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Synthetic Biology: The Next Leap Forward For Mankind

Guided Evolution, Synthetic Biology and Truly Intelligent Design

Eoin Treacy, Investment Director



The genetic code might be the secret to life, but it’s messy. Your own individual genetic code is like your body’s “instruction manual” – it makes you *you* – but it has errors in it. Depending on what these errors are, they leave us with susceptibilities and weaknesses that will eventually kill us.

That’s been the hard reality of life since the dawn of humanity.

But it’ll soon be over.

Within the next ten years a major project will be completed which will map out the function

of every gene in the human body. That might seem like old news but it is what we’ll be able to *do* with that knowledge that will change everything. We’ll have the ability to identify what is necessary, what has been rendered obsolete as a result of evolution and environmental changes, and what would enhance our wellbeing.

In short we’ll be able to take a genetic code – the secret to life itself – and rewrite it.

It’s going to happen. It’s getting major investment capital, and it is going to require the exponential pace of technological development to continue to accelerate in order

to achieve it. Today I want to introduce you to a company helping to make it happen.

Building the synthetic genome

Make no mistake, we’re entering a brave new world. That’s a loaded phrase to use, given that Aldous Huxley’s novel *Brave New World* involved genetic engineering on a vast scale, reorganising society around those with the strongest genetic code. This is a global challenge and, make no mistake, it’s a race. However, it’s one that will benefit the whole of humanity, just like the original Human Genome Project did.

I had the pleasure of chatting



Intelligence bulletins

■ IBM's Watson powering growth

We're already invested in IBM for its work on AI and quantum computing. Last month we got another indication that could be a great move. In a University of North Carolina study, IBM's AI program Watson went head to head with human experts over cancer diagnoses.

In 30% of cases, Watson found a treatment options the human doctors missed. With results like that, it's no surprise Swiss bank UBS believes Watson could make \$17 billion a year for IBM by 2022. It currently makes less than a billion.

■ The next "micro" power station - people walking

Did you know that walking a set distance can generate as much as 5 watts of energy, using specially designed flooring that converts kinetic energy into stored power? It's the next step on the road to innovative renewable energy becoming a part of daily life.

5 watts may not sound like much. But multiply that by hundreds of thousands of people passing through an airport or train station and you start to see the scope.

with Andrew Hessel, one of the true visionaries of genetics, at Singularity University's Exponential Medicine conference at the historic Hotel Del Coronado a few weeks ago.

He recounted the rather humorous anecdote of how earlier this year he and a few well-positioned scientists and researchers arranged a meeting at Harvard Medical School. It had been 25 years since the beginning of the Human Genome Project and the group wanted to discuss the potential for rebooting the mystique of genetics by creating a new ambitious mission.

The problem was, some wag got hold of the story – and since the press had not been invited, dubbed it a "secret meeting". That resulted in front page headlines all over the world. The upshot of that meeting is a plan to build a full set of 26 human chromosomes (three billion base pairs) from scratch within a decade.

Think about that. To build a genome from scratch. Not to adapt one that exists. To create one: a synthetic genome.

The Human Genome Project funded massive leaps in our understanding of how to read DNA, but the new project will go a step forward by advancing the field of synthetic biology and writing the code instead.

