



The “Age” Age

By John Mauldin | October 17, 2015

Transformational Technology and Aging
The “Age” Age
Turn on, Tune in, Get Younger
New Jersey, New York, Atlanta and Miami

As I mentioned in last week’s letter, I traveled to San Francisco last Monday with my friend Patrick Cox, who writes our [Transformational Technology Alert](#) newsletter. We had dinner with Dr. Mike West of Biotime and then spent the next morning at the Buck Institute for Research on Aging. Pat and I decided we would jointly report on what we learned. He has already written his part, which was published last week. I am going to reproduce portions of that letter, which highlight the conversation with Brian Kennedy and his team at the Buck Institute, and then add my own thoughts about our conversation with Mike West the previous night.

(Note that I am excerpting Patrick’s paid letter, which includes comments on companies in his portfolio, rather than his free weekly Transformational Technologies [Tech Digest](#) service. We agreed that it was important to do so in this one case, given the huge significance of the research involved and the Buck Institute’s relationship to it.)

Essentially, we looked at two aspects of aging. The Buck Institute is focused on how to slow down the aging process and reduce the symptoms (such as chronic diseases) that come with aging. Dr. Mike West and his colleagues, as well as a few other firms and researchers, are focused on using our own pluripotent stem cells in ways that would allow us to repair organs in our bodies, thus giving us the opportunity to “grow younger” again. (It’s not quite that simple, as I’ll try to explain later.)

The very good news is that progress is being made. The bad news is that the regulatory environment is impeding progress, as the regulators don’t quite know what to do about the advances that are coming; but even there things may be changing. I recognize this letter will be a little far afield from my usual scribblings on economics and finance, but aging and health are things that concern us all. And if there are a few things you can do to increase your healthspan (not just your lifespan), then the attention you pay to optimizing your health will make all the work you do on your investments even more important and useful. So let’s turn to Pat’s letter, and because I can’t resist, I will insert personal comments in brackets until we get to the end of his letter.

Transformational Technology and Aging

John Mauldin and I were invited to spend the day at “the Buck,” as they say. There, we spoke at length with one of the most important scientists working in biotechnology today: Brian K. Kennedy, PhD, the president and CEO of the Buck Institute for Research on Aging. We were also given the tour of the facility by Mary McEachron, the chief administrative officer and general counsel of the institute.

McEachron, in fact, is largely responsible for the successful founding in 1999 of the world’s first major scientific research institution dedicated to solving the problems of aging. Her role is fitting because she was the attorney most responsible for defending the will of Beryl Hamilton Buck, who wanted to fund an anti-aging institute to be established in Marin County, California. The San Francisco Foundation sued to break the Buck trust, arguing that the money should be spent elsewhere (in San Francisco, apparently) because the county of Marin is one of the wealthier counties in the world.

In a court battle that spanned years, McEachron successfully argued that the scientific mission of the Buck Institute – to solve the problems of aging – would benefit not only San Francisco but the rest of the world as well. I find it somewhat remarkable that anyone could even argue with that premise, but this is the world we live in.

As a TransTech reader, you know that the single greatest predictable problem facing us in the 21st century is aging. Though each one of us faces the problem individually, our society and nation are existentially threatened by the impacts of a population that is increasingly afflicted by age-related diseases.

The United States government is borrowing 30 cents of every dollar it spends already, which happens to be almost the exact percentage of the budget that flows to the aged in the form of Social Security, Medicare, and other transfer payments. The trends that have created this problem, however, are accelerating as the population of transfer-payment recipients grows older and bigger due to increases in lifespans. Simultaneously, of course, the population of younger payers into the system is shrinking along with birth rates.

Part of the reason that I enjoyed visiting Brian Kennedy and the Buck so much was that I was surrounded by very smart people who not only understand how grave this threat is to our system but who also understand that it is solvable. The institute, designed by the renowned architect I.M. Pei, employs about 140 PhDs as well as more than 100 technicians and support staff in 22 labs dedicated to different challenges.

[Not surprisingly, the Institute itself is a marvel of architectural beauty. Pei supposedly came out of retirement to do the design. It is an ongoing project, as he designed several other significant buildings to fit in with the current ones. More on that later.]

Kennedy spends a considerable part of his time explaining the economics of aging. In the last four

or five years, he told us, the community of scientists who research aging has become convinced that we can significantly increase healthspans. The consensus among top scientists is that we have the ability to delay the processes that culminate in the diseases of aging. Meanwhile, progress educating the public is slower, but it is happening.

