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Eoin Treacy, Investment Director

The evolution of technological innovation occurs in anything but a straight line. In fact, it is quite jerky.

In simple terms, there are times in history when something new comes along that changes everything about how we thought the world works. For decades people will have been fulfilling their daily tasks in what they considered a time-honoured fashion. Then something happens and they think about it in a completely different way.

What many people do not understand is that in a period of exponential innovation such as we have today, these kinds of step changes in perception occur at progressively faster speeds. That's the reason we launched *Frontier Tech Investor*: there is never going to be a shortage of things to write to you about or companies to recommend because the pace of innovation is speeding up. The challenge is trying to keep up with it!

But not all individual innovations are created equal. Some really are more important than others because they act as enablers for further innovation. It is these key innovations that contribute to the jerky manner innovation has occurred historically.

I've identified two major innovations that are going to utterly change the world. The first is a "tomorrow's gravy" story. The key piece of technology I'm excited about is simply going to take more time to get up to commercial utility, but it's vital we monitor progress because it is going to be groundbreaking when it is released sometime in the next five years. The second is occurring right now and will frame an investment recommendation we can make money from today. Let me explain.

How new innovations change the way we think

In his 1962 book *The Structure*

of Scientific Revolutions, Thomas Kuhn coined the phrase "paradigm shift" to explain how scientific revolutions occur. He argued, correctly in my opinion, that physics is not some Platonic ideal like arithmetic, love or hate. Instead our understanding of the world is framed by our culture and history which influence how we have come to understand things. He came to this conclusion by reading and comparing Aristotle's physics to Newton's and observing how completely different they are. It was not that Aristotle was stupid, but simply that he was acting with limited information and was performing in a socioeconomic framework that was likely unable to comprehend any other reality.

The story of how Galileo dropped two balls of different weights from the Leaning Tower of Pisa is a great example.

Galileo set out to disprove Aristotle's belief that the heavier ball would fall faster. There was nearly 2,000 years between the two men but had no one, in all that time, thought to question the wisdom of the old master's belief system? Galileo in one fell swoop invented experimentation as a way of testing a hypothesis. It's almost a facile statement today. It's so obvious we find it hard to comprehend. But the reality is that the hypothesis and experiment to verify principle is only 400 years old. Yet it unleashed a flood of experimentation we are still riding today. It was a perfect example of a paradigm shift because something new came along and everything that came before looked like nonsense.

Paradigm shifts might originally have been applied to the scientific method but they are equally evident in the development of technology. What I am most interested in is when a paradigm shift occurs that acts as an enabler for innovation. Let's look at two examples to explain what I mean: the printing press and the internet.

When Newton said he stood on the shoulders of giants, his genius was communicated by the printing press.

Gutenberg and the spread of new ideas

Johannes Gutenberg invented the moveable type printing press and produced about 180 editions of his famous Bibles. That might not sound like many but there were only about 30,000 books in all of Europe at the time. Moveable type created an efficiency in printing that blew woodblock printing out of the water and quickly took over to become the dominant method. Within a few decades, millions of books were being printed.

The printing press was an amazing invention, but it was also transformative for the global economy. Paper was invented in China about 100 AD and migrated to Europe with Arabic colonists in the early 1000s. There were paper mills in Spain as early as 1056 and in France, Germany and England by the early as the 1350s. But the invention of the printing press created a market for paper that allowed the industry to balloon from a niche curiosity to one of the world's largest and most pervasive industries today.

The printing press allowed theological revolutionaries to spread thoughts far and wide by reducing the cost of producing pamphlets to a pittance. In fact, the newsletter business – of which this letter is a proud part – has its roots in the printing of pamphlets to spread new ideas, theories and news.

And of course, the newspaper after all was impossible without the invention of the printing press and the prolific production of paper. By allowing ideas to be both recorded and spread the printing press was one of the greatest enablers of literacy in history. It fuelled scientific discovery. When Newton said he stood on the shoulders of giants, his genius was communicated by the printing press.

Worldwide paradigm shift

The internet is an equally significant invention because once more it has created a step change in how we both record and disperse information, and more recently in how we communicate with one another. By putting the world's greatest

librarian in our pockets, the ease of acquiring knowledge, finding likeminded people and communicating with anyone anywhere has improved without recognition.

Disintermediation has been the buzz word most frequently attached to the internet since the 1990s because it allows the number of transactions that need to take place to move a product from the producer to the end consumer to decrease. Resellers are a dying breed because anything that can be transferred electronically or for a reasonable postage cost is now taking place online. Shopping centres are under enormous pressure from online retailers, while the music, book and entertainment sectors have been revolutionised by the internet.