Introducing the Carlson Curve

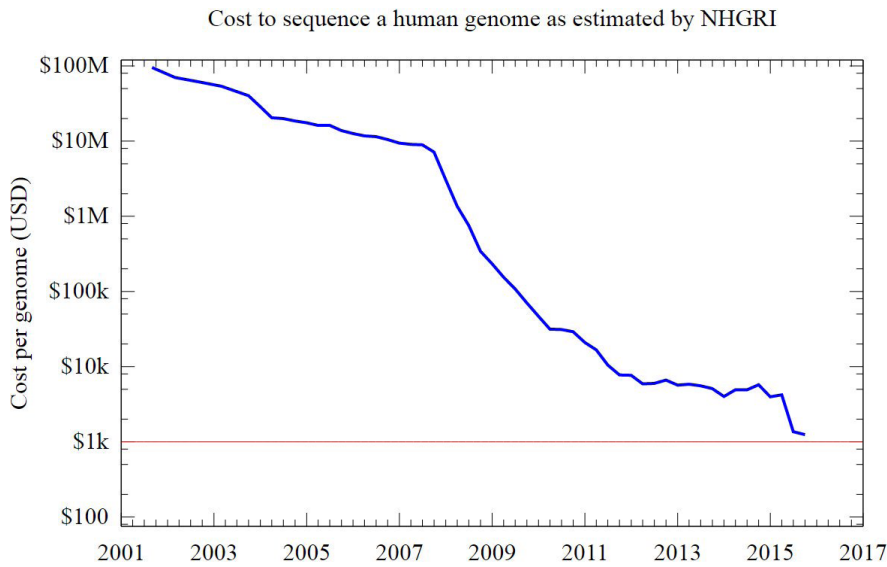
That's going to lead to huge opportunity. It's going to need

new machines, better ways of testing individual genes and innovative ways of populating empty cells. This endeavour is being dubbed the Human Genome Project-write. Here are the group's ambitions in its own words:

The goal of HGP-write is to reduce the costs of engineering and testing large genomes, including a human genome, in cell lines, more than 1,000-fold within ten years, while developing new technologies and an ethical framework for genome-scale engineering as well as transformative medical applications.

That's sounds like a lofty goal and no one is under any illusion that it isn't going to take a lot of hard work. But it is far from unachievable. You might be familiar with Moore's Law, which is most frequently applied to the electronics sector. It has held true for decades that the efficiency of microprocessors doubles about every 18 months, or more specifically that the number of transistors on a chip has doubled at that pace.

In the biotechnology sector, The Economist came up with a similar measure which it named the Carlson Curve. It holds that the cost of sequencing DNA will fall at least as fast as Moore's Law. However, in 2008 it began to accelerate in an exponential manner compared to the linear model used in Moore's Law and continues to outpace what might have been expected under Moore's Law.



Here is a chart of the swift decline of the cost of genetic sequencing, which true to form has occurred in an exponential manner.

If the contraction in price continues in line with Moore’s Law then by my calculations it would be at \$500 at beginning of 2018, \$250 by end of 2019, and \$125 by by the middle of 2021. However if we think in exponential terms, then the pace of decline in sequencing DNA would fall much faster. It would be more like \$500 by the middle of 2017 and \$100 by the middle of 2018.

Regardless of how you calculate it the cost of sequencing is falling at a prodigious rate and is rapidly entering territory where there will be no impediment to anyone having their entire genetic makeup profiled.

Right now you can have your entire genome sequenced for just less than \$1,000. Since companies want to make money, they are probably

going to start offering more services rather than dropping the prices quickly. While that is likely to slow the pace at which consumers can access the

lives. Getting that cost down is integral to the success of the genome writing project because we have to make it easier to winnow out the individual purpose behind each and every gene.

The quantity of data that needs to be understood is mind-boggling and, so far, the study of genetics has been piecemeal. It’s part of the human condition that we want to work on interesting things. So when researchers set about learning what different genes do, they started with the most exciting candidates. The result is that we have a really good understanding of what some genes do but very little understanding of what a good

“Get your genome sequenced for less than the price of a pizza”

technology, it is inevitable that the cost will decline further as the sector gains critical mass and the economics of offering much cheaper testing become unquestionable. Therefore, based on historical precedent, we can expect full genome sequencing for less than \$100 by 2020.

By 2030 it could cost less than a takeaway pizza. By that time, genetic sequencing will be ubiquitous and every child will have their DNA sequenced at birth. Their genetic identity will form an integral part of their healthcare for the rest of their

many others do. The field of genetics is going to be minting PhD students at a rapid rate for the next few years as we learn more and more about our DNA.

How to guide evolution from the lab

In 2010 the J. Craig Venter Institute (JCVI) announced that it had synthesised a chromosome of a bacteria which contained 1.08 million base pairs or lines of code. Here is an important section from the press release:

The proof of principle that genomes can be designed in the computer, chemically made in



the laboratory and transplanted into a recipient cell to produce a new self-replicating cell controlled only by the synthetic genome.

