THE NEXT 500 YEARS

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INTRODUCTION: THE EMBRYOGENESIS OF HUMANITY

Embedded in every single neuron in a human brain is a shared ancestry of humans' genetic code—deoxyribonucleic acid (DNA)—carrying the unique capacity for protecting and preserving the complexity and beauty of all life. This DNA also contains the molecular recipe for the synthesis of human bodies, brains, and minds, whose dreams and technologies have spanned visions of other planets and spacecraft that have reached beyond humankind's first solar system. The fundamental thesis of this book is that the same innate, biological capacities of ingenuity and creation that have enabled humans to build rockets to reach other planets will also be needed for designing and engineering the organisms that will sustainably inhabit those planets.

The missions to other planets, as well as ideas for planetary-scale engineering, are a *necessary duty* for humanity and a logical consequence of our unique cognitive and technological capabilities. There is no other species that leverages, or even can leverage, the frailty of mortality into an intergenerational stability of sentience. As far as we know, humans alone possess an awareness of the possibility of our entire species' extinction and of the Earth's finite life span. Thus, we are the only ones who can actively assess the risks of (and prevent) extinction, not only for ourselves but for all other organisms as well. This is unusual. Most duties in life are chosen, yet there is one that is not. "Extinction

awareness"—and the need to avoid extinction—is the only duty that is activated the moment it is understood.

This gives us an awesome responsibility, power, and opportunity to become the universe's shepherds and guardians of all life-forms—quite literally a duty to the universe—to preserve life. This means we need to prevent the death of not only our species, but of all species on which we depend and any others we may find that are or were threatened—thus, all current, future, and even past life-forms (through de-extinction). This duty is not only for us, but for any species or entities who can engineer themselves to avoid the end of the universe. Even if our species does not survive, this duty is passed on to the next sentience, which will undoubtedly arise.

Regardless of *who* is here in billions of years (ourselves or someone else), life cannot remain on Earth, because the sun will eventually overheat the Earth, likely engulf the Earth, shrivel into a White Dwarf, and die. Earth is the only home we have ever known, and if it remains that way, it will also be our grave. Thus, it is essential for us to land on, live on, and survive on planets around other stars to continue this duty of humanity. To do this, we will need to deploy all the technological, physical, pharmacological, and medical protective measures that we know and will learn, but we can also, for the first time ever, deploy genetic measures of defense. As a part of this moral duty to preserve and protect life, we will eventually need to engineer it. Evolution has created life only in the context of one planet so far—in the Goldilocks zone of a temperate Earth—and it is likely that we, and all other organisms, will need extensive physical *and* genetic help to survive anywhere else—even if just to arrive at our next destination.

Sending any Earth-evolved organism to any other planet would result in almost certain death, which represents the sad, evolutionary "good luck" plan. This limited plan is not our only option. Today, we know enough to be able to modify, tweak, and engineer life to improve the odds of survival or to create entirely new adaptive features and mechanisms. Evolution has finally created an organism that can direct and engineer not only its own development, but also the evolutionary paths of all other life. This stage of "directed evolution" for life,

drawing on all past, current, and future genetic substrates, is an essential step for *life itself* to survive.

To save life, we will need to engineer it. Notably, humans are already *accidentally* engineering life and directing evolution; now it is time to do it with volition, direction, and purpose. Through the use of the collective genetic lessons we have learned from all organisms over billions of years, we have developed many extraordinary technologies that make this possible, and many are highlighted in this book. Our own DNA is composed of relics of what life once was, life as it is today, and the ongoing evolution toward what life will become.

However, with synthetic biology and DNA synthesis costs declining, we can even imagine extinct life returning, as well as means by which to create chimeric or hybrid entities, and this too will be examined in this book. Moreover, by using studies of organisms in extreme environments (extremophiles), we can learn new mechanisms and modalities of adaptation that have enabled alien-like life on Earth, and, indeed, some of this work we have already begun in our laboratory, such as using genes from tardigrades in human cells. These technologies and new methods will enable humans and other organisms to survive in otherwise impossible settings caused by extreme levels of radiation, temperature, or pressure.

This inherent duty of humanity—to preserve life—is as natural as one cell dividing into two. Right now, all humanity is as fragile as an embryo at the single-cell stage. We are an embryo full of extraordinary potential, but only on the primordial beginning step of our home planet. Our next step is to get to a nearby planet (e.g., Mars) and set up a sustainable habitat in order to ensure we have a backup plan for all life, including humanity. This accomplishment would be a point of euphoric celebration, as the tired eyes of a Martian explorer would watch as the sun sets on the dusty horizon, and the air would reveal beautiful blue sunlight diffracting through the thin Martian atmosphere and dust. At long last, we would have two planets to call home around the same sun.

After decades of physical and biotechnological development, we will be able to call many different celestial bodies within our own solar

system home. Through this advancement and capability of testing theories across multiple different worlds, we will acquire the ability to launch toward a second sun by 2500. Once we are an interstellar species, we will effectively have a "solar-system backup plan," drastically decreasing the chances of life's extinction. However, this begs inevitable questions: How many stars would we go to? How do we pick? How far will we travel? Indeed, given enough time, fundamental philosophical questions emerge about the endless expansion or inevitable implosion of the universe, and whether or how humanity should alter the structure of the universe as an extension of this duty. These questions will also be addressed in this book (quick preview: yes).

When given the choice between engineering life or facing inevitable death, there is clearly only one path. The right thing to do, in order to survive extinction, is to engineer at a genetic, cellular, planetary, and interstellar scale. This ensures preservation of humanity and, also, of all other life, which may not arise in the next universe or ever again. Our species' unique moral duty is a duty to the universe and to life itself. To protect the universe, we must alter the universe.

To do this, we need a long-term plan. This book will take you through the first 500 years of such a plan, including lessons from bacteria, viruses, and whole planets, as well as from the first astronauts who pushed the limits of human spaceflight.

