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Age of the Bio-Engineer

Profiting from "the discovery of the century"

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One of the wisest things I've heard Bill Gates say is, "*We always overestimate the change that will occur in the next two years and underestimate the change that will occur in the next ten. Don't let yourself be lulled into inaction.*"

I'm reminded of that when I think about Dolly the sheep. It's been 20 years since the world was astounded when the Roslin Institute in Scotland announced they had successfully cloned a sheep. Dolly went on to become the world's most famous clone and opened up whole new avenues of discovery.

In the last two decades returning previously extinct species to the wild has become a real possibility. Right now there are plans to reintroduce the aurochs to Northern Europe where it is hoped the giant bad tempered cow will play a crucial role in ensuring the sustainability of the natural landscape.

Bringing back extinct species is a laudable goal but its small beer compared to the inspiration Dolly provided to the world's scientists. It's been 20 years since Dolly strutted onto the international stage and in that time the genome has been sequenced, the cost of genetic sequencing has collapsed from $100 million to less than a $1000 and as we're about to see the UK is well represented by companies aiming to drop it even further.

What many people don't know is that Dolly was sheep number 247. The team failed with 246 other candidates and, despite improvements to the method since, the reason we do not have cloned humans is because the process is just not reliable enough. Cloning might have been imperfect but it proved to be the inspiration of a plethora of developing technologies.

Which brings me to today's issue. There have been three key exponential developments since Dolly. Loosely speaking these have been:

1. The *falling cost* of genetic sequencing

As the cost of sequencing has fallen the viability of whole new fields of study has improved. For instance, sequencing our individual microbiome's, the communities of bacteria that call our gut's home and have an inordinate effect on our health is one of the fastest growing fields of study in the world.

2. Our growing ability to *write new* genetic code from scratch

Synthetic biology is even more exciting. It entails writing DNA from scratch. Teams in the USA have completed custom versions of E-coli, yeast and the Human Genome 2.0 project aiming at writing the code for a full human, 3 billion base pairs, is now underway.

One of the fastest growing sectors in cancer treatment is immune-oncology. It is basically training the immune system to identify the tumour as alien so that it can be attacked by the body and killed off. This required routine sequencing of the tumour's unique DNA so a customised solution can be created.

3. The discovery that we can both sequence and *edit* the genome

CRISPR (Clustered regularly interspaced short palindromic repeats) is perhaps most important technology of all. Bloomberg called it "the discovery of the century" – and that could be an understatement. (Bloomberg, of course, won't tell you what to buy to profit from it.)

It was only discovered in 2013 that the Streptococcus pyogenes relies on CAS9 protein to cut into DNA. By exploiting that protein geneticists can now accurately slice open DNA, insert the genetic material they wish and sew it back together. (It's not quite that colloquial but the process is close enough for the purposes of this letter.) It's cheap, fast, effective and went global practically overnight. It's revolutionising the genetics sector even as you read this letter.

Three major trends: one HUGE new industry

We'll discuss all three today. Taken together these developments have given rise to what we call "bio-engineering": the ability to understand and manipulate the living world in the same way we reform the world around us to suit our needs. It could well be the most important trend of the century. And I'd like to introduce you to two fantastic ways of playing it.

This month's issue is different for several reasons. The double recommendation – a mark of how important we consider this trend to be – is but one. You'll also see an analysis of the top ten UK based firms in the sector. These aren't specific recommendations. But they give you a UK perspective on an important tech trend. (One of this month's recommendations is UK listed, too.)

This UK analysis is something I'm going to be doing more frequently. The tech industry is truly global and I don't think we should let "home bias" restrict us from picking the very best companies in the world. We are investing on the *frontier* of new technology, after all. But I know that some brokerages make it difficult to buy foreign shares. So we'll be making a more stringent effort to analyse UK companies in the sectors we're interested in – *as well as* our regular recommendations.

You'll also find three exclusive interviews with experts intimately connected to our recommendations: George Church, Nessan Bermingham and Mirza Cifric. Again, this is all a part of our mission to bring you the very best research, analysis and opportunities from the world of technology. It's been a year now since we started this mission – and we're constantly looking for ways to improve. If you've been with us since the start: THANK YOU!

> It's revolutionishing the genetics sector even as you read this

"The discovery of

the century"

CRISPR isn't the first technique developed for gene editing. But it is the most important to date.

That's not just because of what it does, though being able to rewrite the rules of life themselves is significant enough. It's because CRISPR enables us to do this incredibly quickly and cheaply.

It's rightly being heralded as an enormous breakthrough. As MIT professor David Baltimore put it, "These are monumental moments in the history of research. They don't happen every day." Nobel scientist Craig Mello described it as "a game changer".

The early evidence suggests that isn't hyperbole.

CRISPR (and other associated gene editing techniques) is already being trialled to do everything from "editing" HIV from patients systems, teach the human body to spot and destroy cancer, eliminate malaria via "gene drives" in mosquitos to growing genetically enhanced plants that fight pollution (University of Washington researchers developed Poplar trees that absorbed polluted water through their roots).

The potential uses are so numerous that we could dedicate this entire issue to celebrating and discussing them. But our mission is financial: understanding is just the first step to profiting. (For more information on how CRISPR works, see our interview with the man who helped develop it, professor George Church, later in this issue.)

One indication of how important CRISPR is comes from how many people are willing to fight over it. There's been a fairly nasty and long running patent dispute over who should get credit for it. That dispute is close to a final resolution. I'll come back to that in a second, as it forms part of the rationale behind our first recommendation.

But there's also competition on the national level. As we told you in our forecast issue last December, there's evidence that "Space Race 2.0" could be starting between America and China. This time the goal isn't the moon. It's potentially more significant: they're racing to develop the world's most important new technology.

History shows us that some of the most important inventions come when two global superpowers go head to head in pushing the limits of technology. Technology that could have taken decades to develop is pushed on at a much faster rate.

CRISPR is at the heart of Space Race 2.0

It's easy to understand why. There's nothing like the fear of coming second to accelerate progress and innovation. For us as investors, that can be a real benefit: accelerated innovation can lead to accelerated wealth creation.

Think the US and Russia facing off in the Space Race. It's worth remembering that when JFK decided to send a man to the moon... the technology to do so just didn't exist. It wasn't even close. That was in 1961. Eight years later Neil Armstrong walked on the moon. Those eight years saw a giant leap in the world's technical capabilities. And they led to all manner of "spin out" inventions: satellites, solar panels, lithium batteries, GPS and laptops all came about as a result of the Space Race.

Given the potential, you'd expect competition. But last November we got a glimpse of how that competition extends to the highest level: not just different companies vying for supremacy, but entire nations.

A Chinese research team at Sichuan University became the first group to inject a person with cells edited using CRISPR. The goal is to treat an aggressive form of lung cancer. It was a major development, and one that is particularly relevant given its location. CRISPR was developed and patented in the US. For China to reach such a key milestone first may well have put the US on the back foot.

As Carl June, a specialist at University of Pennsylvania, put

it: "I think this is going to trigger 'Sputnik 2.0', a biomedical duel on progress between China and the United States, which is important since competition usually improves the end product."

I expect American research to accelerate in response. In fact both Chinese and American research projects using CRISPR on human patients are due to begin before the end of March 2017.

Which all creates a fantastic backdrop to our first recommendation...

Buy Editas

Here's a piece of free advice for any budding scientists out there:

Next time you have a great idea, one that you know is patentable, pay the extra couple of hundred dollars and get the expedited decision making.

they got approved first.

That's all in the past now. We're close to a final resolution. I'm reminded of the saying "It's all done bar the shouting". CRISPR is a revolutionary technology and there has been an acrimonious court battle dragging on for the last couple of years over who owns the intellectual property. It's not just money at stake, we're talking Nobel Prize quality innovation, bragging rights and then of course the money, a lot of it.

At MIT last October I was chatting with a doctoral student, during a tour of the genetics labs, about how she was using CRISPR in her research. Her young face lit up at the question because she said it was shaving about a year off the time she had allocated for experimentation. She was ploughing that time

This technology is a dream for Hollywood screenwriters

Three companies have IPOed claiming to own the intellectual property behind CRISPR. These are Editas, Intellia Therapeutics and CRISPR Therapeutics. The intrigue which surrounds ownership of this technology is a dream for Hollywood scriptwriters. It all began when a team at UC Berkeley filed their patents first. A team at MIT and the Broad Institute filed later, but paid for expedited decision so

into expanding the remit of her research. That's inspiring for a student who is looking to start her career in genetic engineering but for companies spending billions on developing new drugs it's ground breaking.

CRISPR changes how genetic editing is done and because the cost is so much lower the scope of what is possible is much greater.

Think of it this way. When costs are high you have to make careful decisions about what to do but when costs are low you can do whatever you want to see what kind of results you get. That's what CRISPR means for pharmaceutical companies and research organisations.