It took six years but the team at JCVI has gone one further and synthesised the same bacteria but with less than half the base pairs.

The new minimal synthetic cell contains only 531,000 base pairs and just 473 genes making it the smallest genome of any self-replicating organism.

Not one of those 473 genes is surplus to requirement, but here is the really interesting thing. The team that built the bacteria don't know what about a third of them do. It knows they are needed to sustain life but not each gene's exact purpose.

This is an incredible achievement for synthetic biology for a number of reasons.

First off, it displays how much can be achieved with imperfect knowledge. Even more exciting is that we know how to get the information required to get a more complete picture. The bigger point is that almost half of the bacteria's DNA is surplus to requirement.

The most basic understanding of evolution is that it represents the survival of the fittest, but if the above example tells us anything it is that evolution is marking us to a curve. It's not an absolute measure. In fact, survival is not much of a measure for anything. Given the choice, would you rather have evolved to thrive or

survive? I don't know about you but just surviving doesn't sound like much fun.

This is a topic both Nick O'Connor and I get rather excited about so we really should set up a podcast to go with this report. Look out for that in the coming weeks. In a recent piece, Nick quoted Matt Ridley's *The Evolution of Everything* on the topic:

The world 'evolution' originally means 'unfolding'. Evolution is a story, a narrative of how things change.

It implies the emergence of something from something else. It has come to carry a connotation of incremental and gradual change, the opposite of sudden revolution.

It brings the implication of change that comes from within, rather than being directed from without. It also usually implies change that has no goal, but is open minded about where it ends up.

Evolution is incredible not just because of the complexity it achieves, but that it does so without meaning to, without planning and without a design.

Nick went on to explore that idea further – in the relationship between the “designed” iPhone and the “evolved” human hand that controls it:

At its core, that's what separates the human hand and the iPhone. One has a designer and one doesn't. As people we're able to design and engineer

tools of great complexity. We're creators.

But what if those two ideas were to collide? What if we could harness the natural, unguided forces of evolution... and instil some form of design on them?

What if the next phase of evolution wasn't spontaneous... but orchestrated by use.

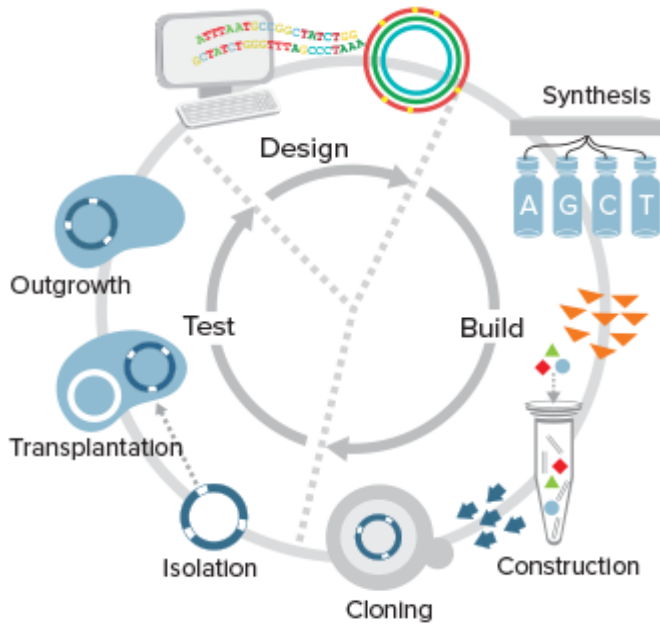
What if the next generations of humanity could say they were a product of intelligent design... but the intelligent design of mankind, not God?

Synthetic yeast

For the last four years the Synthetic Yeast Genome Project has been underway and as of July this year is about 50% complete. The aim of the project is to advance the technology and synthetically build 12 million base pairs, which is orders of magnitude larger than a virus.

I'm impressed by the scale of this endeavour. But can't help asking, why yeast? The answer is that humans have been using yeast for everything from making bread to beer for thousands of years. We know a lot about it. In fact, more is known about the individual strain of yeast the project is attempting to synthesise (*S. cerevisiae*) than other varieties – despite the fact it is larger than other candidates.