For obvious humanitarian reasons, I want the public to understand right now that our most serious problems are solvable. As a financial analyst, however, I realize that this disconnect between reality and public perception is the basis for the biggest financial opportunities of our era. Just as energy can be generated from two systems with different thermal or charge states, transformational investors can profit from the investment community's failure to grasp these enormous but unrecognized forces in the biotech arena.

Kennedy agrees that society will eventually recognize the necessity of anti-aging therapeutics because the problems of aging will worsen until they force us to solve them. Right now, however, our institutions are decades behind the science.

Kennedy pointed out, for example, that NIH funding for scientific research has flatlined. Ironically, this dearth of funding is due largely to budgetary pressures created by societal aging. Lest you decide that increasing the NIH budget is the solution, Kennedy cites calculations that less than one percent of NIH grants support research into the aging pathways. I love [pure science](#) as much as anybody, but we might do better prioritizing research funding for the problems that threaten our health, the economy, and our children's future.

[Longtime readers know that I am a deficit hawk on the budget. We need to move to a balanced budget as quickly as possible. That said, there are some agencies that have far greater impacts on our lives than others. The NIH and DARPA come to mind. Using a small percentage of our national budget to fund ideas and research that are at the edge of human knowledge seems quite reasonable to me. I would like to see the administrators whose funded projects have successful outcomes be given more responsibility and access to further monies. Let's reward competence and tackle problems that profoundly impact the future.]

Another enormous problem is that the FDA utilizes approval methodologies created before the biotech revolution gave us ever-increasing insight into the molecular pathways and mechanisms targeted by drug candidates. As a result, the approval processes – designed when the drug development model resembled a guessing game more than modern science – is unnecessarily expensive and slow.

This regulatory bottleneck is a tragedy because, as Kennedy points out, it will be easier to target aging than to reverse the pathologies – the diseases – that are caused by aging. Targeting aging is also much, much cheaper. The benefits of anti-aging biotechnologies are twofold. Not only are anti-aging therapies far less expensive than disease treatments, they keep people healthier longer so they are able to move out of the recipient column into the contributor column. So the balance sheet is improved from both sides.

[In the next section Pat assumes that you have been a regular reader. Since a part of his service is free, maybe you should consider adding yourself to that list. More information on that later. – John]

A primary focus of the Buck Institute, as you know, has been rapamycin research, which led to the creation of a company that was a recent addition to our portfolio, Mount Tam Biotechnologies (MNTM). You are aware that the company's first compound is TAM-01, an analog of rapamycin intended to treat systemic lupus erythematosus (SLE). TAM-01 improves the side-effect profile associated with rapamycin and could, if human trials replicate the results found in animals, provide the first real therapy for lupus. This achievement in turn would further all of Buck's research.

Because Mount Tam has licensed all of Buck's IP on the use of rapamycin analogs for autoimmune disorders, the roadmap ahead is immense and multifaceted. TAM-01 probably isn't the analog of rapamycin that will be used for life extension purposes, but its financial potential is huge: the direct cost of treating lupus is \$100 billion a year... greater even than for cancer. Here is a [pdf file](#) containing that estimate.

We also spoke with Mount Tam's CEO, Timothy S. Powers, PhD, while we were at Buck and gained real insight into the potential of possible analogs of rapamycin, called rapalogs. By coincidence, the process of finalizing Brian Kennedy's new role as chairman of the Mount Tam board was just being completed. The announcement was made this week. I think this appointment is a major win for Mount Tam, because it puts Kennedy's expertise and credibility inside the company. It's unlikely that anybody knows more about rapamycin and rapalogs than he does.

Kennedy pointed out that the ability of rapamycin to impart life-extending benefits even late in life has come as something of a surprise to the research community. There is, after all, a natural tendency to assume that aging irreversibly damages cells and cellular processes. If this were the case, however, then interventions late in life would provide little benefit to animals, including humans.

In fact, this isn't the case. Diseases do not seem to be caused by physical damage to the body caused by aging, as was previously believed. Rather, the systems of the body are thrown out of whack as we age, causing the impaired functionality that leads to disease. Therefore, a compound that restores biological systems to a healthier state will have a major impact on healthspans for older as well as younger people.

