FRONTIER TECH INVESTOR

ISSUE NO. 23 MARCH 2018

In this issue:

When death becomes optional

How this month's pick could help the "Methuselarity" – the End of Death – become a reality

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I have a strong belief I will be the first in my family to live to be 100.

It's a belief that has been with me since I was a child and might be part of the reason that I have never had a problem with following a life characterised by delayed gratification. I've always felt that I have time. But for many people that is just not the case.

For many, living in the shadow of death, illness or signs of ageing is just another part of life. I'm sorry to say my mother is an example. She is 71 and needs heart valve replacement surgery.

In December she developed a cough that proved persistent so she eventually went to the doctor. It turns out her heart is failing so her lungs were shutting down. She has spent the last three weeks in hospital and has had to be put in isolation because one of the bacteria in her microbiome is immune to antibiotics, so she is contagious. She is now too weak for surgery. The team caring for her are attempting to build her up, so they can attempt the operation, but it's a rather uncertain situation.

I think it's safe to say I'm in a contemplative mood and my mind has been rather focused on ageing of late. It's a subject we'll all have to come to deal with one day. For that reason, I expect this month's issue to be one of the most emotional – and perhaps even provocative – for many readers.

Why? Because I'm going to show you how in the not-too-distant future, death could become optional, thanks to breakthrough new technology under development today. I believe the "End of Death" is not only a possibility but a probability. And the companies fighting to prolong our lives present fantastic investment opportunities.

In short, there is research going on right now that has the real potential to change the nature of the human experience beyond

recognition and by cheating death it will alter the dynamics of the human condition forever.

Did Steve Job's help bring about the End of Death?

It occurs to me that we have something to thank Steve Jobs for and it's not what you think it is.

He gave us the iPhone, iPad, MacBook, elegant design, stuff that just works with no fuss and infused the technology sector with a vision for the future that was all we might have dreamed of.

Then he died.

He was 56 years old.

That sent a jolt around Silicon Valley's board rooms that it's hard for many people to quite understand. Suddenly a big question was being asked.

"What is the point of accumulating all this wealth, if I'm not around to enjoy it?"

Imagine for a moment you are Sergey Brin, currently aged 44, or Larry Page who is also 44. How about Elon Musk who is 46, or Peter Thiel at 50, or Jeff Bezos who is 54. You have more money than you could ever spend, you are known the world over for being a visionary and one of your ilk has just died at the age of 56.

That's not an acceptable outcome and they have decided to do whatever they can to surmount the challenge death presents.

It's not just the CEOs of Alphabet (Google), Tesla/SpaceX, eBay's founder or Amazon's founder that are interested in beating death. Dmitry Buterin, at 24, is one of the newest billionaires following the success of Ethereum. What is one of the first things he has done since accumulating wealth? He's investing in research at the SENS Research Foundation aimed at radical life extension.

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People in Silicon Valley are used to looking at seeming unsolvable problems and coming up with novel solutions that brush away all opposition. Their attention is now turning to death and the first part of that transition has been to reclassify death as a disease that happens to be fatal rather than an inevitable condition.

There's a very real effort under way to defeat death – or at least massively prolong our healthy lifespans – thanks to all these rich billionaires. It's started an investment trend we cannot ignore. We need to be invested in it.

The Methuselarity is near

The Methuselarity is named after the biblical figure who is reputed to have lived for upwards of 969 years. It refers to the time where technology can add more than one year to your lifespan *per year*, meaning you can "outrun" death, if you choose.

I'm 41 years old, and I know what all those other 40-somethings are feeling like. It's the classic time when people tend to have a midlife crisis. We all become less pliable after the age of 30. My eyesight took a dive about 18 months ago and the first grey hairs have started to appear. There are wrinkles where none existed before and I can see my metabolism is beginning to slow down.

I've spent almost 20 years examining trends and I can see where this all ends. Faced with the inevitability of terminal decline many people panic. When I asked my mother as a child if she had a midlife crisis, she replied with her characteristic dry wit that she couldn't afford one. Maybe if you are a billionaire, you fund longevity research.