Let's talk about our recommendation. It's one of the firms at the very beating heart of the industry developing around CRISPR. The firm is Editas.

Buying Editas you are getting an option on the future development of genetic research at every company that licences its patents. New wonder drugs don't come out very often and it's hard to predict which company is going to come up with the next big thing but Editas will get a cut of the profits from just about every drug

Imagine you wanted to predict which actor is going to be the next Hollywood star. You'd have a hard time predicting it. But if you were offered the chance to take a percentage of the earnings of every actor and would still benefit when they became stars... you'd take it, wouldn't you? That's the kind of opportunity CRISPR represents for the genetic editing sector. It's just too good to pass up in my opinion and Editas has been confirmed as the company with the majority of the intellectual property rights.

On the 24th February the US Patent Office gave a partial ruling in favour of Editas. The most important part of the decision is that it gave more favour to Editas than the other two companies.

That's why it's the one to buy. As we move closer to a final settlement of the dispute the odds are strongly in favour of Editas being the company that will come out on top.

As Wired magazine put it, *"On Wednesday, the US Patent Trial and Appeal Board kind of, sort of, almost began to answer [the question of who benefits from patent right to CRISPR]. Berkeley will get the patent for using the system called Crispr-Cas9 in any living cell, from bacteria to blue whales. Broad/MIT gets the patent in eukaryotic cells, which is to say, plants and animals."*

The big reason to own Editas is this: If a company it grants a licence to use CRISPR comes up with a new wonder drug, and that is a strong likelihood, then it will get a percentage of the profits. That can be multiplied over and over for as long as the patent runs.

That's the optionality covered but Editas is also running research projects in its own right. The most notable application it is working on is a cure Leber Congenital Amaurosis and Usher syndrome type 2A. Both are relatively rare genetic diseases causing blindness. They are relatively well understood and therefore represent perfect candidates for the first clinical trials of genetic editing therapies.

The important word in all of this is cure. We are not talking about treatments that require money to be spent on long course over years. Genetic editing is about cures. One shot and done. That's the primary reason genetic editing medicine is so important and why the conventional pharmaceutical business model is likely to go the way of the dinosaur.

Conquering death by editing genes

Cancer is the big objective for just about every company because it is so prevalent and expensive to treat and yet survival rates are highly variable. Editas is working in conjunction with Juno Therapeutics to edit T cells so they can be educated to attack cancer. This is revolutionary because cancer cells are masters of camouflaging themselves from the attention of the body's immune system. Getting our own bodies to fight cancer would be a massive victory. Again this is about cure not treatment.

If you think cancer is a big market, how about Rheumatoid arthritis? I was chatting with rheumatologist recently who defined his field as "whenever they use the word rheumatoid it means they don't know what causes it". It's an autoimmune disease which will be high on the hit list if companies can solve the immuno-oncology riddle using CRISPR.

Could CRISPR help conquer death?

Just so the potential is clear the US National Academy of Sciences released a 261 page document last week on what is and is not going to be permitted with CRISPR. For context here is the exact wording:

"The committee recommends that genome editing for purposes other than treatment or prevention of disease and disability should not proceed at this time, and that it is essential for these public discussions to precede any decisions about whether or how to pursue clinical trials of such applications."

That means the human genome can permissibly be manipulated in the USA to any purpose which is aimed at curing disease and avoiding illness.

If you listen to the way the Salk Institute talks about it death is the most challenging of all diseases. Even if we abandon the desire to live longer there is a huge market for a cure for cognitive decline associated with old age. These are obviously long range aspirations but it is important to realise what the scale of genetic engineering can potentially achieve to understand what the potential for the share it.

The threat to this conclusion lies in just how large the opportunity is. The other two companies,

Name:	**Editas Medicine Inc**
Ticker:	**EDIT:US**
Current Price (06/03/2017):	**$21.02 USD**
Market Cap:	**$771 M (USD)**
52 week high/low:	**$43.99/ $12.43 USD**
Buy up to:	**$30**
1 year forecast:	**$35**
5 year forecast:	**$300**

Data as of 07.03.17

Please note, full performance data is unavailable as the company was listed on 2 February 2016

CRISPR Therapeutics and Intellia Therapeutics are not going to lie quietly while Editas takes all of the rewards. They have banking from investors with deep pockets so the potential for lengthy litigation has to be the base case. At remote but relevant threat is also that a new kind of editing technology will be invented which makes CRISPR obsolete. That's unlikely in the short-term but possibly inevitable over the long-term.

is currently trading on a price to book ratio of 5.15 while the price to sales ratio is 59.8. Those figures highlight how much of optionality is being priced into the share. The promise is very much in the future and Editas' grip on intellectual property that will redefine genetic research. That is why we are putting it in the moonshot category.

It's a buy up to $30, with a five year target of $300.

Editas could grow 900% in the next 5 years

It's important to realise when engaging with companies like Editas that they are in their development stage so it is too early to expect earnings to be positive. The company is still loss making but adjusted EPS are growing at 84% a year but net income is below that of its peers suggesting the company has work to do in order to ensure a sustainable profit. It

The UK firms leading the bio-engineering charge

The exponential pace of technological innovation bears out Bill Gates maxim we really do tend to underestimate what is possible in a decade. It has been two decades since we were introduced to Dolly I thought you might be interested in seeing a Top-10 list of the UK's most exciting genetics companies right now.

Let's run through what's happening in the wider sector, then I'll introduce you to our second pick: my top UK listed opportunity in the genetics/bio-engineering sector.

1. Oxford Nanopore Technologies is still privately held because they have been so successful in securing private funding for the development of the world's only nanopore DNA sequencing device. An IPO may come at some stage but this is a company capable of completely upending the DNA sequencing sector.

Its process is cheap, fast and mobile with the MinION being about the same size as a smartphone which connects to a regular laptop. It is world beating in mapping DNA to libraries of samples where extremely high accuracy is not required. Development work is going into increasing its accuracy for more specific searches of genomes for specific abnormalities.

It is one of the most promising companies the UK has produced in a long time and will play a vital role in delivering a future of personalised medicine we all look forward to at an affordable cost.

2. DNA-Electronics (DNA-e) – has two business lines. LiDia is the company's line of desktop genetic sequencers. These are both quick and accurate. They are larger than what is available from Oxford Nanopore Technologies and the technology is different but they offer accuracy rather

than speed which is the stand out feature.

The other market they are active in is Sepsis which kills more people than bowel and breast cancer combined. Early detection is essential but current blood tests take between 4 and 6 days to identify whether an infection is bacterial or fungal. LiDia gets the answer on day 1 which can have a dramatic effect on patient outcomes.

Headquartered in London with offices in Washington DC and a manufacturing facility in San Diego we'll be keeping an eye out for DNA-Electronics to seek an IPO.

3. 4D Therapeutics (DDDD) is listed on the AIM Index. It's about as close to a pure play on treatments that take advantage of the influence the microbiome has on our health as you are likely to find anywhere.

Here is an educative section from the company's website:

The gut microbiome is a collection of around 2kg of bacteria and there are more microbial cells in the gut than in the entire human body. The volume of genetic information contained with these bacteria dwarfs that of their host – the gut microbiome is thought to consist of 500x more genes than the human genome itself.

All of this genetic information has function. Many of these genes are required for primary metabolic functions, survival and interaction with other organisms in the gut. However, crucially, many of them have functions within the human host itself.

The gut microbiome is commonly understood to influence gastro-intestinal diseases such as infectious diarrhoea.

However, gut bacteria can also impact diseases in remote locations of the body, through modulation of the human immune system, metabolism and even neurological function. This is not simply an ecological effect, it is an evolved functionality that allows bacteria to interact with and modulate the systems of the body.

Understanding and leveraging this functionality is crucial in delivering live biotherapeutics as treatments for diseases such as cancer, rheumatoid arthritis and autism.

With a healthy portfolio of intellectual property DDDD is one to watch as it launched a stage 2 trial of its fledgling Blautix irritable bowel syndrome culture.

4. GlaxoSmithKline (GSK) is a member of the FTSE-100 and it has a problem. It is a problem shared by just about all major pharmaceutical companies but GSK is out there addressing it. The company has had more medicines approved for human consumption than any other since 2008, but for every success there are an unacceptably high number of expensive failures. Less than 1 in five drugs that reach clinical trial stage make it to market.

GSK invested $95 million in Altius Institute for Biomedical Sciences in 2015 to boost its efforts at using genetics to improve success rates.

5 Astra Zeneca (AZN) is also a member of the FTSE and has teamed up with Craig Venter's Human Longevity Inc. to sequence 2 million genomes.

You might have heard of Venter as the guy who beat the publicly funded human genome project to punch and did in a couple of years what it had failed to do in more than a decade. Partnering with Human Longevity Inc. is a big move for Astra Zeneca because it creates a research partnership with the sharpest most experienced minds in the genetics business who are going full steam ahead on synthetic biology.

