly**. Patients with underlying health conditions had a 79% greater chance of requiring advanced care (Begley 2020). Age-associated **immunosenescence** provides an opportunity for the virus to gain a foothold that the body's adaptive immune system cannot fend off (Kaeberlein 2020). Age-related

frailty also tends to lower resistance to stress (Epel 2014). “These are important risk factors, but the real reason COVID-19 kills the elderly is because of aging – specifically, these risk factors are driven by the biological mechanisms of aging,” **says Kaeberlein**. These mechanisms are suggested to have a forthcoming prominence in healthcare.

Currently, however, the biomedical sciences are dominated by the disease-model approach to health extension and prioritizes the study of pathological mechanisms with the goal of discovering treatments for specific diseases. This strategy has undeniably benefitted modern medical care and human health; “many new treatment options are helping people live longer today than ever before” **said Dr. Matt Kaeberlein in 2015**. Even so, medicine has been largely unsuccessful at “postponing, ameliorating, or preventing the accumulation of morbidities during aging,” he says. This approach has significant implications for families that “struggle to care for elderly relatives who survive for years or even decades with reduced quality of life” and nations that “devote an increasing proportion of finite resources toward medical care for their aging populations” (Kaeberlein 2015). There may be room to suggest another philosophy for modern medical practice.

What comes with the challenges of managing chronic disease is an increased emphasis on “basic research in the biology of aging” (Kaeberlein 2015). This effort hopes that by “successfully delaying the intrinsic rate of biological aging” therapeutics could “simultaneously delay the onset and progression of each age-related disease” (Kaeberlein 2015). This new strategy is likely a more effective tactic than those aimed at treating or curing an individual disease, as even if interventions could completely eliminate cancer, heart attack, or diabetes, most people would still fall far short of achieving significantly longer and healthier lives (Perry 2010). In the United States alone, the economic value of this *delayed-aging* scenario may be worth an estimated $7.1 trillion over fifty years, in the form of relaxed insurance costs and continued fiscal contribution (Goldman et al. 2013). Even a “modest one percent reduction to cancer onset” may be worth $500 billion (Murphy & Topel 2005). There is also, however, an undeniable, intrinsic value to individuals for living even a small amount healthier and for a small amount longer that goes beyond any extension of their contribution to the annual GDP.

Understanding the diverse and complex process of aging, nestled between chronic disease and communicable disease susceptibility, represents a fundamental keystone for **efforts in improving both longevity and quality of life**. From studies on the **mechanisms of aging**, there have been nine “hallmarks of aging” proposed by **López-Otín et al. in 2013** as “genomic instability, telomere

attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication." These hallmarks have been established to underlie the progressive loss of physiological integrity that is common among the elderly.

While not all of the hallmarks have been fully prescribed specific interventions that succeed in ameliorating aging, the formalization of the hallmarks has built a strong framework for studies into the normal mechanistic process of aging. And importantly, this endeavor has carved out space for basic science to characterize the interplay between individual hallmarks and related diseases through the experimental aggravation and amelioration of each hallmark, especially within simple model organisms.

There have been a number of **geroscience** interventions speculated to have clinical potential to modulate the hallmarks of aging. Among those are dietary restriction, exercise, telomere modifiers, **mitochondrial-targeted therapeutics**, and mTOR inhibitors (Kaeberlein 2015).

My work in Dr. Adrienne Wang's Lab has both exposed me to and invoked my interest in this aging research. Beyond obvious ethical limitations, long human lifespans make studying the direct mechanisms of aging difficult. Hence, we use the fruit fly *Drosophila melanogaster* as a **model organism** for its well-documented role exploring and quantifying the pathological mechanisms of neurodegenerative disease and how these might interact with the molecular changes associated with age. Among the hallmarks of aging, mitochondrial deficiency stands out as a worthy study candidate as it is attributed to both normal aging and specific mitochondrial disorders. Our work builds upon Dr. Wang's post-doctoral work in the **Kaeberlein lab** where she used a fruit fly model to characterize a mitochondrial mutation implicated in the onset of Leigh Syndrome – also known as juvenile subacute necrotizing encephalomyelopathy – a devastating mitochondrial disorder most common in children. Her work into one of these mutations – a 9-nucleotide deletion compromising a subunit of ETC complex I (so called "ND2") – found the mutant strain to have decreased ETC complex I assembly and function, locomotor and lifespan deficits, as well as a positive response to treatment with the pharmaceutical compound **Rapamycin**, alluding to its potential to ameliorate the physiological manifestations of **mitochondrial dysfunction** (Wang 2016).