However, what I want you to think about right now is how much of an enabler the internet has been for additional innovation. For example, it has enabled businesses to become truly global in perspective. Apple for example has "Designed by Apple in California" printed on many of its products, but parts are manufactured all over the world and most are assembled in China. Managing that kind of global supply chain would be next to near impossible without the internet.

The internet has enabled collaboration like never before. As a result, it has allowed the pace of innovation to pick up. We are social animals and when we can communicate more effectively we get more creative. Without the internet, there would have been no need for broadband and it would have been much more difficult to make the case for fibre optic networks. Software as a service models, which are now proliferating, would have been impossible, while cloud computing or cryptocurrencies (which is really just a case of the internet doing money) could not even have been conceived of without the internet.

The internet was a paradigm shift of even greater significance than the printing press and what it delivered is going to be influencing just about every sector, everywhere, for decades to come.

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I think you probably get the point. Paradigm shifts are important because they literally shift our perception of reality and of what we think of as possible. Right now, I can see two potential sectors evolving in a way that is inevitably going to create the same kind of paradigm shift.

Batteries will change the way we think about energy

The first one is in batteries. The lithium-ion battery was first proposed by British chemist Stanley Whittingham in the early 1970s when he worked for Exxon. It was first commercially released by Sony in 1990 for handheld devices. Meanwhile at the Los Angeles Auto Show in the same year, General Motors unveiled an all-electric concept car, the Impact, and declared it would begin to produce them on a commercial basis. In fact, electric vehicles were among the early solutions for transportation in the 1890s but largely disappeared with the advent of the internal combustion engine.

Today demand for electric vehicles is trending higher because consumers are more environmentally conscious, have been traumatised by the high cost of fuel for more than a decade and have been subject to terrorist attacks from citizens of the world's largest oil-exporting countries. The recent diesel scandal where German automakers programmed cars specifically so they could avoid emissions controls has further damaged consumer faith in the internal combustion engine. Meanwhile Tesla has succeeded where almost every other company has failed, in producing an attractive electric car, which people aspire to own.

More than two million electric vehicles are now on the road globally with around 750,000 sold in 2016 and 547,220 in 2015. Automakers are coming out with ambitious targets for producing

more electric or hybrid vehicles and the UK announced a ban on new diesel and gasoline cars by 2040. However, the fact remains that despite the progress made the sector is still in need of a paradigm shift moment. The time when everyone will suddenly get the message and the argument about whether to own an electric vehicle or not will be nonsensical.

There are some obstacles though. One is simply manufacturing capacity. It is going to take at least another few years before the infrastructure in terms of battery factories, new models and designs are ready to hit the market. It takes a lot of time to retool a factory for a new model. But when that new model is for almost completely different technology then the decision to move a company over to electric vehicles requires institutional and cultural change within management and that takes time.

Another obstacle relates to the battery itself. Right now, they take too long to charge, don't run for long enough and are too expensive. By opening its gigafactory Tesla introduced economies of scale and helped to bring down the cost of batteries. The company estimates the battery will account for a quarter of the cost of its cars. Since the Model 3 is expected to retail for $35,000, that means the cost of the battery has come down significantly in the last few years.

However, the cost of the battery does not mean that the time to recharge and the range will be extended. That is going to require a step change in technology.

The paradigm shift is likely to be represented by solid-state batteries being developed by both Toyota and BMW.

Solid catalysts would deliver faster charging times, similar to refuelling times for gasoline cars and would extend the range. Toyota estimated in 2013 it would have a product on the market by 2020 but pushed it back to 2022 in July. That probably means it has made progress on solving the production issues it has but not yet solved the problem.

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BMW expects to deliver solid-state batteries in 2026

Considering we are now in 2017, it is easy to identify solid-state catalysts as a game-changer for the battery sector – one that will usher in a new era of groundbreaking innovation in the transportation, energy and energy storage sectors. However, it is too early to make a decisive call on which company will be first in delivering it at scale. I also know of a couple of privately held companies pursuing the same prize. Don't get me wrong, I expect 2017 to hit another record in electric vehicles sales, but to get sales up to even an approximation of the 78 million conventional vehicles sold per year, we are going to need a major step up in the technology.