Together they believe 2 million cases is a large enough sample space to generate the data required to allow major discoveries in the medical field well beyond what we know today.

All major pharmaceutical companies have this problem

This isn't the first time such efforts have been made but the difference now is that the cost of sequencing is below $1000 and is decreasing all the time. The cost of doing this kind of research is collapsing so the scope of the research is exploding.

Buy this AIM listed firm

6. Genus PLC (GNS) is a member of FTSE 250 and is the world leader in animal artificial insemination. It houses the world's largest stud bank of what it terms elite genetics.

The business of the company is that as the global population expands and more importantly as calorie consumption trends higher for large numbers of new consumers demand for animal protein is also likely to increase. By facilitating the modernisation of breeding techniques the company has the capacity to revolutionise yields in beef, dairy, pork and most particularly in emerging markets where thoroughbred herds are largely non-existent. Genus is literally a genetic warehouse for cattle and pigs.

7. Abcam (ABC) is AIM listed and grew out of the frustrations some Cambridge postdoctoral students had in finding the antibodies they required to conduct their research. The company now offers an online catalogue for scientists to source best in class antibodies with reliable datasheets that help to promote and accelerate the pace of innovation everywhere.

In essence the company is empowering the global genetics sector with access to quality base ingredients for the drug discovery, diagnostics and basic research fields.

8. Benchmark Holdings PLC (BMK) is a member of the AIM 100 Index. The company is to salmon what Genus is to cattle but it has gone much further. If you like sushi you might have heard of the problems arising from tapeworms in the Pacific variety while the over use of antibiotics in many fish farms in Europe has also caused some concern among consumers here. Benchmark Holdings is losing the loop for food sustainability in aquaculture. It has created vaccines that can be fed to salmon which remove the need for antibiotics.

Sea lice are a major problem for salmon farmers not least because they decrease yield. BMK has a solution to that problem also. It has been selectively breeding salmon for sea lice resistance since 2007 with great success. Here is what they have to say on recent developments.

"We are also on the doorstep of validating some new genetic markers that will further help fuel the selection of the best performing salmon for sea lice robustness."

The company has its roots in salmon but it is also highly active in the tilapia and shrimp markets and it is rapidly investing in the sea bass, sea bream, cobia, seriola and grouper. Considering the fact that 2016 marked the first time aquaculture accounted for more than 50% of all fish consumed world wide this is a growth driven market.

9. Synthace is still privately held but it was the only UK company among the 30 highlighted at the World Economic Forum in 2016 as the leaders in global innovation. Synthace has produced a coding language (Antha) which facilitates the writing of genetic code central to synthetic biology.

Technological innovation is about new discoveries but science is about collaboration. The pace of exponential growth is being fuelled by advances in one sector helping to drive discoveries in another. 3-D printing was all the rage a few years ago and its most useful application may yet reside in the synthetic biology field. That's because 3-D printers can be retooled to print genetic material one base pair at a time. That's why Antha is so important; it's the best available language for biological programming today.

10. Congenica is also still a private company and was spun out from the Welcome Trust

Sanger Institute. It's a data company rising to the challenge of analysing the reams of data that arise from every individual and each of our specific microbiomes. With its Sapientia portal it is one of the few companies with the product aimed squarely at providing clinicians with the tools they require to make actionable decisions. As such it is at the leading edge of providing personalised medicine not at some point in future but today.

You might be wondering why I created a list where half of the entries are not listed companies. It's an important question and one I want to meet head on.

First off we are talking about innovation and the private companies of today will be the public companies of tomorrow. If we really wish to engage with market and the prolific potential for outsized gains we need to be aware of which companies might be worth investing in before the hype surrounding an IPO threatens to bend our rationale decision making.

There is another factor worth considering. Interest rates have been very low for a long time and liquidity has been abundant. Start-up companies have had comparative ease in sourcing funding from private equity firms and large private donors. They have not felt the need to secure stock market listings. That is a situation likely to change as interest rates rise because private equity investors will be forced to be more discerning and will need to demand more in return for an investment. That should result in more companies coming to market.

Buy this AIM listed firm now

I hope you've enjoyed the list but let's go one step further, which one is worth buying now?

I feel like a kid in a sweet shop trying to decide what to buy, they all look so appetising but that's not the point. Let's check the nutritional quality of each. When we put on our rational hats on, the clear path to sustained growth and profit potential is **Abcam.**

It takes us full loop back to Dolly the sheep. One of Abcam's primary business lines are monoclonal antibodies. In other words it is a now an almost £1.8 billion company at least in part because of the ground breaking cloning work achieved in the UK more than two decades ago.

The company has a history of double digit growth and aims to double the size of the business within the next six years. Right now the products they produce in house account for 40% of income. That's up from 3% at the IPO in 2005. The share is trading at a growth multiple but with solid earnings at 70% gross margins fuelling a decade-long history of increasing its dividend it is a share with a solid fundamentals.

The company has a truly global business with revenues originating in North America (44.7%), China (11%), Japan (7.2%), UK (6.5%), Germany (5.4%) and other countries (25.2%)

Abcam represents a clever play on the exponential explosion in the age of scientific inquiry that CRISPR is making possible.

If you want to do research what you need are basic ingredients regardless of what you are doing or where you are. The true strength Abcam has is in the reliability of its products and the database of information it holds relating to the antibodies it sells. Simply what they are selling is commitment to quality so that researchers globally can have faith that the results they achieve are based on reliable inputs. In short the service the company provides is invaluable to the research community.

That's why you need to buy it today. The research sector is on an exponential growth trajectory because of how easy genetic editing now is. Billions are flowing into the sector and importantly the acrimonious intellectual property dispute between Editas, Intellia Therapeutics and CRISPR Therapeutics is approaching a conclusion.

The clear path to sustained growth and profit potential is Abcam

Settling the ownership rights to the intellectual property will unshackle growth potential and this is sector which is about to take off and Abcam is ideally placed to benefit from it.

Just one example of the type of service Abcam provides to researcher is in the relationship it has created with another major UK genetics firm. In 2016 the company signed a licence agreement with Horizon Discovery Group for knockout lines which raised antibody validation standards and improved quality for researchers.

In plain English what that means is when a company like Horizon Discovery Group wants to test a plant or animal's cells for the reactions to different agents it will buy both the agent and reagent from Abcam. It offers products for research in cancer, cardiovascular disease, cell biology, epigenetics and nuclear signalling, development biology, immunology, metabolism, microbiology, neuroscience, signal transduction and stem cells. That's pretty much a full house when it comes to the most exciting areas of research out there.

In addition to its supply of off the shelf products the company also offers a customisation service where clients can supply the company with specific designs for MiRNA panels and monoclonal antibodies.

The company is in the process of transitioning from a small high growth niche player to being a significant player in the markets it is engaged in and this has contributed to headline growth over the last couple of years. That is a testament to the quality of management since very often when a company tries to change it business model to solidify its position as it matures the share price stalls. That has not occurred with Abcam and the strength of the dividend policy is a further testament to regard for shareholder interests.

The biggest threat I can see to Abcam is from a large competitor such as Thermo Fisher Scientific which is also active in the research ingredients business as well as a number of other business lines. That threat could either be reflected by a takeover attempt or an effort to price Abcam out of its dominant markets. Right now the market is expanding so rapidly that there is room for everyone but success breeds competition and Abcam is certainly successful.

From an investor's perspective the weakness of the Pound represents a tailwind since the company derives so much income from outside the UK but it also makes the company a more attractive takeover candidate as we saw with ARM Holdings earlier this year.

I rate Abcam a buy up to 950p with a 12-month target of 1200p and five year target of 2000p if CRISPR research takes off as I expect it to.

Name:	**Abcam plc**
Ticker:	**ABC: LN**
Current Price (06/03/2017):	**913.00p**
Market Cap:	**£1870.2 M**
52 week high/low:	**948.00p/ 572.00p**
Buy up to:	**950p**
1 year forecast:	**1200p**
5 year forecast:	**2000p**

Data as of 07.03.17

5 year Performance:

2012 +5.55% | 2013 +27.45% |2014 -5.14% | 2015 +42.78% | 2016 +15.34%

Meet the man who helped develop CRISPR

Professor George Church

Professor of Genetics, Harvard Medical School

Co-developer of CRISPR-Cas9 Techology

Interview conducted March 2016

Q: You are one of the chief developers of the CRISPR-Cas9 gene editing technology. Can you describe the technology and say how it was developed?

A: In nature, it works to kill bacterial invading viruses by remembering previous invasions.

It does that by keeping a little piece of the DNA from the [invading] virus, and then that makes it super-easy for it to reprogram a cutting machine, the CRISPR nuclease. That's what it does in nature.