So, is there anything to all this talk of radical lifetime extension, beyond the wishful thinking of billionaire 40-somethings?

It turns out there is. It stands to reason that the more we know about our bodies the better equipped we will be for when stuff starts to go wrong. It's not

at all unusual that each of us needs to go in for a "tune-up" somewhere between the age of 60 and 70. If my mother had known 20 years ago that her heart was working with two instead of three valves and that she was playing host to antibiotic immune bacteria, she would not be in the situation she is in today.

It stands to reason that if we're able to spot problems earlier, we stand a better chance of beating them before it's too late.

The "super agers"

Genetic sequencing is a part of this, and the cost continues to fall. I've written to you previously about Illumina (which is still an active pick in the portfolio), which with its current sequencing architecture, anticipates that the cost of full sequencing will fall to $100. That's a 10th of what it is now and represents an exponential pace of decline that is practically unparalleled in any other technology.

The genetic sequencing machines pioneered by Illumina are rapidly delivering decreasing costs so that price will no longer be an obstacle to testing within the next five years. That's why I recommended you buy the share last year.

However, better diagnostics are only going to get us so far.

They will give us a better chance of living longer but are unlikely to deliver on a better quality of life. When we think about longevity, most people would prefer quality than quantity of years.

Here's a great example. My auntie Betty is from Newcastle and is part of an NHS study into "super agers". She is 96 years old and despite having some arthritis in her knees is in perfect health and has suffered zero psychological decay. Her genes have delivered a long life and she is immune to the ravages of Alzheimer's disease.

The race is on to figure out how she and people like her, the so-called "super agers", have avoided cancer, avoided mental decay and lived so long, all without apparent effort or intervention. If this question can be solved, it will deliver the kind of results that could truly mean the question of ageing is solved indefinitely.

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The secret to living forever

It's a monumental challenge but I believe I have identified an investment vector that will give us access to this theme. There is the real chance that death could be optional. As a New Yorker piece that caught my eye put it, the secret to living forever could be buried inside our genetic code:

> *Gordon Lithgow, a leading C. elegans researcher, told me, "At the beginning, we thought it would be simple—a clock! — but we've now found about five hundred and fifty genes in the worm that modulate life span. And I suspect that half of the twenty thousand genes in the worm's genome are somehow involved." That's for a worm with only nine hundred and fifty-nine cells. The code book is far more complex for animals that excite our envy: the bee larva fed copiously on royal jelly that changes into an ageless queen; the Greenland shark that lives five hundred years and doesn't get cancer; even the humble quahog clam, the kind used for chowder, which holds the record at five hundred and seven.*

It comes down to this: **our genes have already figured out how to live forever.**

It's called reproduction. Our bodies just don't get to go along for the ride. Until about 200 years ago, life expectancy was about 40 years, which was old enough to mature, procreate and raise children to the age where they can procreate. That ensured our genes survived and, with that job complete, the body is redundant.

Studies have concluded that by following calorie-restricted diets and foregoing sex we can

fool the body into thinking that reproduction is less likely, which slows down the ageing process. Buddhist monks have long been reputed to have long lives for precisely this reason and that is forming part of how China is researching this issue of longevity. However, I think most of us would agree that does not solve the quality of life problem.

When we get to about 30 years of age the rate at which our cells divide and die slows down and the cells we have get older, start to decay and mutate. It's that decay that contributes to ageing because our cells stop reproducing.

So what cells in the body don't suffer from that slowdown?

Cancer.

Cancer is an aggressive multiplier. Its exponential growth – in people who are often seeing the rest of their systems slowing down – is an anomaly.

One of the biggest challenges researchers have in speeding up our metabolisms is that by increasing cell multiplication they also increase the potential for adults to develop cancer. That is why our best hope of solving for longevity and better quality of life resides in the immuno-oncology sector. Effectively, this involves teaching the body to spot and destroy cancer itself.

Turning your immune system into a cancer-destroying machine

It's at this point this story intersects with another theme we've already invested in: gene editing.