Rapamycin was isolated from a soil sample from Rapa Nui, also known as Easter Island, in 1972. It was soon after found to be a potent antifungal metabolite produced by *Streptomyces hygroscopicus* with immunosuppressive and antiproliferative properties in mammalian cells (Li 2015).

Rapamycin, marketed as **Sirolimus**, was first approved by the US Food and Drug Administration (FDA) in September 1999 and was first marketed under the trade name Rapamune as an immunosuppressive therapeutic to combat organ rejection following transplant. In 2003, a rapamycin derivative was approved for use in coating coronary stents. In 2007 and 2009, two rapamycin derivatives were approved for the intended treatment of advanced renal cancer. Most recently, the compound was approved in 2015 to treat **lymphangioleiomyomatosis** (LAM), a rare progressive lung disease that is caused by unregulated activation of mTOR (Kristof 2010).

Rapamycin is an inhibitor of the (aptly named) mechanistic target of rapamycin (mTOR). This mTOR molecule is a protein kinase involved in a signaling pathway central to cell survival. mTOR activity also influences cell proliferation, cell-cycle progression, mitochondrial metabolism and insulin-like signaling (Kaeberlein 2009). In addition, mTOR activity regulates translation and inhibits autophagy – both of which have been implicated in the normal process of cellular aging (Acevo-Rodríguez et al. 2020).

Within cells, rapamycin binds to the FK506 binding protein 12 (FKBP12), and the FKBP12-rapamycin complex inhibits the activity of mTOR complex 1 (mTORC1). TOR, a ~240 kDa serine/threonine protein kinase serves as a core component to two distinct multi-protein complexes, either mTORC1 or mTORC2, to form the active multi-domain regulator complex, colloquially referred to as mTOR (Kristof 2010). The rapamycin-sensitive mTORC1 arm of the macromolecular complex is defined by the presence of the regulatory associated partner of mTOR ("Raptor"). Following glucose deprivation, hypoxia, amino acid or growth factor-sensing pathways, Raptor links mTOR to one of its many effectors, including the likes of p70S6k, which can phosphorylate downstream pathways including Rag, Rheb, and FKBP38 (Kristof 2010).

By inhibiting the phosphorylating ability of mTOR and regulating proliferation, the activity of rapamycin stands out as a therapeutic for LAM, as well as **many syndromes** where excessive mTOR activity and unregulated growth is a prominent feature (Kristof 2010). As recently as 2019, rapamycin has even **been posed** as a potential therapeutic for Alzheimer's disease (Kaeberlein 2019).

With readily-accessible **genetic tools**, my group at the Wang lab uses **drosophila stocks** with known mutations in mitochondrial proteins that we suspect model both human disease and may exhibit mTOR dysregulation. There are hundreds of proteins involved in normal energy metabolism and the formation of the electron transport chain (ETC) complexes I, II, III, IV, V and pyruvate dehydrogenase (Lake & Thorburn 2016). Each is susceptible to mutations with profound **pathological implications**.

These energy-generating structures give the mitochondria its nickname the *Powerhouse of the Cell*. Pediatric mitochondrial disorders caused by deficiencies in mitochondrial function are a devastating category of disease. Leigh Syndrome, the most common of these diseases, bears symptoms that typically appear in early infancy and progress rapidly until death, usually before patients are 7 years old (Wang 2016). This disorder has been linked to mutations in over 70 different mitochondrial proteins, with the most common deficiencies found in complexes I and IV (Lake & Thorburn 2016).

Our research utilizes drosophila strains with mutations in mitochondrial genes to quantify the physiological deficiencies – decreased lifespan and worsened motor function – caused by mutations in specific ETC complexes and the extent to which these mutations lead to changes in TOR activity. We then test the efficacy of rapamycin as a therapeutic that may ameliorate functional deficiencies. In our preliminary experiments, we have conducted **lifespan analyses** and locomotor assays – testing age-related changes sensitivity to **mechanically-stimulated paralysis** and **climbing behavior** – on cohorts of mitochondrial mutants. These experimental flies were reared alongside a **genotype** that has been previously documented to show an increased lifespan and improved locomotor activity with age when treated with rapamycin and is used as a positive control.