Slowly, people adapted it. As a technology, it became editing: changing from killing viruses to editing DNA very precisely -- not just making a mess, as you might with killing, with cutting, but replacing DNA. That was announced in January 2013 by two groups, mine and one of my ex-post-docs, Feng Zhang, who was by that time an independent investigator at the Broad Institute.

Soon thereafter, it became evident that, unlike some technologies which are hard, this one was easy. There is no way you could have predicted that. It's easy to adapt to other organisms once you solve how to adapt it to humans, which is what we did first.

Q: Can you explain the implications and potential uses of this technology, now and in the future?

A: Any method of gene editing has some similarity to previous genetic engineering tools in what it can be applied to. Those applications include agriculture – plants and animals and to some extent microorganisms like fungi. It can be used for curing genetic diseases. It can be used for fighting infections, just like its original use for cutting viruses. It already is in use for fighting leukaemia and HIV-Aids. I'm being broad here, talking about genome editing – not just CRISPR. It can be used for xenotransplantations – moving organs from pigs to humans – and making those pigs virus-resistant, or making a variety of things virus-resistant.

Finally, it can be used for gene drives, where you can engineer wild populations at low cost and high precision to fight diseases like malaria, dengue, lime disease and so on.

Q: You talk about the application of gene editing technology to cancer and HIV. Any other areas in human therapy where there could be breakthroughs?

A: Gene therapy is a big category that includes classically and typically inserting new genes. Then you can use more precise gene editing to both remove *and* insert, and that's where CRISPR comes in.

There are 2,000 gene therapies in clinical trials, and many of those are already curing people. It doesn't mean they've been approved for general use. They're in the process of doing the gene therapy trials to get a fair number of people cured of, for example, blindness. There are some genetic causes of blindness that are curable by gene therapies. In most cases, you have to do it very early in life, like in young children -- or else they'll be able to cure them to the point where they can see light but they can't interpret the light or stasis because their brains have developed too far.

There are other infectious agents like hepatitis viruses, blood diseases that cause hemolytic anemia -- the list is long. There are thousands of genes that are so well understood that some of them can be addressed by genetic counselling. But once you have a child that has the disease, then you need to have some kind of cure or prevention for the development of downstream technologies.

Q: There are also potential risks and drawbacks. Can you talk about the risks related to CRISPR – for example, the risk of editing errors?

A: Almost every therapy has off-target effects, where it will affect something in addition to its target. Small molecule drugs do, protein drugs do, and CRISPR does.

The difference is that there are computer programs that help you design wherever CRISPR is targeting. If you use those well, then you can find something where there really is no off target. Furthermore, there are ways in which you can change the CRISPR enzyme that makes it much more specific. When you put all these together, you end up with, essentially, off-targets that are undetectable.

Now, that doesn't mean they're undetectable in any reasonable laboratory experiment. It doesn't mean they'll be undetectable if you started treating a billion people with it, or a billion animals or plants. But our bodies are constantly mutating due to radiation and other chemicals, chemotherapies and so forth. So CRISPR is way, way below the

spontaneous rate of mutation. Also, you can direct it. So it's a fairly hypothetical risk.

I think the bigger risk than off-target mutation is the systems risk: that it does what it's supposed to do, but what it's supposed to do has ramifications. It's the reason all new drugs are tested by FDA-approved chemical trials. You see whether all your theories and all your simple tests on animals play out in humans accurately in terms of safety and efficacy.

Q: There's also a risk that parents in the future are going to want designer babies, and pick and choose their future children's traits. How do you rate that risk?

A: Again, that's a risk of all new technologies. If you want your child to have computers and cars and education and so on, all of these could backfire, and they provide the parent with an awful lot of decision-making dilemmas and power. This would be no exception. It's not clear to me that it's more powerful than these other things, because the genetics takes a long time to arrive. It takes 20 years to arrive -- while giving the child a very powerful toy could cause damage right away.

With all these things, you have feedback where you see the impact on society. Usually the things that are hardest to reverse are things that are attractive to society, or some section of society. If we want to prepare ourselves for them, we need to have discussions like the one that we're having right now. It shouldn't be limited to a particular technology, but all ways in which parents can influence their children.

Q: You don't sound terribly concerned about this designer baby prospect.

A: Let's be clear about that: I am terribly concerned about all new technologies. I've seen ways that you can get feedback and do safety testing on all new technologies, and I think that has to be a top priority.

But there are many other technologies that we should be worrying about. And we have standards. We have the EPA [Environmental Protection Agency] and the FDA and their equivalents worldwide that require testing of everything. So I'm very far from unconcerned. And I want everybody else to be concerned -- but to apply their concern to everything that can go wrong.

Q: Gene editing is seen, overall, as a benefit for humanity. But a line is being drawn at germline editing. Your colleague Eric Lander said at a recent conference that germline editing would only be used in rare cases, and that caution should be exercised to making permanent changes to the gene pool. Do you agree?

A: I think that what one person thinks is rare may turn out to be quite common. Calling it rare makes us less cautious, makes us more complacent. As I said, I'm very concerned about this, and if you say that it's rare, then you don't recognize the market forces that might be in place.

For example, right now there are many, many genetic diseases that cause very severe effects in life, like Tay-Sachs. There are individuals affected by it, and in larger numbers, their parents are carriers for it. This is not rare: there are many of them. The way it's currently handled is, two parents know that they're unaffected carriers. For each pregnancy, they will do a prenatal test, and about a quarter of those tests will result in them having to decide on abortion or not – termination. That's a growing industry, if you will. At least half of the people are not comfortable with that outcome, whether it's in their own home or other people's home, and they feel that all embryos are precious.

An alternative would be to engineer the sperm of the father so that no embryo would ever have to be aborted. In fact, you could even reduce the number of spontaneous abortions, which are more natural in some sense. That particular task might be more desirable to a larger number of people, and addresses a medical need as well as a societal need to reduce the number of embryo deaths.

If you edit the male sperm, then half of the children will be born carriers – so the gene will still be there – and half of them will be non-carriers. And both the carriers and non-carriers will be normal. But the genes will still be there.

Q: When Eric Lander says we should exercise caution before

making permanent changes to the gene pool, what are your views?

A: My view is that we should always exercise caution, period, on everything. We don't want to have false complacency into thinking that if we just weighed up the gene pool, then we're all set, because there are many ways in which we can affect society that do not affect the gene pool. We can eliminate a particular disease or trait, or engineer a trait, without changing the total frequency of the DNA variant. So, for example, it makes no difference if you have two copies or one. You can have a huge impact on what the population looks like without changing the number of people that have one copy of the genetic variant.

It's not cautious enough, is what I'm saying. We need to be cautious. He's saying we just need to worry about things that affect the gene pool. I say we need to worry about things that happen much sooner than that.

Affecting the gene pool can take centuries, but we could, in just years, affect the trait pool -- that is to say, what you're actually expressing as traits. There are all kinds of educational and corporate pressures to have all the children in a classroom behave themselves. Without affecting their gene pool, you could have huge impact on the behaviour of children in schools, much as in a variety of other ways. So I would say that caution is not nearly enough.

Q: So we have to be very careful every step of the way.

A: Right. And it's not just germline, it's somatic. In fact, I would be more concerned about somatic -- meaning in the way we normally practice medicine. Because let's say you developed a gene therapy to reduce cognitive decline in Alzheimer's. This sounds very reasonable -- we have a growing ageing population, and this will be very attractive. But there are various ways of doing that.

Some people like Eric will dismiss any drug involving intelligence, because we don't understand it. The fact is, we do understand certain ways of proving cognitive tasks in mice, and if those are tested in humans, specifically under the umbrella of cognitive decline in later years, we can make progress. And if we can make progress, it can be tried out on people that don't yet have any symptoms.

And then it can be tried on people who make money with their intellect, and just want to have higher intellect.

This is all done without germline, but it can spread so much faster than germline. Germline would take 20 years per generation to spread. This could spread in one year. That's the difference between cultural inheritance and DNA inheritance. Cultural inheritance is much scarier and needs caution.

Q: In April, Chinese scientists announced that they edited genes in non-viable embryos. In November, British researchers said they'd successfully treated a one-year-old girl who had leukaemia using gene-edited T cells. Are these in your view positive developments?

A: They're two different things. [As regards the] editing of the T-cells, you can treat AIDS patients and you can treat leukaemia and various cancers using gene editing. You can basically make T cells coming in seem less foreign, less rejected, so they can do their job with killing the cancer. I think that's probably quite good. It's starting to save lives. But it has to go through FDA approval like everything else. This is me saying: let's be cautious *as usual.* It doesn't require a new law. Just make sure that your leukaemia drugs are tested. Don't rush anything.

The Chinese did something, and a lot of people are confused as to whether it's legal. It's perfectly legal in most countries of the world, including the United States and England. They didn't do anything out of the ordinary. They used triploid embryos, which are essentially a waste product of the reproductive medicine, but it was also legal to have done diploid embryos. It's just not legal for any new medical technology to be applied in the broad population without government approval.