Even assuming solid-state batteries are not delivered by Toyota, Panasonic believes it can improve Tesla's battery density by another 30% by 2020. Again, that's solid progress. But what the sector needs is that breakout moment when the logic becomes so compelling that no one will ever want an internal combustion engine again. That's why I referred to it as a tomorrow's gravy story. It's exciting and there is a lot of competition for the prize of the best battery, but until it is actually delivered we are in a holding pattern regarding an investment. I'm satisfied that we have a stake in the industry, via our lithium supplier Orocobre. But I'm on the hunt for more direct ways to play the industry. Look out for those in future issues.

A massive paradigm shift happening right now

Where I see a true paradigm shift underway right now is in biotechnology. We already have positions in the portfolio offering exposure to the emerging synthetic biology and CRISPR sectors. In one of my other services for Southbank Investment Research, *Trigger Point Trader* (which is dedicated to short-term trading in all sectors, not just technology), biotechnology has been the

leading source of profits since inception. In fact, we took a 98% profit last week when Kite Pharma was acquired by Gilead Sciences.

The story of why Gilead Sciences made the acquisition offers a window on what is going on in the sector and why so many companies are so eager to get in on the action.

Gilead Sciences shot to fame when it developed the vaccine for Hepatitis C. However, with such success comes inevitable attempts by competitors to muscle in on a profitable market. The share was among the hardest hit during the biotech shakeout that began in 2015. It needs a blockbuster new product to revitalise flagging sales. That's why it bought Kite Pharma.

Kite Pharma is a leader in the emerging immuno-oncology sector. There are an increasing number of companies emerging in this sector and they all take a slightly different approach to reeducating the immune system to kill cancer cells. The clinical term for this procedure is CAR T-cell therapy.

In simple terms, the immune system produces two kinds of cells: B-cells, which create antibodies; and T-cells, which go out and kill alien invaders. The treatment focuses on extracting T-cells from a blood sample, genetically engineering them so they now have the ability to recognise the cancer cells infecting the patient's body, multiplying them and injecting them back into the patient. When they have been altered from their original state they are called chimeric antigen receptor T-cells (CAR T-cells) because like the Chimera of Greek legend they have the characteristics of more than one cell in the immune system.

The results can be amazing. For the first time, the words "90%" and "remission" can be included in the same sentence. Here is a quote from the Leukemia & Lymphoma Society:

In some studies, up to 90 percent of children and adults with ALL who had either relapsed multiple times, or failed to respond to standard therapies, achieved remission after receiving CAR T-cell therapy.

Let's be very clear. **CAR T-CELL THERAPY CAN CURE CANCER!**

That's today, not in five years. It represents the very definition of a paradigm shift.

Ten years from now we are probably going to be scratching our heads wondering how we could ever have had the barbarity to put anyone through the trauma of chemotherapy.

It's still very early days. CAR T-cell therapy works best right now in blood borne cancers. The focus of attention is now turning to solid cell cancers and there are great hopes equally astounding results will emerge from that research.

Last week Novartis was the first company to receive permission from the US's Food and Drug Administration to market a CAR T-cell therapy. It might be the first but it certainly will not be the last.

Let's be very clear. CAR T-CELL THERAPY CAN CURE CANCER!

The majority of news flow has focused on the $475,000 price tag, which is eye-watering to say the least. Look a little deeper and the company has in fact made deals that customers will only pay if they achieve results within a month of treatment beginning. With a 90% success rate that's not the bargain it sounds.

The reason Novartis can claim $475,000 is good value is because the cost of treating cancer is so high. For example, if a child were to receive a bone marrow transplant the cost would be similar but the results much less impressive.

That represents a big question for healthcare providers because cancer diagnosis is trending progressively higher and is expected to reach upwards of 21 million cases per annum by 2030. Treating cancer successfully could bankrupt the National Health Service and it is already creaking under the strain of treating more

elderly people. The question of how to solve this riddle is where the company I want to talk you about this month comes in.

The government-funded Human Genome Project estimated it would take $2.7 billion to sequence a human genome. It cost Craig Venter $100 million and he did it faster. In 2015 his latest company Human Longevity Inc signed a deal with Discovery Ltd, a South African and UK insurer, to sequence the entire exome for $250. That's 10,000,000 times cheaper than the first estimate for the cost of genetic sequencing.

Illumina is the world leader in producing genetic sequencing machines. It's like owning a stake in the technology behind the printing press itself, rather than a specific publisher or author. In January, it released a new architecture, NovaSeq, it estimates will allow companies to bring the cost of genetic sequencing down to $100 or a million times cheaper than when Craig Venter completed the first genetic sequencing 14 years ago.

