THE NEXT 500 YEARS

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ENGINEERING LIFE TO REACH NEW WORLDS

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Special Thanks: Dr. Matthew MacKay

Dr. Matthew MacKay not only made the beautiful figures in this book, but he was also cocaptain on the quest to detail the 500-year vision presented here. This vision is a shared hope of what can be done, and what must be done, for our species and all others we serve to guard (past, present, and future). He endlessly helped as editor, writer, debater, and visionary. While the biotechnology, engineering, and genetic guardianship ideas in this book are described in the future, hopeful tense, they are actually grounded in Dr. MacKay's published and pioneering work, which has shown that many of these ideas are in fact possible. Many of the constructs for cells, circuits, and planetary design already have a proof of principle from the writings and algorithms he has published, and this book could not have happened without this guiding light and engine of science.

To all humans and any extinction-aware sentience

CONTENTS

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

THE FIRST GENETIC ASTRONAUTS

> My skin had not touched anything in 340 days. . . . anything it touched, it felt like it was on fire.
>
> —Astronaut Scott Kelly

Huddled around glowing monitors full of molecular, genetic, and telemetry data, we were united in our bafflement and concern. We simply could not believe our eyes.

"Are these the highest levels ever seen in a human body?" asked Dr. Cem Meydan. "How did he survive?"

It was a crisp December evening in New York City in 2017, at our genetics laboratory at Weill Cornell Medicine. We had just finished the integrated analysis of all the molecular data (DNA, RNA, proteins, small molecules) from Captain Scott Kelly, who had completed the longest-ever NASA mission in space—almost a complete year (340 consecutive days). Kelly's long-duration spaceflight was part of a unique experiment at NASA called the Twins Study, which leveraged identical twin astronauts (Mark and Scott Kelly) to discern what happens to the human body before, during, and after a year in space. The research spanned ten research teams across the United States; our laboratory worked on the genetic, epigenetic, microbial, and gene-expression analyses. We had comprehensive molecular and genetic data from Scott's time in space,

which we could compare to Mark's time on Earth. Our job was to (1) assess what happened to Scott during such a long mission, (2) learn about the changes as a guide for Mars missions, and (3) plan for ways to mitigate future risks to other astronauts.

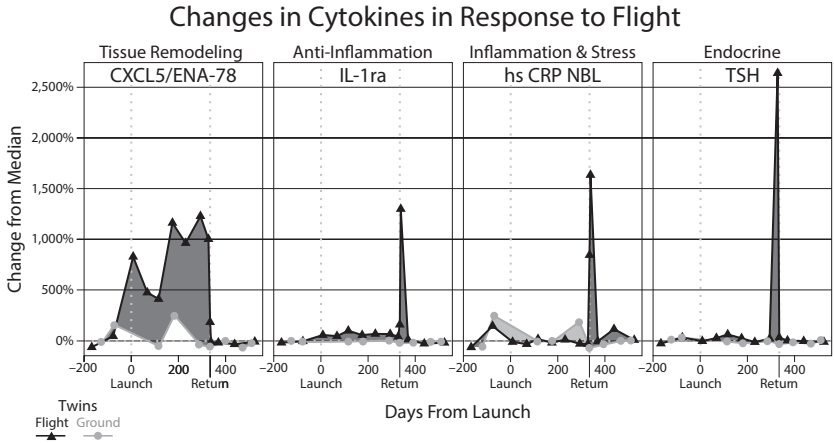
It was clear that his body did not enjoy the return to gravity. Scott himself described the unpleasantness in his book, *Endurance: A Year in Space, a Lifetime of Discovery*. "My ankles swelled up to the size of basketballs," he noted, amazingly with a calm demeanor. "I felt like I needed to go to the emergency room."

Even though he wanted to go to the emergency room, he knew the reason for the body's changes; he had just returned from space! However, this knowledge did not comfort his immune system. He broke out in rashes all over his body, especially where anything touched his skin. His body was even reacting to something as simple as the weight of clothing being pulled down onto his skin by gravity, causing visible irritation. We could see this immune response in the molecular data from his blood work, especially with changes to his proteins and RNA (gene expression). But we all wondered while staring at the monitors . . . Was this reaction part of a normal readaptation to gravity? Does this have any impact for the plans to go to Mars?