1.1 Many cytokines changed expression during the Twins Study, comparing Scott Kelly's cytokine levels (black) to those of his twin brother, Mark Kelly, who remained on Earth (gray). Dotted lines indicate Scott's launch and return to Earth. Cytokine levels are normalized to their median expression across the analyzed time in both bothers. Some cytokines were elevated throughout the whole mission, such as C-X-C motif chemokine 5 (CXCL5), which plays a role in tissue remodeling. Other molecules primarily spiked upon returning to Earth, such as interleukin-1 receptor antagonist (IL-1ra) and C-reactive protein (CRP), which deal with inflammation and thyroid-stimulating hormone (TSH).

We quickly searched across the index of all scientific literature and medical journals to see if anyone had ever seen anything close to these levels, especially for IL-ra1 (>10,000 pg/uL). For IL-ra1, the closest we could find was for patients who had just had a myocardial infarction (a kind of heart attack), from a paper in 2004 (by Patti et al.). For IL-10, spikes were found to be associated with patients who had just survived a severe bacterial infection of the blood (called sepsis).

Somehow, even amid this discomfort, when Scott got back to Earth, he jumped right into his swimming pool and went on to live a normal life in the days and years after. However, these markers were not the only thing that dramatically changed. Other changes could be seen across his tissue systems such as his blood and bones, and we even saw additional molecular changes in his DNA and RNA. We had an unprecedented chance to look at almost everything in the body, from each nucleotide of the genetic code to how cellular responses manifested

across Scott's body, resulting in phenotypical changes. Most of these measures were entirely new metrics for any astronaut, including the first complete genetic profiles (genome), as well as other features (figure 1.2) for a spacefaring human. We used all these data to gauge what happened inside the human body during a year in space.

1.2 Multi-omic monitoring platform for astronauts and relation to the clinic. Four monitoring examples are highlighted, including astronauts, cancer patients, immunotherapy patients, and general patients. Each example highlights different -omic data that can be utilized for regular monitoring and follow-up. Molecular interactions between different -omic data demonstrate the need to integrate all these measurements into one platform.

DNA DAMAGE

We first looked at the impact of radiation, which can damage DNA, cells, proteins, and all the regulatory machinery inside cells. Flying at nearly the speed of light are galactic cosmic rays (GCRs), which originate from stars outside our solar system, and solar energetic particles (SEPs), which originate from our sun itself, both sources of radiation that flew through Scott's body. These particles leave a wake of damage like microscopic bullets through the body. GCRs and SEPs are high-energy particles, usually made from protons, helium, and a subset of high-energy ions (HZE ions, which stands for high [H], proton/atom number [Z], and energy [E]). This damage to astronauts was first observed in 1969 and 1970, when Neil Armstrong wore a foil plate around his ankles as he traveled to the moon and back. On this plate, streaks of these HZE particles can be seen displacing the sensor, like marks made by someone drunkenly playing on a high-energy Etch A Sketch or recordings from a nuclear accelerator laboratory after atoms are smashed into each other. Except, in this case, the accelerator is shooting HZE particles, and the laboratory battleground is, unfortunately, the human body.

These HZE particles normally go unnoticed during the day, but they can appear in unexpected places. When Scott closed his eyes to go to sleep at night on the International Space Station (ISS), he could see streaks of light, as if there were shooting stars behind his eyelids. These magical displays of light were actually the HZE particles blasting his retinal cells and passing through his eyes, erupting in a lightshow of beautiful, but terrifying, cellular damage as a bedtime story.

Given such reports, we were all worried about what we would find inside Scott after such a long mission. As it turns out, we had several surprises. One of the first things we expected was that his telomeres would probably break down and shrink from radiation and the stresses that accompany spaceflight. Telomeres are the ends of human chromosomes, which normally shrink as you get older, and their lengths are also associated with both diet and stress. As they disappear, the chromosomes become less stable, contributing to the normal molecular process of aging. Dr. Susan Bailey led the research to test this question,

and we sent some of our DNA to her lab, and vice versa, to confirm the results.

UNEXPECTED RESPONSES TO SPACEFLIGHT

Strangely, Scott's telomeres got *longer* when he was in space, which is the opposite of what we expected. We then triple-checked both sample sets of DNA from the Bailey lab and our own lab, and this lengthening was indeed confirmed. It was most pronounced in one type of immune cell called T cells (primarily CD4+ T cells, though evidence was also found in CD8+ T cells), with less evidence of telomere lengthening in B cells (CD19+ cells). Overall, multiple sample replicates, extractions, laboratories, and methods (FISH, PCR, nanopore) confirmed the results, leading us to conclude they were correct.

But then the immediate questions were how and why? We looked at the other data we had collected to make sense of it. Weight loss is associated with telomere maintenance, and Scott did lose about 7 percent of his body weight on the mission because of the rigorous conditions of spaceflight, but he also had daily workouts, nutritionally optimized food, and an absence of alcohol. In some ways, his life in space was healthier than it was on Earth. Also, folic-acid metabolism is linked to telomere maintenance, and the folic-acid levels in Scott's blood were also elevated in flight, adding another possibility. He gained two inches in height during the mission. He also was traveling closer to the speed of light.

Some people got very excited when we first reported these results and asked, "Is space the fountain of youth? Can you get taller and younger if you go to space?" Sort of.

First, we have to isolate all the variables and consider what else happened to him. Scott did travel closer to the speed of light, traveling at an average of 7.68 kilometers per second (km/s), which then enables a calculation using Einstein's relativity and time dilation on a human body. Time dilation occurs when an object moves closer to the speed of light, making time move more slowly for the object in motion relative to the reference frame of other objects. This is dependent on several

factors that can be entered into the Einstein/Schwarzschild equation, assuming a few parameters:

(1) A $dr = 0$ (stay at constant radius) and $df = 0$ (same orbital plane);
(2) The ISS orbital speed of 7.68 km/s, with a radius of the ISS at 400 km above the Earth's surface;
(3) The change for Mark Kelly (dt_{MK}) on Earth compared to Scott Kelly (dt_{SK}) on the ISS.

The full equation includes the coordinates of colatitude (theta), the speed of light (c), and the gravitational metric between two spheres (omega), seen here:

$$g = c^2 dr^2 = \left(1 - \frac{r_s}{r}\right) c^2 dt^2 - \left(1 - \frac{r_s}{r}\right)^{-1} dr^2 - r^2 g_\Omega$$

Given this equation, Scott became about 0.1 seconds younger than everyone on Earth, including his brother. Since Scott was born 6 minutes after Mark, this made Scott an additional ~0.1 seconds "younger" than his brother after a year in space. However, even though he is technically younger than what he would have been if he had stayed on Earth, this is not likely a significant factor for his longer telomeres.