Let's think back to Gutenberg for a moment. The first movable type printing press produced books which were extraordinarily expensive because books were so rare. However, the innovation was so extraordinary that it represented one of the first exponential growth drivers in recorded history. That's the kind of growth $100 genome sequencing is likely to deliver. That's only today. If the trend of improvement continues, $10 sequencing is less than a decade away. In fact, as the cost comes down the evolution of sequencing as a service will evolve rapidly. The cost is likely to be negligible because the value will no longer be in sequencing but in deciphering what the information means.

Our top pick for the medical world's most important industry

Veteran subscribers will already be acquainted with how excited we are about CRISPR-Cas9 gene editing. Again, it represents a step change in the cost of editing DNA. Within the two years since its discovery it is now ubiquitous in research labs all over the world. It is fuelling massive innovation in the genetic editing sector and the cost of research is collapsing. It's another paradigm shift.

What we have are two complimenting innovations that would in ordinary circumstances represent paradigm shifts in their own right. Together they could contribute to the delivery of massive reductions in the cost of cancer care over the next decade.

Think about it this way. Compare the experience of having a dental crown fitted a decade ago with how it is done today. When I had my first crown in 2003 the dentist had to take a mould, send it to a lab, wait for the crown to be manufactured, have me come back in and hope if fit correctly. Last month my dentist prepped the tooth, scanned it, used a 3-D printer to create the crown and fit it. The whole process took less than two hours. What once took a whole lab and team of professionals can now be completed on a desktop. It was also cheaper than the crown I had fitted 14 years ago.

I'm not in any way trivialising the complexity of treating cancer. However, the pace of technological innovation is progressing so rapidly that companies aspiring to charge high six-figure price tags may be forced to come up with alternative strategies. If we simply assess the speed with which gene sequencing and gene editing are progressing, coupled with innovations in artificial intelligence and computing power, it is only a matter of time before manufacturing custom CAR T-cell strategies will be possible within the oncology departments of hospitals.

Illumina is ideally positioned to benefit from that rollout. Its latest machines cost upwards of $895,000 but considering what they deliver in terms of genetic sequencing potential, that represents considerable value for labs.

The company's Q2 revenue was 10% higher than Q1 because the new NovaSeq systems sold 30% better than expected. As with many hardware companies Illumina makes more money from consumables than from the machines. That meant consumables represented 61% of revenue in the last quarter while the decline in gross margin was driven by increased headcount to try and fuel new growth. Sales will also be back-loaded for the second half of this year as manufacturing capacity of the NovaSeq ramps up.

The company has an historic price/earnings ratio (P/E) of 65.45 with an estimated P/E for 2018 of 46.36, suggesting investors believe earnings are going to continue to improve over the next 12 months.

The CEO Francis deSouza mentioned at the Goldman Sachs Global Healthcare Conference in June that there are 1,100 immuno-oncology clinical trials ongoing right now which represents a significant growth trajectory for the company.

He also highlighted the fact that there are 70 different operators in the liquid biopsy sector. That requires ultra-deep sequencing of the blood to identify DNA from solid tumours floating around the body. In fact, Illumina is so excited about this route for growth that it split off that segment of the business into a new company called Grail Inc to focus on early diagnosis of cancer. DeSouza quoted Grail's CEO as expecting to gather up to 500 petabytes of information from a single blood sample and that it expects to be the first zettabyte company.

Illumina's share drifted for 18 months following the peak in biotechnology in 2015 but has been on a recovery trajectory since the end of last year as the rollout of the new NovaSeq architecture hit the market. The share broke upwards from its 22-month range in July and consolidated until last week before breaking out again. I recommend buying Illumina up to $240 and expect to see that price surmounted by year end. My three-year target is $500 and five-year target is $750. That is assuming the pace of technological innovation persists.

The threat as with any technology is that something comes out of the blue that is orders of magnitude better. That's never a risk that can completely be ignored. The other big risk of all biotech companies is that politicians target the sector for opprobrium because their products have tended to be rather expensive.

Name:	**BUY: Illumina [ILMN]**
Ticker:	**ILMN**
Current price:	**$207.15**
Buy up to:	**$240**
Market cap:	**$30.070 billion**
52-week high/low:	**$207.49/$199.37**

figures accurate as of last market close: 05.09.2017

Five-year performance:
2012 +74.37% | 2013 +95.24% | 2014 +77.29% | 2015 +10.01% | 2016 -20.43% | 2017 +53.13%

Crypto Roundup 5th September 2017

The tree shakes do you fall?