You're probably familiar with CRISPR – the technology which allows us to edit our genes – already. (If not, check out our past issues for our recommendation in gene editing firm Editas, plus the chapter in publisher Nick O'Connor's book, *The Exponentialist*.)

It is in immuno-oncology that CRISPR is likely to find its most impressive commercial utility. Cancer represents an economic loss to the global economy of $895 billion a year, which is more than any other cause of death.

> Cancer is an almost trillion-dollar opportunity. There is a genuine race on to get products to market.

Immuno-oncology is a technology sector which aims to disrupt cancer's ability to replicate by taking aim at its defence mechanisms, its ability to mask its growth from the immune system and its ability to grow exponentially. All of these attributes are integral to the puzzle of how to deliver on radical life extension.

There is another reason for investing in this sector. It's hot. Like I said, cancer is an almost trillion-dollar opportunity. There is a genuine race on to get products to market. Small companies are being taken over at a prodigious rate because there is no large pharmaceutical company that can risk not having a position in immune-oncology today. That means we have to accept the fact that by investing in immuno-oncology, the company I have chosen stands a high risk of being taken over by a larger company, which will result in a higher price but will also dilute our play on this long-term theme.

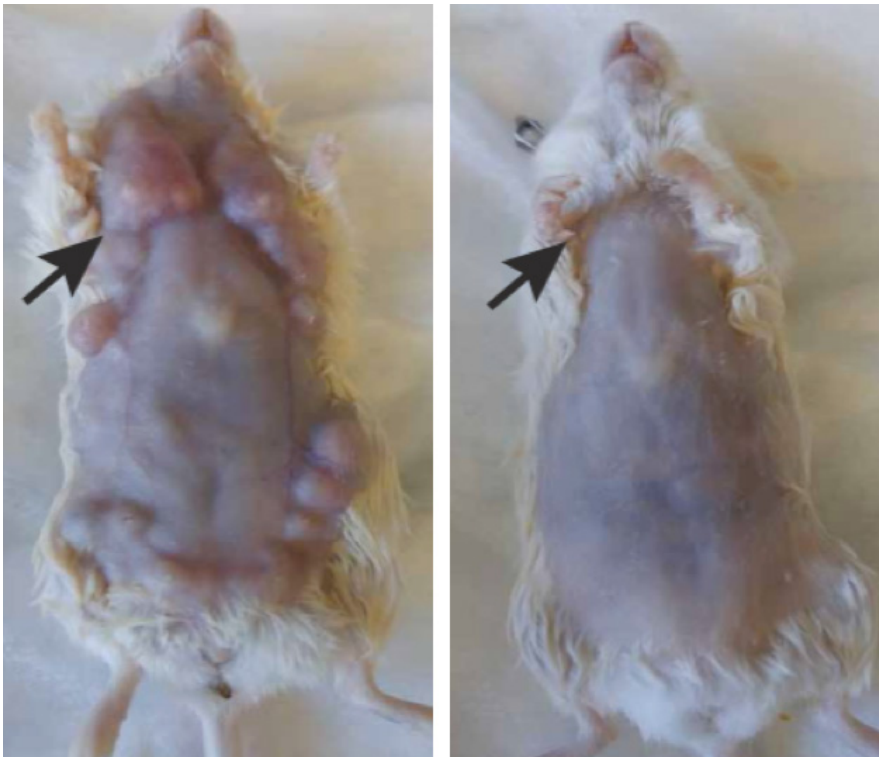
So why is the immune-oncology sector hot? Well it's simple enough, immune-oncology has successfully cured cancer – specifically leukemia. In January 2017 a group of British doctors announced they had successfully "cured" two babies of leukemia using genetically modified cells from a donor. Cured is in inverted commas because you're not allowed to say someone is cured of cancer until they are cancer free for a few years. However, the results are truly amazing nonetheless.

The future is now. Heart-rending pictures of wards of bald children rolling the dice with chemotherapy will soon be a thing of the past. Immuno-oncology works and it removes the need for damaging chemotherapy because it re-educates the immune system to do all the work.