We know this because we saw many other modalities of the biology change as well, such as changes in gene expression (off/on or up/down levels of various genes). We all have thousands of genes that change expression every day, so it was not surprising that we could see genes changing when he got to space and when he came back down to Earth. His altered genes' expression included those responsible for DNA repair and cellular respiration. His immune system was also highly activated, including when he received the first-ever flu vaccine in space. Also, we saw evidence of hypercapnia, which is a condition of too much carbon dioxide in the blood and where one can start to feel light-headed and develop a headache; indeed, this irritation was mentioned by Scott in his book. He noted that he got headaches because of the varying carbon dioxide levels, and whenever the CO_2 scrubbers of the space station would break down, he felt as if he had more headaches during these intervals.

low-level inversions and translocations, which are breaks in the chromosomes, that were continually being healed, replaced with newer cells, and genetically fixed.

Even six months later, some genes were still disrupted in their expression—still adapting—and these are the ones we will cover later in the book, when we discuss the long-term plans for human-genome engineering. The gene expression data showed how the body adapts to space and how, sometimes, it does not completely return to normal. This matches what Scott himself mentioned, that he didn't "feel normal" until seven to eight months after being back on Earth. Also, the work from Dr. Matthias Basner showed that Scott's cognitive speed and accuracy were worse after his return to Earth. In our own work at Cornell with David Lyden, we saw proteins that are normally only in the brain appear in the blood, which matched some of the same genes that created those proteins and indicated a change in the blood-brain barrier. Overall, these molecular changes give us a guide as to which genes may need to be accelerated, decelerated, or otherwise altered to help this response to spaceflight.

Other biological features that could also be tweaked come from clues in the cytokine data, specifically the inflammation markers. Some inflammation markers, like IL-6, went up by thousands of percent on the day he landed, and some even higher two days later. The blood work clearly showed a spike of inflammation cytokines that led to so much pain and is likely why Captain Kelly broke out in rashes. These data were also confirmed with cytokine data from Drs. Tejas Mishra and Michael Snyder from Stanford. When we looked all at the markers together as a pathway, the majority of the functions pointed to muscle regeneration. In short, the pain of using his muscles again was forcing a massive restructuring of the body, with his blood printing the molecular receipt of this expensive physiological purchase. In this amazing event of the human body returning to Earth from space, the blood was screaming out, "Oh crap—gravity! I need to use my muscles again!"

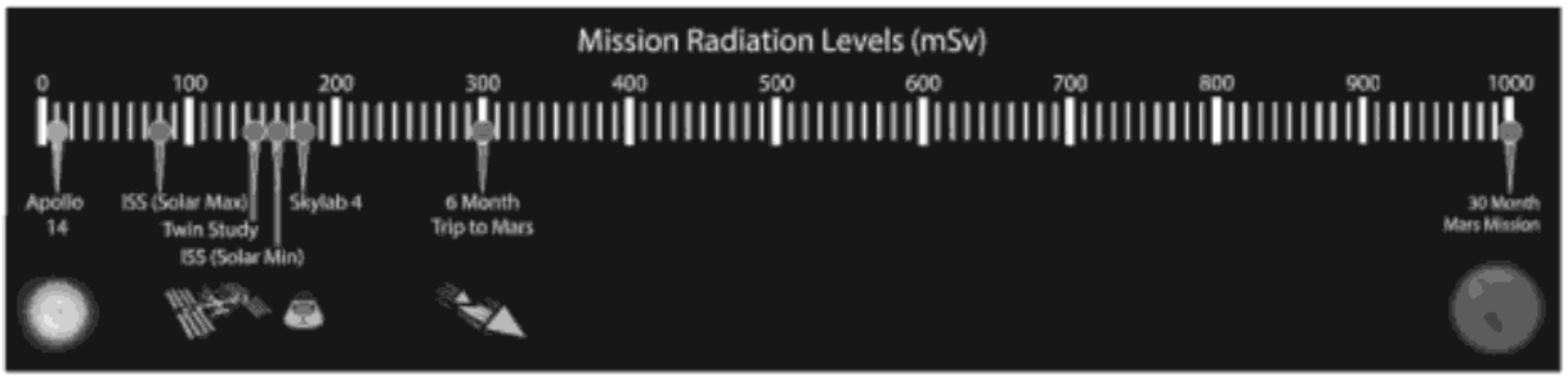
Although landing back on Earth was clearly painful, one good thing about Mars is that it has 38 percent of Earth's gravity. Given that difference, the landing might only constitute 38 percent of an "Oh crap!" moment and 38 percent of a challenge to adapt to the surface when

landing on Mars. From these results, it seems that a person could actually survive the trip to Mars, and then likely survive the landing, to begin building a new, rust-hued home.

FUTURE MISSIONS

A large caveat of the Twins Study is that we only had two subjects, derived from a single embryo, with only one in space for a longer duration—so we can only extrapolate these results to others in a limited way. Moreover, spending a year on the ISS is still within Earth's magnetosphere, which extends roughly out to 65,000 km, and still acts as a protective shield from radiation for astronauts. To get a sense of the challenge for a mission to Mars, we can compare other missions to the expected amount of radiation astronauts will incur on the way to the red planet, which is about 300 millisieverts (mSv), as well as a 30-month round-trip mission, which is about 1,000 mSv (figure 1.3). This would be more than six times the amount of radiation Scott saw in his mission. While such radiation is not pleasant, there are ways this can be addressed and protected against, which will be revealed in later chapters.

Indeed, we do not have to accept these radiation risks without defending ourselves against them. Though we do already protect astronauts physically, pharmacologically, and medically, these mitigations need to be improved, and we should further use any other means of protection for them as well. Notably, the one biological defense mechanism that has not yet been implemented for astronauts (though it has been for patients on Earth for a wide range of conditions) is genetic engineering.



1.3 Radiation metrics for various mission parameters: Estimated and measured radiation metrics for a variety of missions in millisieverts (mSv).