This project has helped to foster what has so far been the most public utility of synthetic biology



Source: J.Craig. Venture Institute

how they succeed in attacking cells.

Immuno-oncology is progressing at a rapid rate. Today it is primarily targeted at re-educating the body's T-cells to attack cancer cells that had previously avoided detection. This is successful against a number of cancers that have high fatality outcomes. We have invested in the immuno-oncology sector previously and I'm sure we will again, but I want to talk to you today about the technology that is going to transform this sector from the cutting edge to the mainstream.

to date, which is in the energy sector. You might remember stories from around 2007 about the prospect of using genetically altered bacteria and yeast to manufacture environmentally friendly versions of jet fuel and gasoline from plant matter.

The logic behind the plan is simple enough. We now use ethanol as an accelerant in gasoline, but it can only be produced from high calorific crops like corn or sugar – and then most of the plant is useless to the purpose of making ethanol. The ambition is to use bacteria and yeast to break down the cellulose material to make higher value products.

These are laudable projects and there are a number of small companies attempting to commercialise various strategies. I'm watching it closely for signs of a breakthrough, but the whole enterprise faces some daunting challenges. The

first is that bottled water is more expensive than gasoline by volume and the price of the commodity is highly variable. The cost of first proving the viability of the projects is prohibitive but getting them up to a scale capable of competing with an oil refinery is a major endeavour in itself. Then, even if successful, it is competing with electricity for the future of motoring and that is a going to be one tough competition. Perhaps most importantly of all, I think there are better uses for the technology that are likely to be much more profitable.

Synthetic biology could help defeat cancer

The first virus ever synthesised was polio. I know, it's not exactly the most hope-inspiring candidate. But the purpose in learning more about infectious diseases is that we can also learn about how to make better vaccines for all sorts of other viruses, and we can figure out

Andrew Hessel and Peter Diamandis outlined at the ExMed conference how teams they are involved with are currently working on machines for much faster genotyping of cancer cells and 3D printers that will synthetically engineer custom viruses to kill them. Because every cancer is different and requires a tailored treatment, this truly represents the holy grail of oncologists globally.

From writing software to writing life: this month's recommendation

This month's recommendation, Autodesk, is not a company one immediately associates with healthcare. It is a software company. It pioneered computer-aided design, where it is still the clear leader. Its software is integral to the creation of just about all designs conducted within a PC environment, whether that is



architectural structures, planes, trains, automobiles or furniture.

You might not have recognised it but Autodesk software such as Maya, Softimage, 3ds Max, Mudbox, Smoke and Flame are the industry standard in Hollywood. These were responsible for much of the special effects in movies like *Alice in Wonderland*, *Harry Potter and the Deathly Hallows – Part 1*, *Inception*, *Iron Man 2*, *King Kong*, *Gladiator* and *Titanic*. The videogame sector produces more revenue than Hollywood and is even more reliant on computer-generated imagery, meaning it has represented rich pickings for Autodesk’s Maya software.

But Autodesk is in the process of making a “pivot” towards a new industry: synthetic biology. Rather than writing *computer* code... it’s developing a wing of the business that writes *genetic* code.

In the past the company has driven technology on by open sourcing it. It looks like it is following the same model with synthetic biology. By open sourcing its discoveries, the company hopes to build an ecosystem of developers around its corporate and hardware architecture. This will give it some level of control over what is likely to be a sector with exponential growth characteristics. So it’s true it might not have made money from the investment put into synthetic biology, but it’s even more likely that it will play a pivotal role in developing