Today there are more than 240 clinical trials focusing on immuno-oncology (CAR-T cells) and there have been remission rates of over 94% in some severe cancer types where hope of survival had all but been extinguished. These hopeless cases are both worthy causes but are also where new therapies often have their genesis because the burden for experimentation is lower. We can expect the work in this area to progress rapidly because the success rates are so high.

When I first read these statistics the remission rates were in the order of 94% for leukemia but researchers were cautious about making the rapid progress in solid tumours. They even opined that it would could take up to five years to get a similar result in these tumors. That all changed in January this year. Less than one year after those two UK babies were declared cancer free, researchers at the Stanford University School of Medicine published research from one of its labs that is now recruiting for a lymphoma study. They discovered that by combining an existing on the market CAR-T cell therapy with another agent and targeting it to specific sites, they were able to totally eliminate cancer in mice.

"When we use these two agents together, we see the elimination of tumours all over the body," said Ronald Levy, MD, professor of oncology. "This approach bypasses the need to identify tumour-specific immune targets and doesn't require wholesale activation of the immune system or customization of a patient's immune cells."



Here (above) is the before and after picture they posted on their website where the mouse is completely cancer free.

This is why I get so excited about technological innovation. What was once impossible is now possible. What even the most enthusiastic advocates thought would take five years, now takes less than one year. That is the very definition of exponential growth on which the whole service is based.

In separate studies, mice have been shown to live 25% longer when senescent cells are cleared away. Senescent is a nice way of saying old. As our body ages, our cells have been multiplying for decades and the old cells that are no longer required build up and often don't die. These old redundant cells tend to hang around and spew out a slew of invective that can contribute to cancer. We might think of them as the grumpy old men of the body. If they can be encouraged to die off, then it frees up resources for the rest of the body and we have the potential to live longer. Clinical trials for this treatment are expected to start in 2018 and I will keep you posted with regard to investment themes as they evolve.

Google's anti-ageing incubator Calico is tight lipped about exactly what it is doing, but it is well funded and has the exclusive aim of ensuring the company's founders live long lives where they will continue to enjoy their wealth. The one animal it is most fascinated with is the naked mole rat, which has an interesting quirk. It defies the

lifespan to metabolism ratios that scale from blue whales down to even mice. The bigger you are and the slower your metabolism, the longer you live. That's why bowhead whales with slow heart rates and enormous size can live to be 200, but mice with quick metabolisms tend to live a lot shorter lives. Naked mole rats can live to be around 30 years old, which breaks the mould of what is called the Gompertzian laws.

The other big point about mole rats is that despite the fact they live up to three times longer than regular mice, they are almost completely immune to cancer and show no signs of ageing. Little wonder then that Calico is paying particularly close attention to this ugly little rodent since it could well offer the genetic sequence we need to radically extend the human lifespan.

Researchers in Japan took this lack of cancer in naked mole rats and found that they tend to have the opposite reaction to humans and mice when tumour-suppressing genes called alternative reading frame (ARF) are activated. This seems to be why naked mole rats avoid cancer but humans and mice don't.

The nexus of longevity study runs straight through oncology. Today we are at the very beginning of delivery of radical life extension but there is no dedicated product in the market just yet. The most likely vector of identifying that product runs through immuno-oncology because cancer is immune to ageing and many of the attempts at extending lifespan tend to stimulate cell mutation. Therefore, it is only by understanding cancer that we can get to the aim of both eradicating the world's biggest killer and also living well into our hundreds.

Introducing this month's pick: a tiny biotech with a huge future (and an impressive pipeline of drugs)

Agios Pharmaceuticals is my number one pick in the immuno-oncology sector. Why? Because it has a slew of drugs under development in the sector. Its pipeline just got a big boost as it received its first royalty payment from a pharma major.

And best of all, it has a drug in clinical trials that could gain Federal Drug Administration (FDA) approval on 21 August 2018. I've already got that date marked in my diary.