In rodent studies, animals that were the equivalent of 65 years old were given rapamycin, yielding major improvements in health as well as a 15% improvement in lifespans. Somewhat greater benefits accrued if therapy began earlier, but the majority of the benefits from anti-aging therapies can be delivered rather late in life. If this model holds for people (and I think it has to), it means 65-year-olds could experience big improvements in apparent age and have their average life expectancies increase from 80 to perhaps 92 via some form of rapamycin. Even if there were only a 10-year increase in health- and lifespans, most of us would be willing to pay a great deal for that benefit – especially because rapamycin treatment would cost much less than treating the diseases it

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acts to prevent.

Though biogerontologists now understand these potentials, it's clear to me that most people do not. When I speak to people about the anti-aging strategies that are being slowed by regulatory burdens, the attitude I see in many older people is that it's already too late for them to benefit from these discoveries. This perception is entirely wrong.

Another common misperception that Kennedy pointed out to John and me is that anti-aging research is going to benefit only the very rich. Once he said this, I realized how often I had encountered this attitude. In fact, rapamycin, metformin, and several other extremely promising anti-aging candidates are not expensive drugs to manufacture. Moreover, anti-aging therapies are going to reduce healthcare costs so much, insurance companies will be happy to pay for them once they are approved. The real reason to support anti-aging efforts is to avoid financial disaster.

[I'm going to go a little deeper into the rapamycin story. The drug originally came from a bacterium discovered on Easter Island a few decades ago. Rapamycin is used in some therapies today but not for its antiaging attributes. A major pharmaceutical company did a study on the drug's anti-aging properties, and then that study was shelved for organizational reasons. The research was passed on and eventually ended up with Mount Tam through the Buck Institute.

It appears that there are two main targets that rapamycin molecules focus on. There are evidently some unpleasant side effects with regard to one of these targets. However, Kennedy and his team at the Buck have cleverly come up with a way to change the rapamycin molecule slightly (thus making it an analog of rapamycin, or a rapalog), so that the altered molecule focuses on the useful target without causing the annoying side effects.

Some of the conversations around the table about the potential for various rapalogs were quite interesting. Since we moved into the realm of speculation, I won't talk about those potentials here, but I will say that there was certainly a lot of enthusiasm around that table. – John]

Though Kennedy has focused a great deal on rapamycin, he has also studied the diabetes drug metformin. He discussed efforts by his friend Dr. Nir Barzilai to get FDA approval for clinical trials that would demonstrate the life-extending benefits of metformin. Barzilai is director of the Institute for Aging Research at the Albert Einstein College of Medicine and the Director of the Paul F. Glenn Center for the Biology of Human Aging Research. If Barzilai is allowed to show in clinical trials that metformin improves the markers of aging, that could open a path for other compounds such as one of the rapalogs under development by Mount Tam.

[Apparently, the entire antiaging community is cheering for Dr. Barzilai's efforts to get the very first approval from the FDA to target aging. Hopefully, his labors will mean that there will be a clear regulatory path for obtaining approval for other potential antiaging medicines. This is an issue we should all be paying attention to.]

The “Age” Age

There is obviously a question as to whether the various compounds that have proven anti-aging effects in animals also produce similar biochemical improvements in humans. Kennedy suggested that, because these compounds work through different pathways, some of them could work together synergistically. Besides rapalogs and metformin, he volunteered that we could see benefits from the compounds that restore mitochondrial function. The best known of these is, of course, nicotinamide riboside (NR), championed by Kennedy’s post-doc advisor at MIT, Leonard Guarente. I’ll have more information in a forthcoming issue about NR and other compounds, such as anatabine citrate, that are backed by considerable research indicating their usefulness as anti-aging supplements. [Patrick will also cover the companies that produce them.]

Kennedy also brought up Valter Longo’s fasting mimicking diet, which I’ve written about extensively and enthusiastically. In fact, Kennedy has collaborated with Longo on much of his research, and they’ve co-authored peer-reviewed journal articles. Not surprisingly, Kennedy’s work has appeared in such top-tier journals as *Cell*, *Nature*, *Science*, *Genes & Development*, and the *Proceedings of the National Academy of Sciences of the United States of America* (PNAS).

I’m running on just a few hours sleep as I write this because I took the redeye home from California to this island in the Gulf where I live. I’ll leave you with a few more interesting thoughts from Brian Kennedy, though. His role as chairman of Mount Tam is more than a way to gain funding for the Buck [which it does]. He said he has “been waiting 25 years to slow aging and extend healthspans,” and he is clearly happy to see anti-aging compounds moving toward approval.