"These are the highest levels of inflammation markers and cytokine stress I've ever seen," I said. "Let's triple-check the data."

We checked with Dr. Scott Smith at NASA, who leads the biochemistry analysis unit for the twins and other astronauts, and he confirmed that the data were correct. He also noted, "This is the highest we've ever seen, by a long shot." Samples were processed in duplicate, just to be sure, and our measurements and computational analyses matched. While inflammation is a normal part of the body's response to stress, here, Captain Kelly's return to gravity catapulted his inflammation markers to unseen heights (figure 1.1).

Specifically, interleukin receptor antagonist 1 (IL-ra1), which is an important natural anti-inflammatory protein, as well as other cytokines, such as IL-6, IL-10, and C-reactive protein (CRP), were all spiking extremely high upon the return to Earth. CCL-2, which is a cytokine (a type of protein that leaves cells to signal other cells) that recruits immune cells to sites of injury or infection, was also spiking very high.

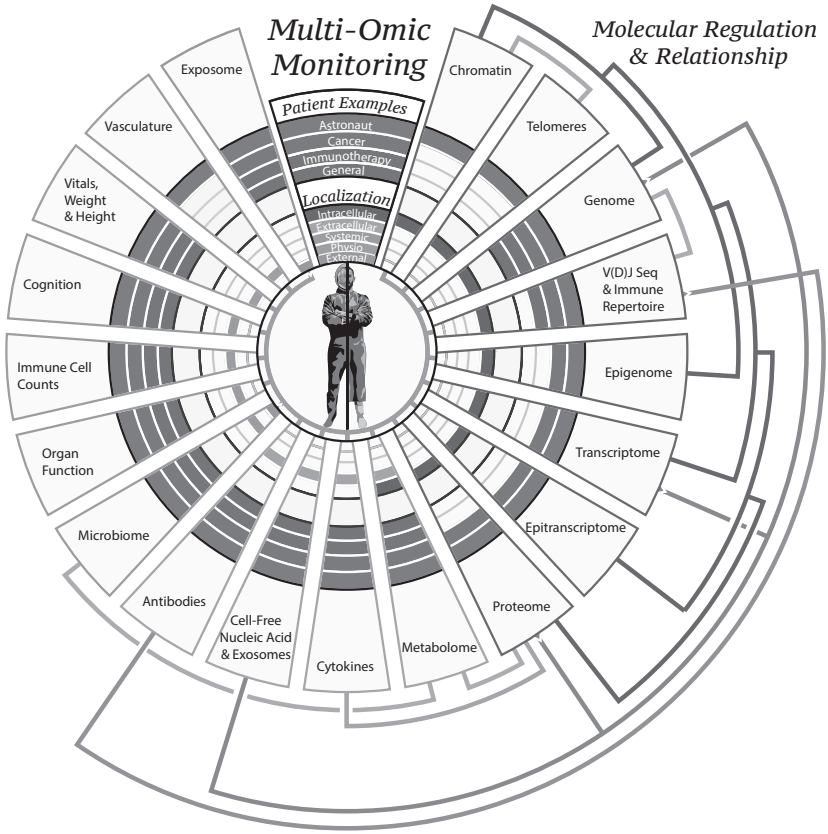


1.1 Many cytokines changed expression during the Twins Study, comparing Scott Kelly's cytokine levels (black) to those of his twin brother, Mark Kelly, who remained on Earth (gray). Dotted lines indicate Scott's launch and return to Earth. Cytokine levels are normalized to their median expression across 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.

We looked at the carbon-dioxide levels on the space station, and though there were some fluctuations, they were not too dramatic and should not have led to physiological changes; we had to look for other causes. As it turns out, breathing in zero gravity is not like breathing on Earth. In particular, every time you breathe out, a small cloud of CO_2 can form in front of your face. This CO_2 minicloud stays by your face, unless you have a fan or move. Thus, some of what we could see in Scott's blood, and likely that of other astronauts, were face-associated, CO_2 miniclouds, more like the atmosphere of Venus than that of Earth.