Sometimes China is characterised as being a lax, loose regulation [environment]. They are not. There is not loose regulation in China. I don't understand how people can be confused about that. They shut down all of genetics, country-wide, in an instant, which would be very

hard to do in other countries. This is for genetic analysis, not just therapy. Furthermore, they have very tight regulations on the Internet. They're not a lax regulation state.

Your question is whether that's a good thing. Again, you need to ask specifically, what are they trying to cure? Plausibly, they're curing or preventing, better yet, many of the things we were talking about. So the scenario I talked about before -- using sperm to prevent serious diseases like Tay-Sachs, which kills babies by four years and is very psychologically detrimental to the whole family -- seems like a good way of reducing abortions and increasing the health of children.

Q: You alluded earlier on to the dispute over which team developed CRISPR-Cas9. You were a significant contributor to that development, yet are not one of the names frequently quoted. Can you talk a little about this?

A: We have patents that were issued for CRISPR in my group. We were arguably one of the first three. I'm glad that we're not part of the dispute. Our patents are unchallenged, which could mean that we added value that was recognisable and unique.

There are the other two groups: Jennifer Doudnas and Feng Zhang's. Jennifer came up with a way to cut DNA, and proved it in a cell-free system, and hypothesized how it might work in human cells. Then our group and Feng Zang showed how you could use it for precise gene editing, meaning homologous recombination and how to do that. So it boils down to, do you want to reward a prophetic and incompletely worked-out protocol, or the actual protocol that does precise gene editing?

By the time we all published in January 2013 – all three groups published in that month – there was only one group that had done precise, homologous recombination in human stem cells, which was ours. And there was only one group that had the guide RNA that turned out to be the one which everyone used, which was ours. Feng Zhang's had done homologous recombination, precise gene editing of human cells, but had not yet done stem cells and had not yet developed the right guide RNA. Jennifer's group only did cutting, not homologous recombination, and again did not have the first guide RNA. So that's what was proven in public at the time.

In most fields, there are lots of inventions that are required for practicing – actually practicing. This will probably be no exception. We've already got some [patents] that are granted and not under contention, and those will be valuable. To make a cellphone, you need thousands of patents. This [CRISPR patent] happens to be one that's getting a lot of scrutiny, but I don't think it's going to be of great financial significance. I could be wrong.

The three companies that started up to do gene therapy are all in Cambridge [Massachusetts], and they're not really interfering with each other. This is a purely academic thing that's going on between universities. There are other companies that are providing tools, and there are companies that are providing transplantation, like eGenesis, and none of these seem to be particularly concerned about this little tempest in a teapot.

Q: So it's really down to each university wanting the prestige?

A: No, I think that's a misunderstanding. This is a formal procedure the patent office did. The universities are responding to the patent office.

It's not universities or people suing each other. It's the patent office saying, 'Hey, I see an interference here where two things came in about the same time. One was a little bit ahead prophetically. The other one was ahead in terms of actually reducing it to practice. We've got to make some kind of decision...' Probably it will end up with each group getting some patents at the end of the day, some claims.

You get into these little disputes of who thought of it first. You can have somebody saying, 'I thought of it but I didn't do it.' Another one says, 'I did it and it took a little extra finesse to get it to work.' So they both get a little credit.

Now it's whoever filed first. And that's the way it has been in the rest of the world for a number of years. The United States just caught up, around the time that this was happening.

Q: You're saying that the financial benefits are going to be minimal to each group?

A: I think the industry will be an amazing industry. There's going to be a lot of wealth created by these little companies in Cambridge. But I don't think they're currently interfering with each other. They're not, as far as we know, working on the same topics.

The real point of patents is that you get a limited monopoly on whatever product you're making. I don't think they're making the same product. Even if they create billions of dollars of wealth, if there are 10 different products per each of the three companies and none of them overlap, then they won't be suing each other, no matter how the patents turn out.

Q: What are some of the other projects you're pursuing at the Church Lab? I believe one is lengthening human life?

A: Right – not lengthening so much as reversing ageing. The problem with getting FDA approval for lengthening life is, say you want your tool bottle to say extend life by 20 years: that's a 20-year study. For ageing reversal, you can demonstrate on animals and then humans in principle in weeks – things like changing muscle strength, reaction time, cognition etc.

There are lots of examples of ageing reversal in animal experiments that are quite convincing. There are probably even more. We're taking the approach of using gene therapy, because it's a much more cost-effective route from an idea to therapy -- since you have an idea, you know the genes involved, and you could make a treatment. And so we have dozens of those currently in pre-clinical animal trials.

Q: You explain that human ageing is one of the primary causes of disease, and given that one of your main concerns is combating disease, reversing ageing is a way to go.

A: Right. I think that in industrialised nations, 90% of people die of a disease that does not afflict 20-year-olds.

In developing nations, you have a slightly different issue, where gene drives might be useful for malaria and other major diseases there. But putting aside the differences in different parts of the world, as the world as a whole becomes more and more industrialised, you have more and more people dying of these diseases of ageing. Before they die, they consume vast amounts of resources from post-retirement, and this could become a huge economic drain in a world population that's becoming on average older.

Q: Any other projects at the Church Lab we should know about?

A: We've historically participated in another revolution, which is in reading DNA. What people sometimes forget is that all of these therapies – genetic and otherwise – are increasingly dependent on our ability to read our genomes.

That revolution was predicted to take somewhere between, optimistically, six decades and six centuries. It ended up being six years. So like CRISPR evolution, which is now three years in, the next gen-sequencing revolution has taken about six years to come down from $3 billion to, as my company just announced, $199 for a complete genome and genetic counselling -- so not just raw data but interpretation.

That will probably continue to come down, and extend to knowing an environment and viruses and life organisms. We don't know whether a particular cough or sneeze is highly pathogenic or completely non-pathogenic. That's the revolution in analysis that could be as big or bigger than some of these therapeutic uses we're talking about.

Q: There was an Economist article about you in 2014 headlined 'Welcome to my Genome' where you had made your genome public and allowed everyone to come and rummage through your DNA. How is that project going, and are you able to persuade many other people to do as you did?

A: Many of the projects we do are meant to provide a roadmap. It's not so important who gets credit or who gets the money, it's to show that it's possible. Over the decade, we've been promoting this idea of sharing data – both sharing it back to the person who donated their time and medical records as a patient, and sharing it with everyone worldwide. If everybody in the world had their

genome in a vault in their home, no one would benefit. The idea of sharing was bizarre 10 years ago, but now it's generally useful.

Whatever the status of the Personal Genome Project itself, which has now expanded worldwide to many countries including Canada England Korea Austria and so forth, what's more important is the impact it's had on almost the entire field of medical research, where sharing is now the norm, where it used to be the exception. That's extremely important, because that's the way we're going to make all these connections between genes, environments and traits that will help provide preventative medicine for everyone. Rather than reactive waiting until you get a metastasis, we'll find increasing number of ways of completely avoiding cancer.

Most people don't die of cancer. We'd like that to be *all* people *never get it*, rather than 'we have something that will extend your life in a very painful way for the next two or three months for hundreds of thousands of dollars.' That is the way that most cancer research and most cancer dollars have gone. We need to be looking at correlations and causations in the population.

Q: You are the founder or co-founder of many companies. Can you talk a little about that?

A: There are about nine that are starting up this year. When you add them to the 12 – depends how well they do – that are in the incubation phase. We have a terrific incubator at Harvard called the Wyss Institute for Biologically Inspired Engineering. It helps them to get started without panicking about financial support. They can test out their ideas and then calmly launch. Some of the recent companies that are fully launched are things like Warp Drive Bio, which makes small molecule chemicals that have evolved in the wild, in the war between bacteria and fungae, but that can be used for various human diseases. Editas just had an IPO: it provides gene editing therapies for a variety of human diseases, infectious and inherited.

Q: Are you a cofounder of Editas as well?

A: Yes. Jennifer Doudna and I were looking into how to co-found a gene editing company. We recruited three more co-founders. And then I also worked with Jennifer on Caribou, which then co-founded Intelia, which is the second of the three companies in Cambridge.

Q: Do you have financial stakes in these companies?

A: Yes – in Intelia, Editas, and Warp Drive Bio, and in fact in all the ones I founded. I'm very careful about listing all my conflicts of interest both on my website and in every talk that I give, or article.

Q: It sounds like gene-related technology is going to potentially be of great benefit to humanity. What I take from my conversation from you is that we should be embracing this technology, proceeding with caution – but that overall it's a good thing.

A: Yes. I don't think we should relax our protocols for testing safety and efficacy, but I agree with everything you said. Proceed with caution, as we always have, or almost always have, and focus on prevention whenever we can, because that's really where we have the biggest impact.