Let's take Agios' primary commercial drug first. It is called Idhifa and is being marketed by Celgene. It treats blood cancer, specifically acute myeloid leukaemia (AML). This is a disease that attacks the bone marrow and inhibits the production of platelets, red and white blood cells. Idhifa focuses on crowding out leukaemia so that normal function can continue and the bone marrow can return to making healthy blood.

Agios received its first royalty revenue for Idhifa in the last few months. While $1.2 million is a pittance in the pharmaceutical sector, it marked an important juncture for the company. It's the company's first revenue but the success of the new drug means the company's pipeline has now got some credibility.

But that's not the only drug in the pipeline. On 15 February the FDA granted Priority Review to Agios' Ivosidenib compound, which is also aimed at AML.

Idhifa acts by targeting ADH2 proteins, which is a by-product of the mutation of many cancers.

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Ivosidenib is a first-in-class drug that targets the ADH1 protein and is intended to be a highly targeted treatment for all patients that harbour that ADH1 mutation. That means Ivosidenib has the potential to be prescribed for both blood and solid tumours, which obviously increases its potential market.

On this occasion the company owns all the intellectual property with regard to the Ivosidenib-based compound so the potential

for profiting from a successful launch are greater. The FDA has set 21 August 2018 as the decision day for Ivosidenib so it will be a big day for Agios. The company also expects to file a European Marketing Authorisation Application (MAA) at the end of this year.

The next item on its pipeline is a compound called AG-881, which is further back on the development track but is essentially a combination of both Idhifa and Ivosidenib.

Pyruvate kinase (PK) is a genetic disease which affects how red blood cells turn sugar (glucose) into energy. Agios' AG-348 compound is another first-in-class investigational therapy and it has been granted orphan drug designation and fast track designation by the FDA.

Could Agios be a prime takeover target?

There is another reason I am bringing Agios to your attention. In my research into J. Craig Venter's Human Longevity Inc, I looked at the people that sit on this private company's board. Alon Colowick stuck out. He is an executive vice president at Celgene which is the world's largest biotechnology firm. Agios has a strong relationship with Celgene and has sold exclusive marketing rights to its Idhifa leukemia drug to it. As its clinical trials progress, it has the potential to become an acquisition target for Celgene or indeed for Human Longevity Inc.

Agios has a market cap of $4.64 billion and $1 billion in cash which ensures it has enough funding to back up its R&D pipelines for the next three years. With the promising release of its drugs there is the real possibility that it will be revenue positive if not already taken over in that time.

The share broke up out of a medium-term base formation in September and remains on an upward trajectory. I rate it a buy up to $100. My 12-month forecast is for the share to rally back to $120 and to hit at least $180 within the next three years.

The risk, as with any small company focused on R&D, is that the clinical trials do not pan out as hoped for or that another company beats it to the market with a competing product. That is why I am placing this share in the moonshot category.

Longevity is a theme that we are going to see develop rapidly over the course of the next few years aided by the evolution of genetic sequencing, CRISPR gene editing and cancer research.

Cancer alone is an $895 billion business opportunity but no one can put a price on 30 extra years of excellent quality health. That is priceless, which is why it is such an exciting investment opportunity. Agios' focus on renewing the way our body creates blood is a novel take on cancer treatment and opens up the potential for a longevity theme as the company's products come to market. I believe this is not going to be the only position we have in the longevity theme because it is going to represent a high-growth market segment where competition will increase as the commercial reality of the market evolves.

Action to take:	**Buy Agios**
Ticker:	**AGIO:US**
Previous close 06/03/18:	**$84.23**
Market cap:	**$4.82 billion**
52-week high/low:	**84.85-45.11**

Figures accurate as of last market close: 06.03.2018

Past performance:

SolarWindow update

Elsewhere in our portfolio, two news items have made headlines for SolarWindow over the last week. The first is that the US Securities and Exchange Commission (SEC) has unilaterally moved the share on to the OTC Markets Group Pink Sheets platform.

That introduces a caveat emptor designation from the regulator, citing public interest concerns, but the SEC has not provided any detail on how it reached that conclusion. We can surmise that the swift run up in the shares was eye opening for everyone since the company does not yet have a product in the market.