These developments really are historic, and I think things are going to accelerate quickly on the anti-aging front. You’ve undoubtedly heard the current era labeled with one monicker or another. “This is the age of (fill in the blank).” Kennedy gets it right, however, when he says, “This is the Age age.”

If you’d like to learn more about the ongoing shift in scientific attitudes about aging, I recommend “[Geroscience: Linking Aging to Chronic Disease](#),” by Brian Kennedy et al. in *Cell*. The summary couldn’t be plainer: “Mammalian aging can be delayed with genetic, dietary, and pharmacologic approaches. Given that the elderly population is dramatically increasing and that aging is the greatest risk factor for a majority of chronic diseases driving both morbidity and mortality, it is critical to expand geroscience research directed at extending human healthspan.”

Note, by the way, that this article is co-authored by Kennedy’s friend, Claudio Franceschi, who coined the term *inflammaging*. If you’ve been following my work, you know how much I admire Franceschi’s work.

[Okay, the rest of what follows is from John.]

To say that I was blown away by the quality of the labs and research facilities we visited is an

understatement. We were allowed to stop and talk with various researchers, many of whom appeared to be quite young; and once they understood our interest, they waxed very enthusiastic about the areas in which they're working. Everywhere you turned, it seemed, they were inventing entirely new processes to increase the speed of research and using the latest and greatest in computer hardware and software and other marvelous technological gizmos (that's a scientific term, I think).

Nobody asked me to make this pitch, but I'm going to. I know that lots of people donate huge sums to universities to build buildings and fund research. I know, because I asked, that someone could donate \$40–\$50 million to build one of the two remaining labs at the Buck, and a similar amount would help staff and equip it. What better way to leave a memorial and help us all live longer.

The 22 labs at the Buck Institute are all focused on various aspects of the aging process, and there are cooperative studies with researchers all around the world. The Buck seems to be at the epicenter of a lot of the research, and anything you could do to help them would be helping all of humanity.

Turn on, Tune in, Get Younger

While the people at the Buck are focused on finding ways to help us live longer, Dr. Mike West and Biotime are focused on *reversing* the aging process. Mike is probably the leading stem cell researcher in the world, and his firm has created or accumulated the bulk of the intellectual property in the stem cell world.

About two years ago I “donated” a plug of skin from my left shoulder to Biotime for research. Among other things, they ran a full genome on me, and somewhere on the Web all 3 billion of my DNA base pairs are listed. You can clone me if you like; but if you're going to that much trouble, I would suggest you make a few modifications. John Mauldin 1.0 has a few problems.

Mike also took some of that skin, turned it into an adult pluripotent stem cell, let that cell divide repeatedly, and then had some of those cells become heart cells. So in a petri dish in Walnut Creek, California, I got to see my heart cells beating. I actually have some pictures of my cells in action. Now that's cool in and of itself, but up until a few years ago those heart cells would had to have been adult heart cells, and 66 years old.

A few years ago, Mike published a peer-reviewed study and filed patents on a methodology to return my adult stem cells to their original condition. So what was beating in that petri dish was a cluster of brand-new heart cells. Since my present heart seems to be working fine, replacing it with similarly aged cells isn't really high on my to do list; but I suppose I could become quite enthusiastic at some point about getting a brand-new heart with a 100-year warranty.

Mike can already turn those skin cells into the cells of more than half of my organs, and there doesn't seem to be any reason he can't do the others. The issue isn't really creating them in a petri

dish but rather getting them back into my body to re-create and grow from within. There are some organs that appear to be easier to actually do that with than others, at least in animal models, and so it is likely that researchers will work with those organs first.

Mike is a very cautious individual, especially when making statements about his ability to perform on certain timelines. I've been trying for some time to get him to commit to a date by which we are going to see the first human trials on the reversal of aging of some human organ. But he knows better than to predict.

Part of the problem is to find a regulatory venue that will allow such procedures to be attempted. It's all well and good to say, "Just go to some little Third World country," but you need some rather sophisticated health and medical technologies as well as scientific collaborators. Given that Japan has just released a new set of guidelines on stem cell therapies that apparently open the way to actual therapeutic studies and research, we might see the first such therapies developed in Japan. By the way, that is total speculation on both Pat's and my part. Mike would neither confirm nor deny that there any conversations being conducted with the Japanese. I should note that he also has several subsidiaries in Israel, so...