GENETIC DEFENSES

Given the clear risks for long-duration missions to other planets (e.g., Mars) and the challenges of later-stage (e.g., interstellar) missions that would put humans in more dangerous environments with more radiation and less ability to create food and maintain proper metabolism, an exploration into our genetic defenses is warranted. In other words, if we can learn the secrets of all other species and craft a series of genetic protections, we would be embarking on not only a needed means of survival, but also a manifestation of our own genetic duty. We do everything we can to keep astronauts safe through engineering their rockets and ships, but could we make some of the protections on the inside, within the astronauts themselves? Should we do such a thing? Is it right to genetically modify astronauts?

Some of these abstract questions became tangible with He Jiankui, who began to genetically modify human embryos using CRISPR (discussed more in later chapters), two of whom were born in 2018. He did all the work in secret and misled the Institutional Review Board (IRB) at his university, kicking off an angry response when he decided to bring gene-edited babies into the world.

Such a process of bringing groundbreaking medical technologies into the world is the absolute worst way to do it—in secret with little oversight—but the idea is no longer hypothetical. The question now is: How do we actually start to regulate genetically engineering embryos or make sure it doesn't go wrong? Numerous examples exist for precision medicine in health and disease, but what is needed to help patients on Earth and future astronauts is more *predictive medicine*. Can a scientist actually engineer something and predict what happens? That is the best test of knowledge.

To this end, the first draft of the 500-year plan was posted on our lab's website in 2011, which included many of the ideas in this book. It was also the first year we submitted the genome and metagenome proposal to NASA, where we had almost none of the information described in this current chapter. Most of the ideas that seemed impossible in 2011 have already become reality, especially the ease with which we

can now edit and modify genomes and epigenome (the regulatory landscape of the genome).

But beyond the rapid advancement of science, this plan represents hope and belief in the long-term survival of humans. One of my favorite things about humanity is that we are the only species we know of that can actually create 5-, 500-, or 5,000-year plans, or comprehend any multigenerational plan. Almost all the people who will benefit from such a plan will be born after the death of the plan's creators, yet such plans get made and can serve humanity like an intergenerational Olympic torch, bringing the bright light of past and planned progress to keep hope ignited and eyes looking forward.

The rest of this book will lay out this plan, which addresses the technical, philosophical, and ethical framework for engineering genomes, ecosystems, and planets. While seemingly abstract and almost unbelievable in scope, this large-scale engineering effort is not our first attempt. Mars will, in fact, be the second planet on which we have performed planetary-scale measurements, modeling, and engineering. In 2021, we are doing this planetary-scale engineering on Earth to continue our survival and leave a better planet for the next generations, but, sadly, with scant coordination or planning. We need to do such planetary and biological engineering with far greater precision in the future to fulfill our species' unique role of Shepherds and Guardians. It is no longer a question of "if" we can engineer life—only "how." Engineering life now exists within our generation and will continue to be improved and utilized for generations to come, be it those who exist in 500 years, 5,000 years, or much further into the future.

Engineering is humanity's innate duty, needed to ensure the survival of life.

gift—a gift that must be preserved, protected, and used before it disappears forever.

THE BLUEPRINT

Importantly, the ability to plan this far into our future was not feasible before now. The current era of humanity is different, both in *degree* and *type*. First, the degree: Before the late 1900s, we lacked the fundamental tools to even begin to describe a plan which enables the preservation of humanity through expanding to other planets. We barely had a sense of the large diversity of the biological systems on Earth—which will undoubtedly contribute to our ability to live in new environments to which we have never been exposed. Before the past few decades, we did not even know what comprised genes, let alone how many existed in human cells or those in other species. Now, we know the dynamics of thousands of genes, and we have mapped them and their functions (functional genomics) across many species. We have more genetic data than ever, and these data are rapidly growing, along with the continual production of more data in related scientific, cultural, technological, and computational fields.

The second shift in this era is in its *type*: exploring other worlds is now possible. However, the concept of sending humans to the moon or Mars was pure fantasy until fairly recently, such as in 1906, when the first plane become airborne. The first humans landed on the moon in 1969. The first spacecraft to leave our solar system was only in 2004 (Voyager 1). Whereas airplane flights were once rare, now we have tens of thousands of flights around the world departing by the minute. Similarly, before we only had a few spacecraft in flight, but now we have an ever-expanding list of countries planning lunar, Martian, and even longer missions (figure 2.1). Current plans even call for a small helicopter (Dragonfly) to be present on the surface of Titan in 2036 and boots on Mars around the same time. The twenty-first century represents a unique timeframe for humanity, both in its *type* of progress as well as its *degree* of planning.

These missions exemplify how humans have the ability to think 100, 1,000, 100 million, or many more years further ahead. If we want

grouped by locations, including low-earth orbit (LEO), the Moon, Mars, asteroids, outer planets within our solar system, and exoplanets. Years are given on the bottom and mission details are highlighted on each line.

the diversity of humanity (be it in the form of music, art, science, literature, engineering, dance, and or anything else) as well as the diversity of life that has ever been, or is currently, on Earth to persist, we need to expand the catalog of Earth's life beyond the only home it has ever known. We should not abandon our current ship—the Earth—but should instead increase the number of ships on which we live. Currently, all known life exists on a very fragile raft adrift in a vast ocean of the universe's threats of extinction. Our responsibility to preserve life extends beyond our own, to a broader comprehension of the organisms that we ingest or utilize and of how other life-forms interact and sustain each other; this extension is often called the "metaspecies," "pangenome," or sometimes the "holobiont."

A vision of humanity as Shepherds should leverage our *unique* abilities as a species to preserve life and place us as careful Guardians of all life. For life to do anything, it must first exist. Any human dream, construct, ethic, art, manufacture, invention, creation, poem, synthesized molecule, or thread of fabric can only be made if we are still alive to make it. Regardless of your priorities and goals, you must *exist* to bring them to fruition. Even if you have no goals, existence is a prerequisite to holding an empty cup of ideas. Thus, we have a responsibility before us; we hold a heavy, hard weight in our collective palms. Only our own eyes can see the danger on the horizon, and only our actions can save the life we see around us.