Cost to Develop a New Drug

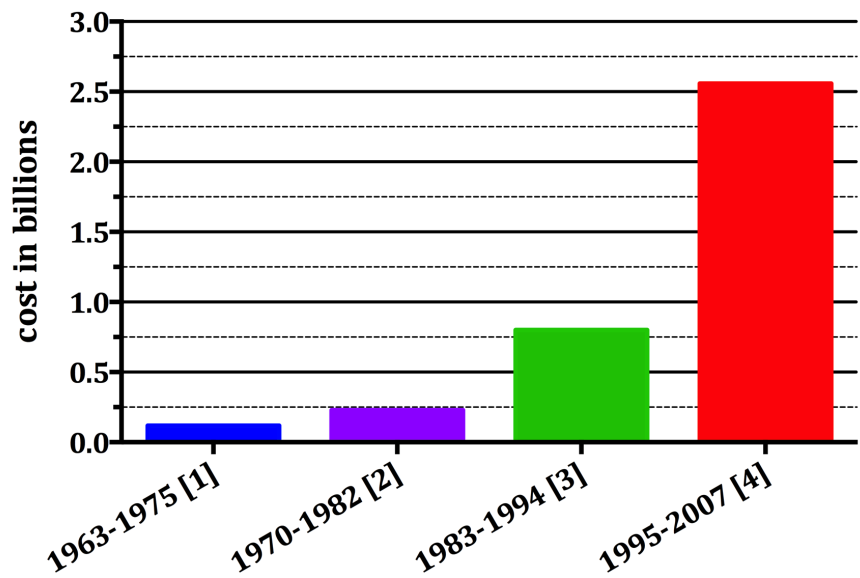


Figure: Cost to develop a new drug. Cost in billions is represented according to the contemporary values of the period. Graph data collected from published CSDD Tufts studies [1-4].

Source: Dilworth IP Intellectual Property Law

business models for synthetic biology as it develops.

Andrew Hessel’s team of 90 people at Autodesk, amid a total workforce of 9,500, is like a drop in the ocean, but the work he is pioneering is potentially pivotal to the future of the company. He has already bioprinted a synthetic virus and his eventual aim is to make use of 3D printers to build custom viruses to kill off cancer.

But here’s the strange part. Autodesk might not make any money from the work he is pioneering. That’s because the classic drug discovery model is broken. It is costing more and more money to come up with new drugs so the value proposition is just now compelling to deal with niche

problems, as the chart above shows:

In fact, drug discovery has been on an exponential decline for nearly 60 years, while getting more and more expensive; the exact opposite of Moore’s Law.

It is getting harder and hard for classic pharmaceutical companies to come up with new drugs. This means they have to aim for blockbuster treatments that will cure a lot of people and compensate the company for spending billions on development.

With his Pink Army Cooperative, Hessel wants to build customised drugs for individuals instead of developing blockbuster drugs for everyone. Rather than test

thousands of people to create a drug, he is making treatments for individuals and only tests them on that person's individual cells. That takes the time to

with nothing to show for it at the end?

The company embarked on a big change earlier this year by

is the perfect time to be thinking about investing.

Personally, I think the company has made a very shrewd move in supporting the genesis of synthetic biology. Right now it is a sector that is really only just getting off the ground. The potential for the company to develop the software which will drive the growth of the sector going forward is a tantalising possibility. I recommend buying Autodesk because I believe it has big things ahead of it. And it's not a "pure play" on synthetic biology. I think it will benefit from the growth of design, computer games and virtual reality – and you get the optionality on synthetic biology for free.

Drug discovery is the exact opposite of Moore's Law

develop a drug down from a decade to months. He is surfing the wave of the declining price of sequencing DNA to develop cheap ways of developing drugs and he is creating custom viruses to achieve it.

The type of virus used is rather special and worth taking a little time to learn about. It's called an oncolytic virus. This is a virus whose primary food is cancer cells. It is normally very weak and completely harmless to humans. However, cancer cells have mutated surfaces and are, to simplify, damaged. As a result, the oncolytic virus latches on, multiplies within the cancer cell and kills it off. When the cancer cell ruptures, it then spreads the oncolytic virus to other cancer cells and the process begins again.

Here's the kicker: Autodesk has agreed to give away the rights to any patents Hessel's team comes up with in the name of helping to drive the technology forward. It's an incredibly generous gesture for a profit-oriented company. That said, I know you must be thinking: why lead us on this merry chase

moving on to a subscription model for almost all of its software. That's an important step because the company is betting that it will be able to broaden the customer base by removing the initial hurdle to entry, while extending the revenue stream from those customers. As the cost of producing apps decreases and mobile devices become more powerful and deliver better virtual reality content, demand for better graphics should drive growth.