All we know is that he is actively looking for the right venue to undertake this crucial work.

I took a bit of a different tack and asked him how likely it is that we will see human trials within five years. He very quickly said that we would. I then asked if we would see human trials within three years, and he quickly realized where I was trying to go. He just smiled, shrugged his shoulders, and said "Maybe."

There's a lot of work to be done, but five years ago Mike told me that he thought it would be possible to reverse the aging process within 30 years. So all you and I have to do is figure out how to make it another 25 years. By the way, they'll be making us "younger" one organ at a time (and hopefully starting in less than five years!), so within 20 or 25 years you might be running around with a number of very youthful organs in your aging body. I assume they'll start with the critical-path organs.

So in any event, it's important that researchers at the Buck Institute continue to develop ways to slow down the aging process so that we can all live long enough to benefit from the age-reversal therapies that are coming our way.

And let me follow up Pat's comment about the cost of antiaging medicines. Much of what Mike West does will be able to be duplicated as technology continues to advance, and over time the costs will come down radically. The first few patients may end up spending quite a bit of money, but as Biotime's new technologies and systems are developed and new procedures are created and become standard, they will eventually be affordable by everyone, or at least that is the hope. With all the other cool medical developments coming our way, we'll have to figure out what to do with our longer and healthier lifespans. I'm up for that particular challenge.

As I mentioned above, Pat writes a free weekly letter, the [Tech Digest](#). I would strongly urge you to click the link, put your email address in the box, and subscribe. It's 100% free, and you'll receive Patrick's weekly articles with NO future obligation.

I met Pat some six or seven years ago. I started reading his letter, we communicated, and became "besties," as my kids say. We share a passion for understanding how the world is transforming around us.

In my travels I get to meet a lot of smart people. Pat is certainly one of the smartest. He is a true polymath, with an astonishingly wide grasp of technologies. He has an amazing network of people who keep him informed of the latest research, not just in biotechnology but all across the tech landscape. Amazingly, he seems to understand how it all fits together. He previously wrote for another publisher, but I was able to get him to agree to come write for us at Mauldin Economics.

I rarely make a promotional pitch for one of the letters published by my firm, but I'm going to make an exception here. Pat writes an in-depth monthly letter that is a must-read for anyone looking to invest in the cutting-edge companies that are truly transforming the world around us. If you delve further into the companies Pat writes about, I think you'll be amazed at the breadth and depth of the science involved. Plus, we have an experienced investment team that backs Pat up on entry and exit points, for those who don't want to buy, hold, and forget.

While Pat's letter is not exactly cheap, neither is it out of the range of most of you. If you're looking for somebody to reliably lead you through the minefield of new technologies, Pat is your guy. If you decide to give Pat's letter a try, you will have 90 days from the time you respond to decide whether [Transformational Technology Alert](#) is right for you. If you decide it isn't, you can have your entire subscription fee promptly returned to you by simply calling Mauldin Economics customer care.

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At the very least, get Pat's free weekly letter and read it for a few weeks to get a feel for how the man thinks and writes. I believe you'll find it well worth your time.

New Jersey, New York, Atlanta, and Miami

I find myself in Princeton, New Jersey, today on a personal visit, although I did happen to meet Paul Krugman's general contractor at a reception last night and was actually able to confirm that we both have the same dining room table. I had been told that by mutual friends. Seeing as it's an unusual table and, well, kind of a techie table, I can only assume that we both have one because we share a love for science fiction (and not because there is any resonance with regard to our economic views). Anyway, who knew? I decided it was probably better not to drop in unannounced last night, but maybe some other time...

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I will be at the Jersey Shore on Monday for a meeting with my team and another publisher before taking the ferry to Manhattan, where I will hopefully get together with my friend Jack Rivkin before heading back to Dallas. In a few weeks I will be in Atlanta for a board meeting of Galectin Therapeutics and then move quickly on to Miami to speak at the [T3 Financial Festival](#) on November 6–8. So far, the travel in November seems to be pretty tame, which is good, because I am working aggressively on my book.

It's time to hit the send button as there are people waiting on me for lunch. This has been a fascinating week. It wasn't all biotech and antiaging; I learned a great deal when I was in Portland with my hosts Aequitas Capital, and I hope to be able to share much of that learning with you over the coming months. You have a great week, eat healthy, and stay young!

Your planning to keep on working for quite some time analyst,



John Mauldin

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