Assuming this responsibility for current, past, and pending life-forms, we will then need a plan that will expand beyond the life span of our first sun, which gives us a maximum of 4–5 billion years. But even that maximum is highly unlikely to be the longest timeframe, given historical precedent. Any number of world-ending, catastrophic events can happen before then. For example, another asteroid could smash into the Earth and—as happened to the dinosaurs—we would all be obliterated. Based on our current planetary science estimates, we are actually past due for a planetary-scale catastrophic event—without even taking into account all of the harm that humans have inflicted upon our home planet. However, at the maximum, we have about four billion years; a finite time.

Our current sun will eventually run out of fuel and destroy all the inner planets: Mercury, Venus, Earth, and Mars will all be charred to a cinder. This inevitable red giant phase of the sun will obliterate everything that has ever been created, learned, or understood on this planet, notwithstanding the radio waves and other electromagnetic radiation broadcast since the early 1930s. Unless we find a way to somehow stabilize our collapsing sun, all of our technological, artistic, scientific, and cultural creations—indeed *all* of Earth's creations—will be destroyed if they stay here. We need a global plan to expand beyond this planet.

The *implementation* of any global plan would not be possible without the *means* to support both global coordination and communication. The internet and advanced forms of transportation have brought us this world only very recently. The constant and ubiquitous intercommunication of internet-connected devices is something most of us now take for granted. This connectivity has also led to an expanded industrial revolution and new "information age" that can rapidly build or destroy entire cities and countries. Somewhat like a drunken toddler with a flamethrower in one hand and a nuclear detonator in the other, we have emerged with an accidental empowerment to influence our entire planet's atmosphere and country-scale ecologies. These powers were born in the womb of cheap high-carbon energy sources, which now threaten our entire planet. As worrisome as it has been to watch the CO_2 levels on our planet rise, this may have been an inevitable progression of civilization. Now, with the ability to understand how these technologies can negatively impact our planet, as well as technologies to monitor and disseminate them (with global communication), we not only can fix the damage we have inflicted on Earth, but can begin to build better, cleaner civilizations on this world (and others) and ensure our own long-term survival, as well as that of any other species.

This key principle—the survival of as many of the life-forms and molecules as possible—is a new kind of ethics, a molecular and genetic ethics, which gives a purpose and duty to this idea of preservation. This is the highest (deontogenic) duty because all else depends on it.

DEONTOGENIC ETHICS

Deontogenics is a new kind of ethics originating from deontology (from the Greek *deon*, meaning "obligation or duty," and *ology*, meaning "study") and *genetikos* (from the Greek meaning "genitive or generative"). Deontogenic ethics is based on two simple assumptions. First, assume that only some species or entities have an awareness of extinction. Second, assume that existence is essential for any other goal/idea to be accomplished—in short, *existence precedes essence*. Therefore, to accomplish any goal or idea, sentient species (currently humans) need to ensure their own existence and that of all other species that enable their survival. Any act that consciously preserves the existence of life's molecules (currently nucleic acid-based) across time is ethical. Anything that does not is unethical.

Deontogenic ethics is related to, yet distinct from, deontological ethics, such as that formulated by Immanuel Kant. He argued that the morality of an action is based on whether that action itself is right or wrong, regardless of the outcome. Kant's "categorical imperative" asked people to think, before taking any action, "What if everyone did this? What if my action were suddenly a maxim for everyone? What would the world look like?" Deontological ethics is often seen as being in conflict with utilitarian ethics, such as that of Jeremy Bentham and John Stuart Mill, who aimed for "the greatest good for the greatest number." In utilitarian ethical frameworks, the outcome and consequences are usually more important than the action itself.

But utilitarian ethics also faces challenges of quantification and application. What is good, and how is it measured? What if there are situations that are technically "better" but actually worse for the average person? Derek Parfit wrote in his book *Reasons and Persons* about a "repugnant conclusion" of applying some of these utilitarian frameworks. For example, it would technically be "better" to have a large population with lower average happiness versus a smaller population with a higher average happiness. Another established ethical principle asks what would be "fair," regardless of which body you might be born into (e.g., rich or poor, powerful or meek), and was proposed as the "veil of ignorance" by John Rawls. Yet preceding *all* these discussions,

The third path is just avoidance. It might sound like, "I'm not directly related to this work, so I don't need to do anything." Here, too, this view is misguided. In all countries with space programs, taxes support the work on space biology, rocket engineering, flight logistics, and astronaut facilities. As such, the citizens of all these countries are already involved. Moreover, citizens don't have to be intimately involved with a national or international project to support or appreciate the benefits of such a project, such as peacekeeping forces from the United Nations or work on global disease tracking from the World Health Organization.

The fourth path of resistance is based upon the longest-possible view of the universe and so can lead to indifference. One might say, "If we leave this sun, we will just have to leave the next sun, and then again, again, and again. Where does it end? Won't we all just die anyway when the universe ends?" This contention is based on the second law of thermodynamics, which includes the biggest system of all—the universe. The fate of the universe depends on its total energy and matter, yet "regular matter" makes up only ~5 percent. The density and activity of dark matter (27 percent) and dark energy (68 percent) are the biggest factors. Nonetheless, after trillions of years, the plan of simply expanding to more and more solar systems will not be our best choice. After millions, billions, or potentially trillions of years of interstellar travel, it will eventually be as trivial as it is to go from NYC to Paris today. After visiting many stars and gaining first-hand experience and data on how stars form and die, we may be able to engineer our way through this problem, as we have countless others. But can we make it to the end? What is the end?

The current understanding is that the universe will end in one of two ways. First (most likely), it could be from the universe expanding endlessly, called the "big freeze" of the universe. This is when planets continue to drift apart, then cells, then molecules, then atoms, and then, eventually, even the very, very old (10^{35} years) protons themselves will be too far away from each other to interact. The other potential avenue of our universe's demise could be in the "big crunch," where eventually the universe will stop expanding and then begin to fall back in on

itself. In this scenario, dark and visible matter/energy of the universe becomes dense enough to drive all mass to continuously move closer together and possibly lead to a new big bang (more in the last chapter).

