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Introduction

What doesn't fit is often what is getting at something exciting!

—DR. EVELYN WITKIN, AMERICAN GENETICIST WHO TURNED 100 ON MARCH 9, 2021

IN THE LATE 1990S, I was a graduate student in the lab of Jim Spudich, in the Department of Biochemistry at Stanford University. I studied how the motor protein myosin—the molecular motor that powers our muscles and makes our hearts pump—works, by swapping parts from myosins of "slow" and "fast" organisms, and then testing how those swaps affected its activity. I loved that protein; understanding how a sequence of amino acids arranged the right way could take energy and turn it into movement by swinging its "lever arm" a small distance was one of the most interesting questions I could imagine at the time. But when I explained my research to people at parties who asked me, "What do you do?" they would nod and politely smile, then ask when I would graduate. That would be the end of the discussion.

That all changed a few months later after I heard a fantastic talk by Dr. Cynthia Kenyon, a professor from the University of California, San Francisco (UCSF). Cynthia is a lively, engaging speaker and she told the audience about her lab's work on aging and longevity in a small worm, the nematode *Caenorhabditis elegans*. Her lab had found that changing a *single gene* could double the lifespan of these animals,[1] and she showed movies of the mutant worms crawling around at an age when normal worms were already decrepit and dying. This was an "Aha!" moment that made it clear that she wasn't talking about extending the end of life, but rather the youthful, healthy part of life, an outcome that we would all like to experience. That gene, called *daf-2*, turned out to encode an insulin/IGF-1 receptor, meaning it could matter for people, too, since our bodies also have insulin. After hearing her talk, I knew what I wanted to do: find out how those mutant worms were so healthy. Soon after, I asked Cynthia if I could come to her lab for my postdoctoral research,[2] and she agreed. At that point, when people asked me what I was going to do, there was a noticeable difference. It turns out that almost everyone is interested in aging research, and everyone has an opinion about it. It quickly became obvious that one's likelihood of supporting the idea of aging research is generally correlated with one's age, and I got several exhortations to "work faster!"

I decided to write this book after developing a class at Princeton, "Molecular Mechanisms of Longevity: The Genetics, Genomics, and Cell Biology of Aging," to teach students about my research field. While preparing for that class, I realized that we (the royal We, being researchers in the field of aging and longevity) have made many molecular insights in the past two decades that would be good to convey to the general public. While the popular science market for longevity books is saturated—no one needs another celebrity's viewpoint on aging or another diet book, and several excellent introductory books already exist—at least a few people might want to have a molecular explanation of the exciting work that has been done in this arena. As I will explain, we have found out a LOT in the past two decades about how longevity is regulated, which can give us clues about how we might slow aging. We now have a better grasp of the genetic pathways and cellular processes that communicate from one cell to another how to tune the rate of aging, and we also better understand the reasons that longevity is regulated at all. These insights have then led to ideas about how to slow age-related decline, and we have some good candidates for those medicines now. Some of this excitement has recently been turned into serious biotech development, with many companies focused on longevity and aging springing up in the past few years.

I have been lucky enough to be right in the middle of things since 2000, since new genes that control longevity had just been revealed. The millennium was a real turning point: after bacteria and yeast, *C. elegans* was the first multicellular organism whose genome was sequenced, and *Drosophila* quickly followed. Those large-scale projects were a direct benefit of the approaches developed for the Human Genome Project and allowed biologists to carry out experiments that had not been previously possible on a genome-wide scale. RNA interference (RNAi), a mechanism that causes the messenger RNA (mRNA) of a gene of interest to be degraded, was first described in detail by Craig Mello and Andrew Fire in *C. elegans* in 1998,[3] and it was quickly employed by the worm field to test *all of the genes in the genome* for every characteristic of interest—including aging—through new tools to easily knock down gene expression levels.[4] This ability to rapidly test many genes in worms quickly led to an explosion of functional genomics (that is, testing of all genes in a genome for a particular activity), and the field has been expanding in many directions ever since.

I got into the aging field because I was fascinated with the question of how longevity and aging are controlled genetically and biochemically. The tools that were newly available at the time, genomic expression microarrays and RNAi, allowed a previously unimaginable ability to probe long-lived mutants (that is, animals with changes to their DNA that affect a gene) and to learn what was going on inside them. The existence of complete genome sequences for all of these organisms also ushered in new genomic approaches, such as DNA microarrays and later next-generation sequencing, allowing the analysis of every gene simultaneously and giving us unprecedented insights into the inner workings of cells as they age. The amount of data available to researchers has been exploding ever since. Genetic and genomic methods have led the way in longevity research, and large-scale studies of metabolism have added to our understanding. Meanwhile, new molecular tools, particularly the gene-editing tool CRISPR and stem-cell approaches, offer the exciting possibility that we might even modify ourselves to achieve better health.[5]