Meet the competition: an interview with Intellia CEO Nessan Bermingham

Interview with Intellia CEO Nessan Bermingham

February 2017

As you've seen today, one of the biggest scientific breakthroughs of the last decade is a technology known by its acronym CRISPR-Cas9. Simply put, it allows a gene to be cut and pasted as if in a computer word-processing program. The implications for human health are boundless: a whole slew of diseases that are deadly today could potentially be cured, and cured quickly, tomorrow.

A key figure in the invention of the technology was Jennifer Doudna, a Harvard-educated biochemist who grew up in Hawaii and was named by Time Magazine in 2015 as one of the

100 most influential people in the world. That was a year after she teamed up with Nessan Bermingham to found Intellia Therapeutics.

Intellia is one of the handful of companies today that's focusing on turning CRISPR-Cas9 into a revenue generator. It's a competitor to our pick this month, Editas. Frontier Tech Investor caught up with Bermingham, its CEO and President, for a wide-ranging conversation on the future with CRISPR.

Q: Nessan Bermingham, can you explain in your own words what your company does exactly?

A: Intellia is a genome editing company. We are developing a technology called CRISPR-Cas9 to allow us to go into a human genome and modify the genome in such a way as to address basic disease. In some instances, that disease may have a genetic foundation -- for example things like TTR, cystic fibrosis, Duchenne muscular dystrophy. There are also examples of non-genetic or non-human-genome-driven diseases: things like cancer, autoimmune inflammatory diseases, and things like infectious diseases such as HBV [the Hepatitis B Virus].

The analogy that people use is Microsoft Office. Effectively, you're going in, you're working on specific regions of DNA, and you change that DNA to drive a specific edit that you're interested in. Either you're style-checking and fixing a misspelled gene, or you're deleting a paragraph or a region, or you're inserting a whole new paragraph or a whole new chapter into that document.

The CRISPR-Cas9 technology allows us to do one of the first steps of that. So CRISPR-Cas9 is effectively a pair of molecular scissors that identifies the bacteria and uses their defense system. Basically, an infectious agent infects the bacteria. This CRISPR system gets switched on, and it goes and chops off the infectious agent before it can do any harm. They're very good molecular scissors.

What you're doing is coopting that pair of molecular scissors and targeting it to different regions of the genome. The way the system actually works is, you have to effectively put a zip code on it that's called a guide. That zip code basically tells it where to go and stop and cut in a very targeted fashion within the human genome.

In every one of our cells, there's a repair mechanism that's already there. If I take a cell from your body and look at that cell, you'll have hundreds, thousands or tens of thousands of breaks in your DNA across your chromosome. Because of that, your cell has a repair system to fix those breaks. We're using the Crispr-Cas9 system to cut, and we're using a system already in your cell to actually repair. We're able to direct or influence how it repairs it to either switch something off, delete some DNA, insert some DNA or repair some segment of DNA.

Q: Can you give me a sense of how important this CRISPR-Cas9 technology is, and what the potential breakthroughs are?

A: There are a couple of key things about it. We do not understand the full breadth of application of this technology. People are really talking about it being a breakthrough approach that has the potential to revolutionize medicine as we think about it today. What does that mean?

When you think about diseases ranging from Gaucher disease or cystic fibrosis to things like Parkinson's or Alzheimer's or schizophrenia or bipolar disorder, there's a very strong genetic component or element in each of those diseases. In some cases, it's 100 percent. In other cases, it may be 40 percent or 50 percent. This goes back to nurture versus nature. So underlying all our diseases is a genetic component, a genetic aspect.

What this technology allows us to do is to start to explore the genome in a more targeted fashion to figure out what is associated with the disease and what could be driving it -- either singularly, or in a combination fashion, through maybe 5, 10 or 15 genes associated with it -- then start exploring those and utilize that information to very quickly move into developing a therapeutic.

This is the first technology that has been developed that enables you to very easily and quickly explore the genome and then coopt that into an actual therapeutic opportunity. In addition, it's the first example that we're aware of that can have the potential to enable us to target multiple regions of the genome at the same time, or in and around the same time. That's very important when you think of moving from single-genome diseases -- such as cystic fibrosis -- into far more complex diseases, such as Alzheimer's or Parkinson's disease.

The other aspect of it is, if you think about the last 10 or 15 years, there's been a lot of discussion about the concept of personalized medicine: developing a medicine that is specifically designed for your genome. And that's been very much at the conceptual level. The reality is that we've never had the tool or tools to enable us to actually do that.

Today, you can have patients that can come in and literally have their genome sequenced. Illumina is sequencing genomes for $100. You can sequence an individual, and you can have an opportunity to design your CRISPR-Cas9 system specific to your genome. And that's important.

Think about a bell curve. You have a large number of patients that have the same mutation or very similar mutations in the same region. That's the peak of that bell curve. But you also have patients on either side of the tails. They may be the only person with that mutation driving that disease. How do we think about personalizing medicine so we can treat that patient, who may be the only or one of a handful of patients that has that mutation that is leading to, for instance, cystic fibrosis? This therapeutic approach gives us the potential to actually be able to address those individuals that no technology today is positioned to do.

Q: What is Intellia concretely making in terms of products? Which diseases are you specifically looking to tackle? And have you teamed up with any pharmaceutical companies to bring drugs to the market?

A: There are two primary places where we've focused on today. The first is ex vivo: taking cells out of the body, modifying those cells and putting them back in. On that side, we have a deal with Novartis for two key applications. One is modifying cells for immuno-oncology: CAR-T. Modifying them to develop new generations of CAR-T products.

The second one with Novartis is modifying hematopoietic stem cells to drive therapeutic effect. Where there may be mutation or a disease associated with HSC, you can effectively repair or address through a modification of that HSC.

Behind that, we have a subsivion called Extellia that continues to build on ex vivo modification of cells in the area of immuno-oncology and also in the area of autoimmune inflammatory disease. So that's our ex vivo approach.

In vivo, we're looking at the liver: taking a delivery system called lipid nanoparticles and encapsulating the drug in these lipid nanoparticles. You know, when you put a fat drop in water and it forms a sphere? It's a bit like that -- but in the middle of that sphere is a drug. Basically, you're injecting that into the body. The type of lipid nanoparticles that we use hold to the liver. They get taken up by hepatocytes in the liver and release the drug into the hepatocyte cells.

Q: These tests are done on humans or animals?

A: We take an animal - in this case a rodent - and inject our drug into their tail vein, so it's a single injection. Our drug hones to the animal's liver, and it goes in. We want to switch that gene off that was toxic to the animal.

This is the first example of a medically appropriate delivery system that showed in vivo editing in an animal. We presented that in August of last year, and continue to deveop our technology beyond that.

When we think about the concept of a patient coming in with a genetic disease and getting a single treatment, or a handful of treatments and cures, this technology has the potential to actually realize that, versus common therapeutic approaches that are a chronic treatment

of that patient for the rest of their life. If you think about the social and economic impact of that type of curative approach, it's tremendous. And when we think about the potential for a personalized aspect of an area of medicine that we've been unable to tap across humanity today…

Q: How much money did you raise in your IPO last year?

A: We raised just over $120 million in the IPO. We did a private placement, because of a deal with Regeneron Pharmaceuticals.

Q: How long is it going to be before you can actually take something onto the market that will generate a revenue stream? What's the timeline?

A: There are a couple of considerations there. The first is, from a regulatory standpoint, the path to the clinic. And also the appropriate safety profile. One needs to be thoughtful, as you think about a new therapeutic modality being delivered to a human for the first time.

The second aspect is the indication itself, and what type of indication you are deploying your technology to address initially. Within Intellia, we are looking at indications where there's a clear genetic association with a target gene, a target DNA -- ensuring that we have a direct association of our target to a disease, that there's a real medical need that pertains to that disease.

When you think about editing a gene, given that there's never been a technology to allow you to explore that before, no one really knows what level of editing you need to repair the disease itself. Do you need to fix 10 percent, 50 percent, or 100 percent? For example, for cystic fibrosis, people talk about an 18% repair of the FTR being therapeutically appropriate. In replacement therapy, people talk about 8%. So it very much depends on the disease you're going after, and the level of editing you need to aspire to to be able to have that therapeutic effect.

Then you get into the usual things about manufacturing scale-up and quality control assurance. What we've told the market is that we expect our first IND (Investigational New Drug) with Novartis to be filed in 2018 for HSCs. In conversation with the regulatory bodies, as we develop a clinical path for that, that will certainly determine the appropriate timeline for commercialisation.

An IND is where you go to the regulatory bodies and say: 'Here is my data package from a safety and efficacy standpoint in animal models. I believe that this is a safe product and has the potential to be effective in progressing us now into treating a human.' The FDA reviews that package. They [may help] direct you as you think about the components of that package. They will turn around and say, 'Yes, we approve your IND, and you can now start to dose a patient and move into human clinical studies.' Or: 'We'd like to do this additional experiment or provide additional information in this area before we will allow you to go into human clinical trials.'