Outside of the technological challenge of solving these two scenarios, which are currently unsolved, there is also an ethical question. Should we restructure fundamental atomic and physical properties of the universe in order to preserve life? What if the universe has already had a big crunch, or several? Perhaps such cosmic cycling is what preceded our own "big bang," and life could arise again in the new universe. Moreover, life could arise in a better form in the new universe, and if we stopped this from happening, we could be doing harm to life's prospects. How can we know the impact of our decisions here in the long term?

Here, the question is easily resolved by deontogenic ethics. We know that humans are still the only species with the knowledge of extinction, and thus, we have a duty of stewardship of our own species and that of others. A worse outcome than a universe with imperfect life is a universe with no life, since then there is nothing to protect or maintain the universe, as well as its life, and that is a risk that is too great to accept. The scale of the hubris does not obviate its necessity. If the intent is to preserve life, which has the ability to preserve the rest of the universe, and if the act of doing so does not itself harm what it is trying to protect, then ultimately the most moral thing to do is to act.

Moreover, life likely would not need to end. After *that long* of a time period, humans (or our derivative species or robot brethren) will be substantially different and probably much more technologically advanced. It may even be possible that by that time (billions or trillions of years from now), we will have the ability to measure, manipulate, and use dark matter, spacetime, or other tools to enable changes to the structure of the universe itself. This new era that is trillions of years ahead may include spacetime folding for long-distance travel and matter manipulation at the scale of entire stars, galaxies, or even scales across the universe.

We may have to confront a choice of either letting the universe die, hoping that life will be born again, or actively preventing its death

and restructuring it to preserve life. Considering molecular and deontogenic ethics, we only have one choice. If we are to preserve all life, we will have to restructure the universe itself in order to survive it; our duty is to engineer.

This duty to engineer and protect life is the only duty that is immediately activated upon comprehension. Other duties, such as those to one's children, country, family, or religion, can sometimes be delayed, switched around, or even abdicated. But the duty to the universe, and to all life, is something that will always hold true for us, as well as for any subsequent species or entity (made of any matter) that realizes this responsibility. This is a duty that enables, for the first time, a piece of the universe to keep the universe's creations sustained, protected, and thriving.

3

PHASE 1: THE LANDSCAPE OF FUNCTIONAL GENOMICS (2010–2020)

> What is the philosophy of the gene? Is it a valid philosophy? There has been too much acceptance of one philosophy without questioning the origin of this philosophy. When one starts to question the reasoning behind the origin of the present notion of the gene (held by most geneticists) the opportunity for questioning its validity becomes apparent.
>
> —Barbara McClintock

We have two options to enable the transition of Earth's life to start living away from its protection (stable gravity, magnetosphere, atmosphere, pressure), much like a bird leaving the nest for the first time. One possibility is we simply allow evolution to gradually select for characteristics required to survive on these new planets—natural selection. This is basically a "sink or swim" approach to life's survival, except with no lifeguards and with bricks tied to your feet. Though this type of selection could gradually work, it would take an extremely long time, or may simply work too slowly to even be viable. On the harshest new planets, any Earth-based organisms might die before they're even capable of reproducing.

Our second option to enable Earth's life to live on other planets is to preemptively direct this genetic process, so that the life we send is already capable of surviving in its new home. More complex, yes—but also more humane. However, to do this we need a better understanding of the "functional" elements of all genomes in the metaspecies so

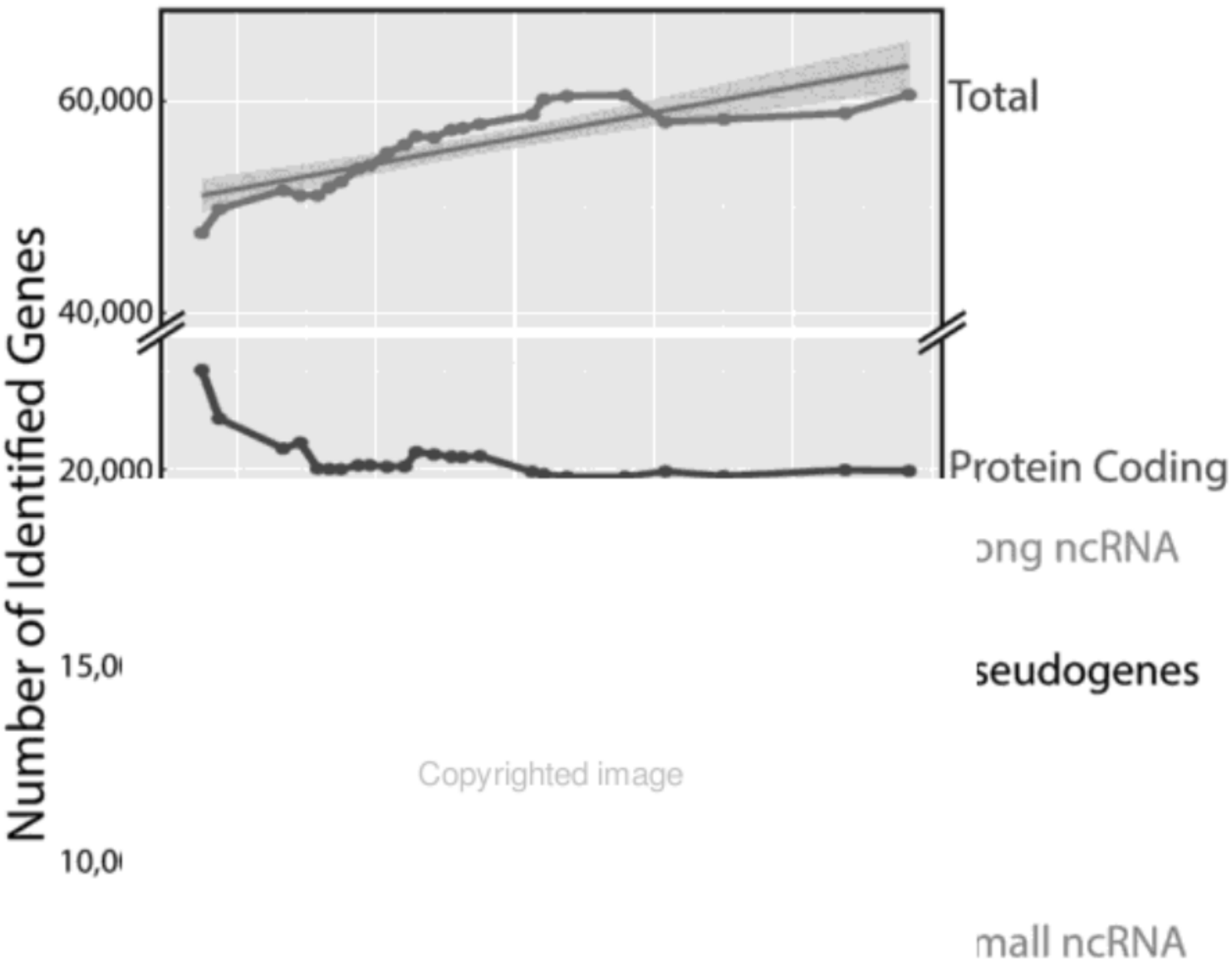
that we can better engineer and protect them. To make this a reality, we must first comprehensively map the functional elements of the human genome, our metagenome, and other intermingled species (the holobiont or metaspecies), so that we have an exhaustive list of what must be protected, what can be edited, and what abilities are even possible to engineer based on Earth's current biological catalog. Before we build genomes from scratch (as we will discuss later), we need to know what we even *can* build.