Because of the nature of the question—understanding how aging works—the field is extremely broad. One can attack the aging question from many different viewpoints: demography, population genetics, evolution, model-system genetics, molecular biology, cell biology, nutrition science, and pharmacology. All of these perspectives are helpful in understanding how aging works and whether we can slow it down. While I will tell you about my lab's work (and I'll try not to *only* talk about our work), I will also explain the latest work throughout the field. It's a fast-moving field, with new discoveries all the time, and inevitably a few things will be missed, but I'll try to give you a good understanding of not only what we know but *how* we know it—the work that was done to figure things out.

What you will not find in this book are descriptions of what I or other scientists eat, or weigh, or how often we exercise—all information that has somehow become the norm for pop-sci books and articles on aging and the researchers who work on aging. As a scientist, I can't stand reading this information—those are all "*n* of 1" experiments whose results we don't yet know, so I won't report them—it's just bad science. Additionally, I've noticed an odd cult-of-personality air about some aging books, and those cults usually leave out the contributions of female scientists. And I'm not a longevity evangelist; I'm not trying to sell you something, no supplements or drugs or diet plans. I just want to tell you what we know about aging and how we came to these conclusions.

Finally, I won't be using the popular phrase, "*. . . , at least in worms and flies*," which seems to pepper most books on aging. I am an unapologetic model-system advocate, for one simple reason: almost everything we know at the molecular level about the underlying mechanisms controlling (regulating) longevity is because of the work that was done first in invertebrate model systems, and then *tested later* in higher organisms (mammals like mice), a fact that is often overlooked and underreported. Beyond that, the tools that allow us to do the work, all the way up through human cells, have been identified, characterized, and tested in these simpler model systems before being adapted for use in mammals. (The most powerful yet may be CRISPR, which was first discovered in bacteria.) Without model systems, our understanding of longevity regulation would be very poor indeed. For that reason, I won't just be talking about studies of humans with some verification in mice, but I'll try to describe how we really learned about the molecular goings-on inside all of our cells, which relies on studies in small invertebrate systems. For the Sarah Palins of the world, who do not acknowledge the contributions of fundamental ("basic") research to medicine,* this will be a shock, but for the rest of you I hope it will give a fairer insight into how scientists actually learn how things work, and how we might apply what we've learned to help people live better, longer—as Palin would say, *I kid you not*.

In this book, I hope to let you know what we've discovered about longevity in recent years. But before diving into the science, I'll discuss *why* we should study aging—it's not always immediately obvious, but understanding aging could help our whole society in the long run, even economically (chapter 1)—longevity is not just for billionaires. There are many evolutionary theories about *why* we age (chapter 2), but molecular techniques are now helping us better understand this question and adjust our theories accordingly. In

* "You've heard about some of these pet projects, they really don't make a whole lot of sense and sometimes these dollars go to projects that have little or nothing to do with the public good. Things like fruit fly research in Paris, France. I kid you not" (Sarah Palin quoted in Adam Rutherford, "Palin and the Fruit Fly," *Guardian*, October 27, 2008, https://www.theguardian.com/commentisfree/2008/oct/27/sarahpalin-genetics-fruit-flies).

chapter 3, we'll start to see how modern genetic and genomic techniques can reveal the secrets of centenarians' long lifespans; but to experimentally test them we need to use model organisms—that is, well-studied animals we can grow in the lab and genetically manipulate so that we can test hypotheses (chapter 4). Of course, in order to study aging, we have to establish some definitions of what it means, and how we can measure these changes with age (chapter 5). In later chapters, I'll describe what we currently know about longevity pathways (chapters 6–10) and interventions in detail, so that you'll recognize the molecules that are being targeted for clinical treatment (chapter 17). Reproduction and mating are intimately linked with longevity, as I'll describe in chapters 11 and 12. What we can sense can also influence how long we live (chapter 13), while aging can affect what we can sense and our cognitive function (chapter 14). Some of the newest thoughts in the field concern how we might inherit factors from our ancestors that affect aging (chapter 15), and that what we eat and the microbes that inhabit our gut might also influence aging (chapter 16). Finally, I'll discuss the current state of longevity biotech, and how we might go about finding treatments for age-related decline (chapter 17).

We are right in the middle of the business of understanding the processes that regulate aging, and it is an exciting time because we are still in that era of discovery. I don't want to imply that we know all of the answers at this time. Instead, what I hope to convey is what we do know and, more importantly, *how* we know it, and what we might be able to do with that wealth of data. With this information at our disposal, we should all be able to make wise decisions about how to manage our own longevity.

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