Q: In terms of knowing when you'll actually get some revenue and the timeline for eventual profits, is that too far ahead to predict?

A: We are not providing any visibility on that. It's a new therapeutic modality. Interaction with the regulatory bodies both in Europe and in the U.S. will be an important aspect of determining that timeline and path through the clinic and ultimately to commercialization.

For some indications, it tends to be fast, because it's a small patient population. For cardiovascular, where you may have to treat thousands of patients, it's a much longer timeline. So it depends on the regulatory interactions, but also on the indications you select as your first indications to move into the clinic.

Q: So people who are investing in you, and in CRISPR, are taking a long view, right?

A: Certainly, the investors that participated and bought equity in the company today are all sophisticated investors that continue to support the company. Both of our partners, Regeneron and Novartis, have bought equity in Intellia. When you look at new therapeutic modalities, one has got to be thoughtful about the timeline.

But I also think what excites investors here is truly the potential. When you think about a therapeutic modality like this, the spectrum of opportunity is quite significant.

Q: Your company is pursuing a therapeutic course with CRISPR. But there are other potentialities: of Crispr being used in eugenics, producing designer babies, etc. How can we make sure that doesn't happen?

A: This is a very important question that we as a society have to engage on and are already engaging on. We cannot police the world. We have to be responsible individuals.

I think one of the conversations that's been missed within the broader public domain is nature versus nurture. You can only do so much by targeting the genome. When it comes to designer babies, the attribution they want to change - eye color, hair color, height, IQ, fitness - is ultimately going to be driven very much by the nature aspect of the environment that they're being brought up in, versus the overall genetic component of those individuals.

It's important to note too that technology is not the fix for everything. At the end of the day, we've got to realize that we're back to nature versus nurture. There are some aspects that you can handle with technology: when you think about mutations associated with disease, you know the underlying mutations associated with these diseases.

When you talk about other non-potentially therapeutic aspects or applications of the technology, what are we doing there? Are we talking about changing somebody's IQ? Well, you know what? If you look at the genetic data that's out there, it's better for you to read to your child every night before they go to bed for half an hour or 20 minutes than any modification done to the genome. If you think about obesity, it is better for you to have a healthy diet and to stop going to fast food chains than any genetic modification that can be made to you.

Q: China is coming into the genetics market in a big way. Is that something that might cause you to have concern about your future profitability? Don't countries such as China have a slightly more relaxed regulatory environment and the ability to shoot through easier or faster in getting regulatory approval?

A: Given that our target opportunity right now is in North America and Europe, that's our primary focus. There's an appropriate regulatory system to ensure that we are developing and deploying safe and efficacious medicines. If certain countries decide that they want to short-circuit that, one needs to be very thoughtful about the potential liability associated with it.

You have a gene therapy approved in oncology in China that has not been approved in the U.S. or in Europe. It's not being used here. So when we think about ensuring that we have a safety package that is appropriate for the drug that we're developing, and that we are at some point hopefully commercializing, we need to ensure that we're giving patients what they need. Short-circuiting the system may allow you to get something faster to the marketplace in, for example, China, but the uncertainty is not insignificant.

Understanding the wider market – how genetic engineering could become a part of daily life

Interview with Mirza Cifric, CEO of VeritasGenetics

January 2017

In 1984, a Harvard Ph.D. student by the name of George Church came up with the first method for sequencing a human genome. Later that decade, together with a team of others, he helped set up the Human Genome Project, with the sole purpose of sequencing each and every one of the 3.3 billion base-pairs within a human genome. The project took years and billions of dollars, but its mission was accomplished.v

Today, Church -- a professor of

genetics at Harvard Medical School -- has co-founded a company called VeritasGenetics whose myGenome product (launched earlier this year) does exactly the same thing: It maps your genome, only at a cost of exactly $999. Frontier Tech Investor caught up with the company's CEO, Mirza Cifric, to learn more about myGenome and find out why we should map our genome in the first place.

FTI: Why was Veritas founded?

MC: The company really came from the long-term commitment on the part of George Church and the two other co-founders from the Personal Genome Project to the idea that we have this tremendous opportunity to engage as many people as possible on this planet to have their genetic information, and to use that genetic information to proactively manage their health, quality of life and longevity.

One of the objectives of the Personal Genome Project was, and is, to make such information widely available to researchers, because the team recognized early on that there were severe limitations in the so-called 'walled gardens' of data, where research was done in different pockets, wasn't shared in standardized ways, and so forth. That's why PGP [the Personal Genome Project] was such a tremendously important and pioneering project when it started.

Looking back to see how effective the penetration has been, the reality is that the price point and a number of other things have been a barrier to sequencing hundreds of thousands and even millions of people. So we've created Veritas for the express purpose of making genetics accessible to people. That has several components to it. It's not just about cost, although that is a big barrier. It's also about genetic counselling: how you deliver this information in a way that individuals understand, in a way that's actionable, and various other things.

We felt that the business was the right mechanism to do that: that a venture that has investment and capitals and teams focused on scale and efficiency in delivery is a way to do this -- to make genetics accessible to as many people as possible on the planet. And that's really the express purpose behind the founding of Veritas.

Q: Your myGenome sequencer came out in March and costs $999. How is it doing?

A: To clarify, there are, in this business, people who create and manufacture equipment, and people who use that equipment to sequence, produce and then analyse the data and come out with the answers. We are the latter: so we are in the business of interpreting the genome. We use data that is manufactured by Illumina, which currently is the sole provider of genome sequencing equipment in the marketplace.

What we announced in March and then made available later in the summer was a product that is a $999 whole genome -- sequenced, analysed and reported -- rather than a piece of equipment.

That was, and is, a momentous occasion. Many people have been involved in this industry to bring the cost down - to make it scalable. Nothing in history has gone down in cost so rapidly. Over 10 years, the whole genome sequencing has gone down by a factor of a million. It cost $3 billion to do the first individual genome, and this was a very large-scale, industry/academic partnership effort, and an international one. It took 10 years to do one person. It cost $3 billion, and was funded by institutes such as the National Institutes of Health (NIH) and government and so forth.

Then people like George [Church] went to work to bring that cost down tremendously. If you compare to computers -- and you're quite aware of the impact that computers have made on our lives for the last 10 and 20 years -- computers have not gone down [in cost] by a factor of a million!

Also, you've literally gone from rooms and rooms and rooms of computers to a desktop machine. And that's what happened in sequencing technology over the last 10 years. You now have something that fits on the desktop. So it's the beginning of a very interesting era.

It also brings up various questions: Why does everybody need their genome done? To me,

there's no better analogy than the conversations [we had] in the 1980s: 'Why does everybody need a computer in their house?' That's how early we are in this space and in this process. The products in their initial versions are not as elaborate as they will be in a year or two or three or five. I just want to impress upon you that it's a lot about timing.

The other thing that this business is about that's different from other futuristic technologies is that we're dealing with people's health and with human beings. We have a regulatory environment, we have certain ethical responsibilities, and it's a complex world. But it is one that we are taking a leadership position in.

Q: So how is myGenome doing?

A: It's doing great. We are reporting our first thousand customers right now, and our pipeline of genomes for 2017 is many, many thousands.

Q: Why do people pay for myGenome? What is their intention? Are they trying to find out if they have deadly diseases?

A: That's a very common misconception about genetics and knowing your genome. There are very few, what I'd call, binary diseases. If you think about the last century in infectious diseases, more people died from pneumonia and diarrhoea and basic infectious diseases than did in the First and Second World Wars combined.

We're now faced with modern diseases, and they accumulate over time. It's a combination of genetic and environmental factors, but they play together. So it's really hard for an individual to reconcile what environmental factors will influence them specifically -- because we know that for two siblings from the same family, they'll react differently to different things, let alone two unrelated individuals.

Individuals come to have their genome sequenced at this early time usually because of life events. There are people who are simply proactive and want to understand. There are people who have a family history. There are people who have been misdiagnosed, or not diagnosed, but who have a sneaky suspicion that something is wrong with them and are wondering if it has a genetic underlining.

Here's what's different about how Veritas is doing this. Up until now, all genetic tests effectively involved the following: you provide the sample, they look at your genes, issue the report, give you a written report in a couple of pages, the doctor looks at it, and you go away and never look back at it again.

This is not what your genetics is about. There is a vast amount of information, some of which we know today, and more and more that's coming every day. And this is what Veritas is doing differently. We are creating an engagement platform. We are going to give you the report on your genome today based on the current state-of-the-art scientific understanding: what variants and mutations mean, what diseases and risks and propensity for certain foods or nutrition or fitness or a reaction to drugs [you might have].

The moment we do that, there's another publication out there. There's more information. So we want you to use your genome to keep going back and uncover more and more about yourself as more and more scientific data becomes available. That's what's critically different about what Veritas is doing, and that's what's critically different about how we want people to engage with us.