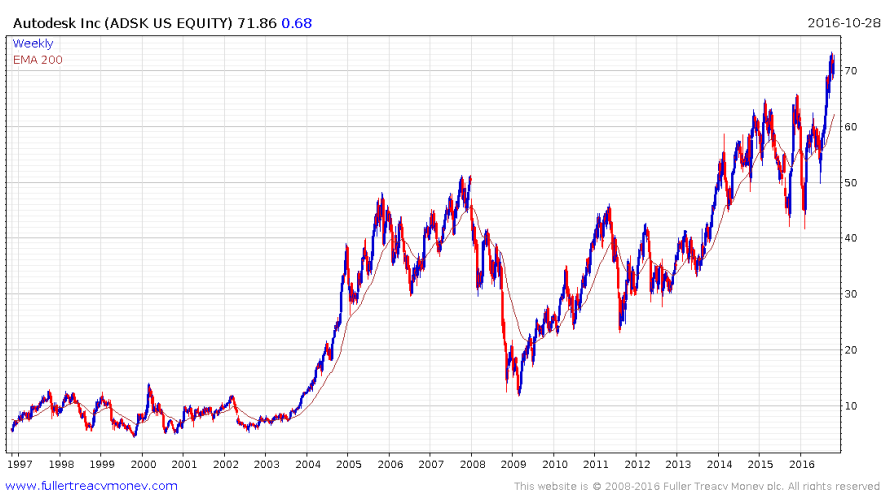
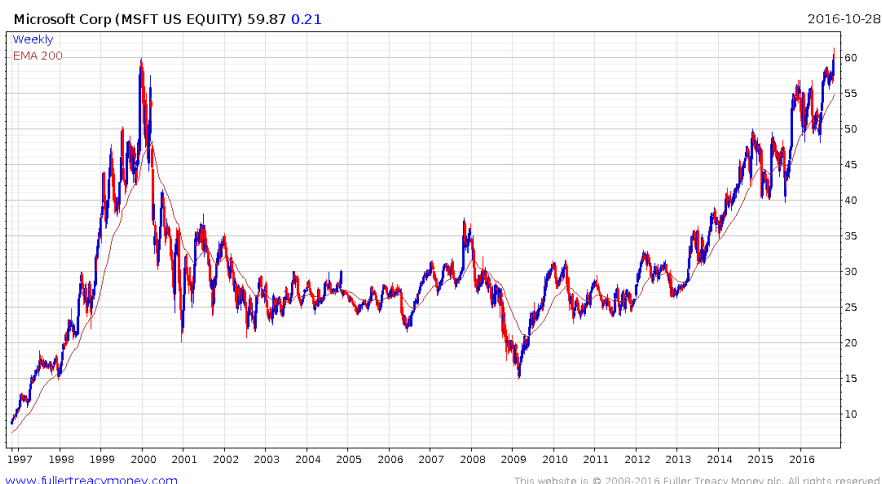
If Autodesk can achieve the same success from moving to a subscription model as Adobe Systems and Microsoft, then this

The risk of course is that one of its "core" businesses like the virtual reality sector either does not evolve as anticipated or other software companies gain market share as it develops. Technology is a very competitive field so that possibility cannot be fully discounted. The most pressing risk is that the share has been subject to quite acute



volatility over the last decade. By investing now we are betting that this will moderate due to less lumpy sales resulting from the subscription model. If the subscription doesn't work then the consistency we are hoping for may not evolve.

That said, I believe synthetic biology is going to be huge. It's a theme we'll be covering in detail through 2017 and beyond – so look out for more recommendations. This could be the first of many.



Name:	Autodesk Inc. (ADSK)
Ticker:	ADSK:US
Current Price (01/11/2016):	\$72.28
Market Cap:	\$15,909.7M
52 week high/low:	\$73.40/\$41.60
Buy between range:	\$65 and \$75

Data as of 01.11.16

Performance:

**2011 -20.60% | 2012 +416.55% | 2013 +42.35% | 2014 +19.36%
| 2015 +1.45% | 2016 (HY) -10.82% |**

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