Though our own genome is the most well-studied genome to date, we have yet to completely unravel all of its mysteries. How many genes do we have? What are they doing? How are they regulated? Are there some "do not disturb" areas of the genome alongside those that can be more readily modified, altered, or manipulated? What about for other species?

Answers to all these questions are essential for the subsequent steps of biological engineering. Beyond this, we need a better understanding of how life responds to space travel through adapting the methods employed in the NASA Twins Study (chapter 1) to more astronauts and species. As of the time of this publication, there have only been 570 human beings who have ever been in space, 100 km above the surface where the atmosphere thins away and the sky becomes black. Once space tourism launches (e.g., SpaceX and Blue Origin) and newer space agencies begin regular human flights (e.g., Israeli and Indian), the amount of data generated will increase exponentially. At the same time, the work on animal and plant models (at NASA's GeneLab, as the largest and best example) will also increase. A cotton plant has even already been grown on the moon thanks to China's Chang'e-4 mission. Lunar socks made from this rugged cotton are not yet available for order, but it is only a matter of time.

But while all this momentum is exciting, the question still remains: What should we engineer? First, we must define substrates and some basic knowledge to understand what we *can* engineer. To capture this perspective, we must first build a context, from the genome, to genes, to cells and tissues, to the whole body, and then to the entire ecosystem. Only once we have all the molecular mortar and genetic bricks, can we build the biggest structures, including ones that reach the stars.

Excitingly, the pace of discovery of new genes within the human genome has not slowed since 2001. Work from many researchers in individual laboratories, as well as across large consortia such as the Encyclopedia of DNA Elements (ENCODE), has been quickly uncovering new genes within the 3.1B letter book of life, averaging about 1,000 new genes every year. The number of genes increased to beyond 60,000 in 2020, and more are likely to be uncovered in years to come. Although the number of protein-coding genes, which made the enzymes, protein complexes, and amino-acid-based functional elements in our cells, has stayed relatively constant at 20,000 genes, the number of noncoding genes that are clearly defined is continuously increasing (figure 3.1). This means that some of the most critical genes for adaptation to spaceflight may still be awaiting discovery.



3.1 The number of identified human genes over time: The GENCODE gene-annotation count for each category of genes, including the total, protein-coding, long noncoding, small noncoding, and pseudogenes.

These discovery efforts are still ongoing because the substrate of DNA just holds the information of the human genome, whereas the active form (RNA) can be exquisitely specific to each cell, tissue, or time of development, and, thus, can take extraordinary effort to find. For example, fetal hemoglobin is the molecule that fetuses use to process the majority of the oxygen in their bodies, but this gene is turned off around birth and usually never seen again. To address this challenge of spatiotemporal complexity and genes that may be very rarely expressed (in time and/or space), several ongoing projects are building an atlas for each cell type in the human body, including the BrainSpan project led by Nenad Sestan and the Human Cell Atlas (www.humancellatlas.org) led by Aviv Regev, both of which can help discern how may genes are truly present in the cell from that very first cell.

But discovering genes is not just an endeavor for the human genome. There are several large-scale projects and databases that store genetic information as it is growing over time. This includes GenBank (more on this when we get to CRISPR), which keeps all sequence data generated around the world, as well as the European Molecular Biology Laboratory, KBase, the DNA Data Bank of Japan, and the newest member of the genetic database, the Chinese National GeneBank. Two of the largest projects in the world for mapping the genomes are the Earth BioGenome Project and the Vertebrate Genomes Project, both of which are discovering thousands of genes every week across a range of habitats.

GENETIC CHANGES

Whenever the number of genes reaches the final, "true" number, or a near asymptote, it will not remain that way forever. Life is always evolving, and even old "dead" genes, like pseudogenes, can "return to life" and be functional again. These genes are relics of genetic information that are still present within the human genome and serve as an evolutionary palimpsest for what has happened to human biology over millions of years. Our genome is essentially an old piece of paper with billions of overlapping scribbles and edits of evolutionarily selected "notes," which we now have the ability not only to read, but to see *what* changed and *how*. One process is called exonization, where a portion of

a gene that is not currently transcribed into a protein becomes mutated and then turns into an exon, which can be used as part of a new RNA or protein element. Also, almost all genes undergo some splicing, with internal elements of the genes being mixed and matched to create a new function. This splicing process can occur in the case of disease (such as myelodysplastic syndrome), sex determination for male versus female, or specific immune responses.

Beyond the genesis or recycling of a new genetic component in the toolkit of life, there is also a simpler way to get new genetic functions, which can just occur with "selection." Some instances of rapid evolutionary selection have occurred within only the past few hundred years. Most visible in daily life is the ability for humans to digest and process the lactose in milk as adults (lactase persistence), an ability that normally is absent in mammals beyond the infant years. Also, the genes that enable free diving at great depths and larger spleens have been selected for in the Polynesian islands; hence, these islanders can now dive deeper and longer than other humans. Finally, there is some evidence that genetic selection (for the EPAS1 gene) in Sherpas and Himalayan climbers has led to them being better adapted at life in high elevations. Evolution has already given humanity some recent adaptations, which only took a few dozen generations.