We also looked at the dynamics in Scott's microbiome, which are the microorganisms (bacteria, viruses, fungi, and other small, nonhuman cells) inside his body. Specifically, we wanted to see what happened to the microbiome during spaceflight. We observed some changes in flight for the ratio of species, specifically for the Firmicutes/Bacteroides (F/B) ratio, using stool data from Drs. Stefan Green, Fred Turek, and Martha Hotz Vitaterna and some of our own data from skin and oral swabs. However, the total diversity was mostly maintained, which is good news. They did eventually return to normal, so there were no big red flags in the microbiome.

But other molecules in Scott's blood did show some unusual features. The mitochondria, which are normally resting inside cells and carrying on cellular respiration to ensure that cells can literally breathe and get energy, were spiking in his blood during the flight—especially when he first got to space. A normal person would have 500 copies of mitochondrial DNA per milliliter (mL) of blood, but Scott showed levels as high as 6,500 copies/mL, based on data from Drs. Kiichi Nakahira and Augustine Choi. We then examined the RNA in the blood, working with Stacy Horner and Nandan Gokhale at Duke University, and there, too, we could see higher levels of mitochondria.

This was an entirely new measure of stress for astronauts, but it has been seen before in other contexts. At Columbia University in New York City, there are laboratories that study extreme variations in mitochondria and even "mitochondrial psychobiology" (in work by Drs. Andrea Baccarelli and Martin Picard), where they have looked in Earth-bound individuals for changes in mtDNA in the blood of people undergoing stressful situations. This includes an interesting study of people

who gave speeches in a room full of strangers, where the researchers also observed spikes in the blood's mtDNA levels after the talks. Thus, there is ample evidence that mtDNA can appear after general bodily stress, the anxiety of public speaking, or other senses of danger as well.

But—why would human cells start to produce or eject their own means of energy? Here, too, other studies have given clues as to what was happening during a year in space. A 2018 paper (by Ingelsson et al.) showed that white blood cells (lymphocytes) can eject their mtDNA as a way to prime the immune system. These "DNA webs" serve as a warning sign for other immune cells to prepare to fight an infection or defend against a cellular threat, and it seems these webs work in space just as well as they do on Earth. Work from Afshin Beheshti at NASA and our group has now seen the mtDNA stress appear in multiple astronauts, along with other RNA signatures of spaceflight (including small RNAs called miRNAs). All of these surprises, from telomeres, gene expression changes, hypoxic miniclouds, immune stress, mtDNA, and inflammation, happened quickly and seemed to be a rapid, unexpected response to spaceflight, which hopefully would return to normal.

RETURNING TO EARTH

Fortunately, almost everything is plastic and malleable about the human body's response to long-term spaceflight. While Scott did gain two inches of height, this gain was just from the lack of compression on his spinal column, and his newfound height disappeared within a few hours of returning to Earth. Also, within forty-eight hours, Scott's telomeres had returned to normal length, and most of his blood and physiological markers were within normal ranges. For his gene-expression dynamics, 91 percent of the changes that occurred while he was in flight returned to normal within six months of returning to Earth.

Thus, most of Scott's spaceflight-induced gene expression returned to normal, but not all. Some genes did carry a "molecular echo" of their time in space, still actively working to continue DNA damage repair and maintain DNA stability. These data also matched what we observed when we examined his chromosomes for other breaks or damage. Even after returning to Earth, Scott showed continual signs of

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!"

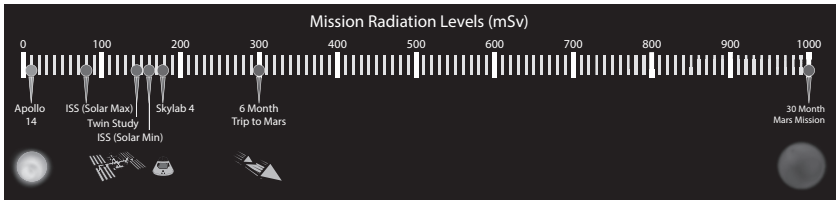
Although landing back on Earth was clearly painful, one good thing about Mars is that it has 38 percent of Earth's gravity. Given that difference, the landing might only constitute 38 percent of an "Oh crap!" moment and 38 percent of a challenge to adapt to the surface when

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.

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