In our unpublished work, we have characterized mutants with deficiencies in the mitochondrial electron transport chain. One strain, colloquially referred to as **TTC19**, is homozygous for a nonsense mutation in the tetratricopeptide repeat domain 19 gene which encodes for a protein with a tetratricopeptide repeat (TPR) domain that embeds in the inner mitochondrial membrane and is involved in the formation of mitochondrial ETC complex III. Another strain, referred to as **SIRUP**, possesses a TALEN-induced two base pair deletion that results in a null allele for the starvation-upregulated protein, a gene that encodes a critical assembly factor for the enzyme succinate dehydrogenase (SDH), also known as ETC complex II.

The mitochondrially-deficient mutant strains exhibit decreased lifespan and reduced climbing ability as compared to the control. Drosophila lifespan models human longevity and locomotor activity models age-related declines in motor function, which we use as an indicator of relative healthspan. Some of the findings thus far also suggest rapamycin may partially rescue some of the these phenotypes back to wildtype levels, but further research is needed to establish the efficacy of rapamycin in treating diseases caused by deficiencies in complex II and complex III of the ETC.

Rather applicable to the COVID-19 pandemic, where a compromised immune system poses a serious threat to the elderly, rapamycin was initially proposed as a potential therapeutic for its

immunosuppressive qualities that come from mTOR inhibition. As a therapy, it has been shown to have the ability "to **boost response to the flu vaccine** and simultaneously **reduce the risk of respiratory infections** in otherwise healthy people over the age of 65" (Kaeberlein 2020). "Protection against Alzheimer's, heart disease, cancer and other age-related diseases," Kaeberlein says, "would be a nice side effect to such an immune-boosting therapy."

From fruit fly to frontline, the process of developing a therapeutic is an immensely laborious and resource-exhausting process. The clinical trials alone have estimated costs of $19 million. This small but necessary step makes up less than one percent of the overall cost of a drug's development (Moore 2018). The median overall cost hovers above $2 billion USD, with **some research and development** totaling over $5 billion (Herper 2013). When attaining **FDA approval**, a novel drug undergoes a series of clinical trials in which its off-target interactions are documented, and its effectivity is validated. Given that human lives are at stake, this process is especially essential for ensuring only safe and effective therapeutics reach the market.

There is clearly potential for rapamycin (and other mTOR inhibiting analogues) as an anti-aging therapeutic beyond its currently-FDA-approved immunosuppressive capability. Research in the field has yet to reach a point of diminishing returns when studying interventions that promise to combat the ailments of our modern aging world. However, we still must consider and prepare to accommodate a **handful of challenges** that have arisen from clinical-observational review. These challenges include: **insulin sensitivity**, **wide-ranging dosage curves**, paradoxical **inflammatory manifestations**, unknown **interactions with gut microbiota**, or in existing applications, low efficacy to risk ratio **as compared to alternatives**.

Ironing out these intricacies is a **long and arduous task** – due, in no small part, to the **fractally-scalable** nature of biomedical research – that is represented by the high R&D costs. It requires extensive understanding on a breadth of scientific literature and imposes significant consequences for the modern scientific community.

Changes in the publishing world, both technological and economic, have led to increasing efficiency in the production of publications. Transdisciplinary studies have discovered an exponential growth rate in the volume of scientific literature. Using text analysis of phrases from titles and abstracts of various publications and found that while the number of publications grows exponentially, the "space of unique scientific ideas" has expanded only linearly (Fortunato 2018). This growing

competition for publication and funding space has important implications for the objectivity and integrity of research.

Scientists, like all humans, certainly have ties to the outcome of their own research that makes separating from ingrained biases difficult. Pharmaceutical research certainly has a financial stake in the outcome of its result, motivated to promote medications with unrealistic expectations for what they can produce. Academic scientists also face a *publish or perish* culture, especially within the biomedical community when facing the rise in society's alarming medical conditions. Papers are less likely to be well-received nor cited if they report negative results (Fanelli 2010) This leads to journals preferentially publishing high-impact, significant, positive results (Fanelli 2010, Fortunato 2018). The resulting system seems to deter safer, incremental research, and biases scientists to produce publishable results at all costs. It pressures researchers to go with one method of data interpretation that results in a data point that is "significant or otherwise novel and unexpected, gradually encouraging researchers to investigate "more and more unlikely hypotheses" (Ioannidis 2005). A pressure to test an increased number of contrived relationships certainly contributes to the false positives and exaggerated results that are rampant symptoms of this practice. These factors have the collective side effect of making science feel *fast*: research is fragmented, competition is fierce, and single studies are often given more emphasis than is given to those that incorporate a larger scope (Ioannidis 2011).