GENETIC REGULATION

While the genome (all of your DNA) and transcriptome (all of your RNA) define the cell's basic building blocks and potential, their regulation is controlled by additional molecules that sit on their bases and are collectively called the epigenome and the epitranscriptome, with "epi" meaning "above." There are hundreds of chemical marks that define when, how, and where DNA and RNA are deployed and used in cells. They can range from very small chemical changes—such as DNA methylation, wherein only four atoms (CH_3) are added to a cytosine (letter "C") in DNA to help control a gene's function—to large changes to the DNA or the proteins around which it is wrapped.

For RNA, the same principles apply, with slight chemical modifications like methylation modulating the function of a given RNA, which

was first defined as the epitranscriptome by our laboratory and others in 2012. There are now over 115 known RNA modifications, which span all domains of life, and which represent a remarkable plasticity of RNA, just like DNA and the epigenome, in controlling the state, localization, translation speed, and stability of RNA. Just as DNA cannot be imagined without the context of its modifications and packaging, the same is true of RNA, too.

Almost all RNA-based viruses have modified RNAs, including the human immunodeficiency virus (HIV), Zika, and hepatitis C virus (HCV). Work from Dr. Stacy Horner's laboratory at Duke and our own has shown that these modifications change how fast the viruses grow, are released, and interact with host cells. RNA modifications have been seen in almost every tested organism, including viruses, plants, bacteria, fungi, and animals. It is now understood that, like the epigenome, the epitranscriptome serves as a set of hidden "levers" that control the function of RNA. These levers are potential substrates for future cellular engineering.

CELLS

Every multicellular organism begins as one cell, which contains all of the intricate instructions to synthesize, organize, and regulate not only this cell but the development and maintenance of all cells that will inevitably comprise the organism. All of these instructions are encoded in the first cell's DNA. This underscores the complexity of the genome and how each cell's expression must be controlled in specific ways depending on its function. The cells hailing from each tissue in the human body (e.g., muscle, lung, heart, liver) harbor a unique epigenetic signature, which enables the maintenance of tissue-specific functions through the control of gene regulation, as just discussed.

Our knowledge of the total number of unique cells, or cell types, is still growing. Previous estimates put the number of unique cell types in the human body at ~300, but new estimates from the Human Cell Atlas have shown that we may have thousands of cell types and subtypes, each harboring a unique function for a specific physiological state or

response to stimuli. But even cells of the same cell type will not be identical. A cell's "presentation" of molecules on their surface can radically change depending on internal variables such as genetic mutations or altered states of their epigenome, transcriptome, and proteome, as well as external stimuli including drugs and interactions with other cells. This novel presentation is most pronounced with a neoantigen, when a cancer cell creates an entirely new molecule on the surface of a cell. Given its unique presentation, which wouldn't be found in normal cells, this offers a unique target for safer cancer therapies.

The human body has about 30 trillion human cells plus another 30–40 trillion bacterial cells, for a total of about 70 trillion cells. If your body were a democracy, the human cells would often be the *minority or equal* party. You (as a human) would never win an election. Your loss of control would likely result in you rolling around in the soil or lying in a bathtub full of yogurt, which I do sometimes on Sundays. Regardless of how you spend your Sundays, there are a lot of microbes in, on, and around your body. There are in fact so many microbes that they compose the bulk of the cells on Earth. This is a humbling and exciting statistic, and one which is vividly apparent for anyone who has ever had explosive diarrhea.

While bacterial genomes are smaller in size (2–10 megabases vs. 3.1 gigabases for human), their biochemical activity is as important as, and sometimes more important than, the human component. Estimates by Lee Hood showed that 36 percent of the small molecules in the human body are either made by, or processed by, the microbiome. And about 25 percent of drugs that are designed for human disease can also affect the growth and biology of the body's microbial cells. As such, a treatment for a disease is never a treatment for one person; rather, it is a treatment for all cells across all kingdoms/domains of life.

Yet this is only one facet within the large complexity in studying disease and predicting treatment response. Our continual understanding of the true complexity of biology has enabled predictive modeling and patient-specific customized therapies as the new medical paradigm. Centers for "precision medicine" and "personalized medicine" have become common at hospitals and medical centers around the world,

the British Isles. Together with partners from a breadth of UK-wide institutions, museums, and universities, the Wellcome Sanger Institute serves as a hub for the sequencing of these genomes, and our operational pipelines will play a central role in delivering the generation of these genetic codes. This will create an extraordinary, first-ever, planetary-scale map of genomes. But that only encompasses everything below our feet—what about above us, in space?

Much of what we know about the space station's metagenome comes from Dr. Kasthuri Venkateswaran at NASA's Jet Propulsion Laboratory (JPL). Evidence of organisms rapidly adapting to space, including antibiotic resistance, has been observed since the early 2000s and has direct implications for crew health and safety. While other sampling efforts have indicated that the organisms are adapting, they may not necessarily become dangerous. As is the case with most things in biology, the impact is case and time dependent. Until 2015, it was not possible to monitor these changes in real time on the ISS, but then an idea for an experiment was born.

DNA IN SPACE

Ideally, one could just sequence the DNA or RNA of any organism of interest right on the ISS, but the machines to perform such tasks were too large. Most DNA sequencers, while extremely fast and high throughput (e.g., Illumina), were all too heavy to justify the cost of putting them in space. But, in 2012, Oxford Nanopore Technologies announced a miniature sequencer called the MinION that would fit in the palm of your hand and only weighed 0.3 kg. Then, in 2014, they gave my lab at Weill Cornell and others early access. In 2015, we made sequencing in space a reality. It turns out, all you need are reagents, a computer (even a tablet), the MinION, and some guts.

While planning the logistics for the Twins Study, I asked NASA if it would be possible to get a nanopore sequencer on the ISS, and they suggested I meet Drs. Aaron Burton and Sarah Castro-Wallace. It turns out they had already begun planning a mission along these lines, so we joined forces for the Biomolecule Sequencer (BSeq) mission along with Kate Rubins and Charles Chiu.