Meanwhile, the second piece of news coming out today is that the company announced a 34% boost to efficiency for its cells from the last time it made an announcement in 2014. This was reported by the National Renewable Energy Laboratory's Device Performance Measurement Laboratory. The boost to greater efficiency appears to have been achieved with the help of Raynergy Tek from Taiwan, which SolarWindow is collaborating with to get commercial production underway.

As a Pink Sheets-traded stock, SolarWindow is now less liquid than it was previously. Some subscribers have reported that Hargreaves Lansdown is not able to make a market in the share. That is a function of how many potential buyers there are for it rather than any prohibition on trading. With illiquid instruments the key to successful selling is to do so on strength when enthusiasm is high and there are more willing buyers to absorb out supply.

The share collapsed to a low of $3.31 last week and has since rallied back to test the $5.50 area. Admittedly that is a fraction of the 29 December peak of $10.50 but the announcement of officially verified efficiency gains will act as a tailwind for the share.

In point of fact, generally speaking OTC shares are considered penny shares in the US when their price is below $5 so SolarWindow does not meet that minimum criteria. The essence of this market call is to bet on a revolutionary technological product that is still in development. I recommended the share at $3.88 and continue to believe it represents a high-risk potential innovation in the energy sector which could have transformative effects on the solar market. However, since it is now traded on the Pink Sheets I am moving the position to a hold, not least because of the difficulty some subscribers have had in selling it.

Data as of 06/02/2018

Energy

Company	Ticker	Rec Date	Price Then	Price Now	Gain/ loss %
Orocobre Ltd	ORE. AX	07/04/16	A$ 2.92	A$ 5.68	94.52
Ormat Technologies	ORA on NYSE	06/06/17	$58.79	$56.03	-4.69
Smart Metering Systems	SMS LN	03/10/17	735.5p	690p	-6.19
Sherritt International Corp	S CN	06/02/18	C$1.18	C$1.30	10.17

Technology

Company	Ticker	Rec Date	Price Then	Price Now	Gain/ loss %
Cyberdyne	7779	30/05/16	JPY 2,353	JPY 1,507	-35.95
IBM	IBM LN	07/06/16	$153.33	$156.95	2.36
SAIC	SAIC US	05/07/16	$58.20	$75.49	29.71
Garmin	GRMN US	02/08/16	$55.75	$59.60	6.91
2U INC	TWOU: US	06/02/17	$33.25	$69.10	107.82
Cisco Systems Inc.	CSCO: US	03/04/17	$33.80	$44.52	31.72
Advanced Micro Devices	AMD US	26/07/17	$14.76	$11.91	-19.31
Microsoft	MSFT	31/07/17	$73.04	$93.64	28.20
Northrup Grumman	NOC US	06/07/17	$301.66	$344.79	14.22

Medical

Company	Ticker	Rec Date	Price Then	Price Now	Gain/ loss %
Terra Tech Corp	TRTC	11/10/16	$0.41	$0.26	-36.29
Autodesk	ADSK	19/07/17	$108.83	$118.87	9.23
Abcam	ABC	07/03/17	907.5p	1176p	29.59
Zynerba Pharmaceuticals Inc	ZYNE: US	03/04/17	$20.10	$9.66	-51.94
Illumina	ILMN	04/09/17	$207.15	$230.88	11.42
PureTech Health	PRTC-L	09/01/18	155.75p	172p	10.43
Agios	AGIO	06/03/18	$84.23	$84.23	0

Moonshot

Company	Ticker	Rec Date	Price Then	Price Now	Gain/ loss %
SolarWindow	WNDW	07/04/16	$3.96	$5.63	42.17
Alkane Resources Ltd	ALK: AU	05/09/16	AU$ 0.31	AU$ 0.29	-4.92
Editas	EDIT: US	07/03/17	$21.02	$38.48	80.83
Haydale Graphene Industries	HAYD	02/5/17	178.5p	117.50p	-34.17

For the full portfolio including live prices, please visit the *Frontier Tech Investor* subscriber area. **You can view that by following this link.**