On the other side of this initiative, competition is encouraged, if not applauded in scientifically advanced countries because it increases the efficiency and productivity of researchers. Nobel laureate designations, for instance, are reserved for discoveries that open new avenues of research or that yield practical applications in several branches of science and medicine. For example, Thomas Hunt Morgan (whose model organism was of course the *Drosophila melanogaster*), was awarded the Nobel Prize in Physiology and Medicine in 1933 for his discoveries that would establish the basis of the modern science of genetics (Moore 1983). From his work in identifying and tracing mutations, he demonstrated that *genes* are carried on some enigmatic material that would later come to be known as *chromosomes*. Morgan's discoveries paved the way for an array of molecular biologists who were frequently (and deservedly) accompanied by Nobel prizes themselves. Of note have been **Avery and MacLeod**, **Hershey and Chase**, **Watson and Crick** (and **Rosalind Franklin**), and **Jennifer Doudna**, among others.

As of 2019, the molecular causes of nearly 6,500 human diseases have been identified, yet only about 500 have effective treatments (WIPO 2019). By 2030, it is likely that science and medicine will have seen promise for genetic technologies in treating and even curing the diseases that currently seem out of reach. There is certainly an application for such a technology in targeting the genes that regulate aging and the molecular processes that they represent. In principle, targeting these processes should be effective at 'delaying onset and perhaps even reversing the pathologies of specific age-related diseases" (Kaeberlein 2019). Given the **undesirable consequences** of implementing widespread genetic engineering technologies – even if they promise to eliminate genetic diseases and enhance lives – the question of "whether or **how we want to limit** them remains **open and pressing**" (Evans 2003).

As technological advances are clearly of significant clinical importance, the **future of healthcare** will hopefully come to benefit continued improvements to both **productivity and compassion**. Likely, new advances will have incredible implications as they are gradually integrated into normal use. Some of these more broad-reaching technologies may resemble **an improved EHR system** that harnesses **the power of AI** to allow more efficient and reliable physician-patient interaction, **widespread telemedicine** that extends the range of medical care, and a **computational model of the brain**. As for further improvements, aspiring physicians should be taught about systems science that addresses determinants of disease – age, psychological, social, and economic factors – that are not traditionally emphasized in disease diagnoses. As an emphasis on prevention is slowly integrated into the organization and practice of medicine, the "unabated, economically unsustainable burden of chronic disease can be stemmed" (Marvasti & Stafford 2012).

Science, at its core, is a struggle to produce knowledge for the benefit of all of humanity against the cognitive (and moral) limitations of individual human beings. However, we have been made aware of the rampant publication biases and incentive for p-hacking that are fueled by scientists' own acts of self-preservation. To remedy this ailment of the modern **scientific process**, we can seek to channel a mentality that has been referred to as the "**Slow Science Movement**." It encompasses the incremental, methodical, and critical thinking that science needs to be most effective and trustworthy; "time to think, to read, and to fail" (SSA 2010).

There are serious implications that our aging population has on the modern healthcare model which will require a massive, interdisciplinary effort to address. These issues invoke both a personal and social responsibility to better understand the underlying complex mechanism of aging. By

extending these findings to age-related diseases or by targeting the rate of aging itself, we may be able improve both lifespan and quality of life.

In an article detailing the movement, Dr. Paul Sutter concludes:

"The progressive accumulation of scientific knowledge is not a sprint. It does not leap from discovery to discovery, impatiently waiting for the next miracle cure, constantly rewriting, and overhauling long-held beliefs at a moment's notice. Sure, science is a process of continual, never-ending updates, but it is a slow, gradual exercise that creaks and groans forward through the years, decades, and even centuries. If a headline claims a major new discovery will completely change our paradigms, it is likely incorrect. Not because the result may be incomplete or even incorrect, but because, mathematically, not all that is published can be correct. As such, science must take pride in vetting each new piece of evidence before its normalization into existing frameworks but be prepared to dismantle that framework in favor of a new one if the evidence accumulates beyond a certain critical threshold. Individual scientists routinely focus on almost bizarrely narrow problems, a subset of a subset of a subset of a larger theory. This is where the real progress in science is made: tiny efforts, slowly inching outwards and pushing on the boundaries of our knowledge" (Sutter 2018).

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