At the time of writing bitcoin and Ethereum prices are winding off their all time highs. Bitcoin surged past US$5,000 and Ethereum was up again close to US$400.

Now they're heading back towards and possibly under US$4,000 and US$300 respectively. Why? Well part in part is psychological resistance at those high figures. And part of it is a seemingly global crackdown on cryptocurrency by governments.

Also it's quite likely that a lot of automated trading executed sales up around US$5,000 and since then there's been a spate of margin calls and short positions close out on the down run.

Should you worry? Nope. This is affectionately known as 'tree shaking'. It's part of the crypto game to see who will fall from the tree and who's going to stay up there. Remember this is a long term, financial revolution. See dips and falls as entry points if that fits your strategy. Crypto-cost averaging (a little in each week or month) helps to iron out volatility like this.

Paris Shillton

To 'shill' a crypto is to blatantly advertise, plug, support, and promote it to the wider community. You will often see on Twitter 'famous' crypto investors or developers 'shilling' their favourite crypto. More often than not they have a vested-interest (i.e. They hold it) in that crypto. And with more awareness and notoriety it's got a better chance of increasing in value multiple-times.

One of the biggest 'shills' of recent time has been boxing superstar, Floyd Mayweather Junior and the STOX crypto. Initially this 'celebrity shill' helped push STOX significantly higher leading up to Mayweather's recent fight. But since then STOX has crashed.

The most recent 'shill' though is Paris Hilton who just came out on Instagram and Twitter saying she's, 'Looking forward to participating in the new **@LydianCoinLtd** Token!' When Paris 'Shillton' starts to get involved in crypto like this we do have to ask the question....have we reached peak crypto?

China says NO!

Adding to the recent volatility (probably thanks to Paris 'Shillton') China has come out with a blanket ban on all crypto 'Initial Coin Offerings' (ICOs). They argue that 90% of all ICOs are basically fraudulent and illegally raising money.

As you'd expect this sent crypto markets into a panic. Hence the price falls. Of course this isn't the first time China said 'no' to crypto. They did the same thing to bitcoin back in December 2013 after giving bitcoin the green light weeks earlier in November.

Are we worried about China banning ICOs? No. We think it's just a measure to allow the government to catch up with the pace of change. Once they realise how big an opportunity this is for their country and their people, they'll open the doors again. Back flipping on crypto seems to be a common occurrence with China, this is just history repeating in our view.

Energy

Company	Ticker	Rec Date	Price Then	Price Now	Gain/ loss %
Orocobre Ltd	ORE. AX	07/04/16	A$ 2.92	A$ 3.91	33.90
Ormat Technologies	ORA on NYSE	06/06/17	$58.79	$57.37	-2.42%

Technology

Company	Ticker	Rec Date	Price Then	Price Now	Gain/ loss %
Cyberdyne	7779	30/05/16	JPY 2,353	JPY 1,468	-37.61
IBM	IBM LN	07/06/16	$153.33	$144.08	-6.03
SAIC	SAIC US	05/07/16	$58.17	$74.42	27.87
Garmin	GRMN US	02/08/16	$55.75	$51.82	-7.05
2U INC	TWOU: US	06/02/17	$33.25	$49.92	50.14
Cisco Systems Inc.	CSCO: US	03/04/17	$33.80	$32.30	-4.44
Advanced Micro Devices	AMD US	26/07/17	£14.76	£13.19	-10.64
Microsoft	MSFT	31/07/17	£73.04	£73.94	1.23

Medical

Company	Ticker	Rec Date	Price Then	Price Now	Gain/ loss %
Terra Tech Corp	TRTC	11/10/16	$0.41	$0.25	-40.53
Autodesk	ADSK	19/07/17	$108.83	$113.71	4.48
Abcam	ABC	07/03/17	907.5p	1071p	18.02
Zynerba Pharmaceuticals Inc	ZYNE: US	03/04/17	$20.10	$6.35	-68.41
Illumina	ILMN	04/09/17	$207.15	$207.15	0

Moonshot

Company	Ticker	Rec Date	Price Then	Price Now	Gain/ loss %
SolarWindow	WNDW	07/04/16	$3.96	$4.68	18.18
Alkane Resources Ltd	ALK: AU	05/09/16	AU$ 0.31	AU$ 0.40	29.15
Editas	EDIT: US	07/03/17	$21.02	$20.59	-3.24
Haydale Graphene Industries	HAYD	02/5/17	178.5p	177.50p	-0.56

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