This is why I focus on the consumer. The doctor is interested in a particular question, at a particular time, in a particular context. But you ought to be more vested in your personal health than anybody else over your entire lifetime.

Q: So you're looking for repeat customers who will come back each time and pay $999, or whatever the price may be, to get these screening tests done over and over?

A: Yes, we are looking for repeat customers, but the price point is going to be very different. Once we sequence your genome and we digitize it, it's done. It's in a database, and it's a digital file, and it's very inexpensive for us to go back and alter that data. The repeat cost for you to re-analyse is going to be very inexpensive. As a matter of fact, in our model we will

continuously give you free information. We will charge you when we need to go look back and have the clinical team look at your data and look for some particular clinical question that you may have.

You can find yourself saying 'I'm about to have kids. Those guys sequenced my genome. Every week I get a little bit more information.'

A gene for grey hair has come out - would you like to know if you have it or not? If you do, you can click on it and get the answer. This is the way that people are going to live with genetics in the future.

Q: Pitching forward 10 or 20 years, you say that genetics and genetic equipment are going to be as important to us inside the home as the computer. How? What specific products or technologies will have that kind of everyday impact on us? What will you be putting out on the market that we should look forward to?

A: The benefits of having your genome sequenced and stored digitally once are obvious: you only need to do it once. And yes, it costs $1,000, but you have it.

The negative [aspect] is that it's basically static information. We know that things are constantly changing in your body: We always say that genes plus environment equals trait. It's the interplay between your specific genes and environmental factors.

What we are doing here is building on top of this baseline, and creating product after product that is going to use the same technology of sequencing, because it is extremely powerful and extremely cost-effective. We are building product after product that will make its way into your home soon, that will continuously analyse those dynamic parts in your body -- what is happening with your immune system, with your protein levels? -- and correlating that to your baseline.

Let's say we sequence your genome, and we find that you have certain mutations that predispose you to have rheumatoid arthritis. Let's say that you're a person in your 30's and you're not super-concerned. Yes, you know that grandma had it, and there's some family history, but rheumatoid arthritis is not an acute condition -- not until you get it later in your life. So now we need to monitor what is happening with your rheumatoid arthritis.

Here is what happens today. You go in and say, 'I have a family history of rheumatoid arthritis.' Your doctor says 'Eat these foods, don't eat those foods.' You look at it, and two weeks later you forget about it and move on. And 30 years later, you walk in, and they tell you: 'You have full-blown rheumatoid arthritis. Take these medicines that are going to have serious consequences for your liver, kidneys, etc.' That's the state of affairs today.

We're changing that paradigm completely. We're going to say, 'You have a genetic risk of rheumatoid arthritis. Now we can measure these things in your blood every six months. Go and eat different foods, and let's measure and give you real feedback by changing your diet, environment, nutritional supplements.'

Q: So these instruments of measurement will be placed inside the home and won't require you going to the lab every time?

A: You certainly will not have to go to a lab -- just as today, as a [Veritas] client, you don't have to go to a lab to have your whole genome sequenced. We send you a kit, you spit in a tube, you mail it to us, and we provide the result on the map. And this is how it's going to work.

The disconnect is the following. There is a notion in this industry that eventually you're going to provide this sample on your iPhone, or that there will be sensors in your body. I am convinced of that. What I am not convinced of is the timing.

For the foreseeable future, we're building our business around the central lab model, where we send stuff to your home, you collect the sample, you send it to us, and within days you get the result on your app and it continues to populate. That little heart on your Apple iPhone with all those data points that are missing because you don't have them and there's nowhere to find them -- we are going to be the company to populate that.

Our app is currently working on the iPhone. We are the company that has put your genome on the iPhone today.

Q: With myGenome, how do you communicate worrying news to your customers?

A: When we see a serious mutation for something like breast cancer in the genome, we don't report that through an email or through an app. That kind of information is provided by a genetic counsellor -- a person with 15 years of experience in communicating this kind of information, giving advice to the person on the other side, where they should go, what they should do with the information, help them understand it so that they're not alarmed.

Q: Isn't there a risk that once people have their genes sequenced, and genetic editing becomes possible, they will want to change things?

A: What you'll find consistently with people in our community is that we're motivated to do the right thing: to give people the information first and foremost, to treat serious and debilitating disease, and avoid a development of disease over time. If you think about something like Alzheimer's, which has a clear genetic underpinning, and if you think about the impact on healthcare and the impact on families, on care givers, and the fact that it's diagnosed only when it's really too late, all of these technologies are going towards giving people the opportunity to live a better quality of life over a longer period of time.

Q: **Your co-founder George Church played a very key role in the development of the CRISPR-Cas9 technology and the ability to edit genes. How will that impact your company?**

A: Tremendously, I think, as it goes through its own regulatory hurdles, and as it demonstrates its safety and efficacy in one application after another, which will take time and a lot of effort and investment.

If you look at the first set of companies using this technology, they're using it not to make designer improvements to things. They're using it to make significant breakthroughs in drug discovery, to understand how our human biology works by using this very precise tool in the research phase of it, the output of which, ultimately, is the drug that's going to save lives. So there's a long way for gene editing technologies that are going to have to go through a development cycle and a regulatory cycle and so forth.

One of the things we do at Veritas is that we sequence the parents before they're having a child for serious inherited genetic conditions. Today, for those people who know they have a risk -- and some people have it simply from family history or other concerns, but now they have a genetic test to definitively answer that -- they go through IVF. They have several embryos, and they test the genetics of the embryo to pick one that does not result in [serious inherited genetic conditions]. There are many examples of severe, debilitating neurological disorders where the children live only a couple of years, rare genetic conditions and so forth.

[With CRISPR and similar] technologies, you will need to know what to edit. And frankly, the more we know about our genes, and the more people we sequence, [the better.]

At Veritas, our goal is to sequence millions of people and make their de-identified information available to researchers who will better understand the biology and the disease and then whatever intervention technologies may or may not materialize over the next 20 years. Where you edit a gene and why is based on understanding the gene and its interplay, and understanding that on a very large scale. That's the contribution that we are focused on making.

Q: You recently drew $30 million in funding, a lot of it from Asia and specifically China. Why the interest from that part of the world?

A: This is a piece of technology and capability that's been in the making for many, many years.

It is in its time, now. [This] is the age of the genome, at this right price point.

Who's going to adopt it more

rapidly is a multi-layered question. We sell our product in over 30 countries now. We have much more accessible tests. We have gene panels that look at two, or 10, or 20 genes and only cost a few hundred dollars. We sell those all over the world: from Eastern Europe to Latin America to Europe and Asia. In a number of countries and places, people are embracing prevention mainly because the treatment options are very limited.

If you live in the Philippines, knowing about your BRCA breast-cancer mutation is probably a life-and-death situation, because no one can afford a $250,000 treatment for breast cancer when it develops. So this cultural notion of prevention and understanding your health in places where people are used to paying out of pocket -- versus expecting everything to be reimbursed and paid -- is why you see a focus on this in Asia, and a huge investment. A recent Washington Post article showed a $9 billion investment by China in this space. How do you deal with a population of that size that's not able to afford the cost of medicine? The answer is most likely in prevention.

We welcome this paradigm shift, and we'll see who adopts it faster and who jumps ahead.

Q: So your market is going to be more international than U.S.-based?

A: We do have a lab in China. We have our own subsidiary there, our sister company that's staffed with our folks, and we see a tremendous opportunity in China.

The best analogy is cellphone versus landline. Why build landlines when cellphones are now available? Just build some towers and go wireless. The same goes for keeping old generational diagnostic technologies, or going straight to genetics. [Genetics] is cutting-edge, better, cheaper and more accessible.

Our market is very global and international. But our myGenome product is available only in the U.S. It is a complex product to deliver globally. There are language barriers, there is a lot of information, there is a means of continuously engaging people. We're going to slowly roll that out in countries as we figure out the logistics more than anything else.

The myGenome product is currently only available in the U.S. It's very different if you're [just] looking at two genes and reporting, versus [mapping] the whole genome, and doing it in 15 different languages, and having genetic counselling support available, etc.

This is why I emphasize that it's early days. But it's an incredibly exciting time for this technology, which has been in development for many years. We will look back in a few years, and there will be no question that every single new-born should have their genome done, and every single person should have their genome available to them. It's not a question of if, it's a question of when.

Energy

Company	Ticker	Rec Date	Price Then	Price Now	Gain/ loss %
Orocobre Ltd	ORE. AX	07/04/16	A$ 2.92	A$ 3.00	2.74

Technology

Company	Ticker	Rec Date	Price Then	Price Now	Gain/ loss %
Cyberdyne	7779	30/05/16	JPY 2,353	JPY 1566	-33.45
IBM	IBM LN	07/06/16	$153.33	$180.47	17.7
SAIC	SAIC US	05/07/16	$58.17	$87.31	50.02
Garmin	GRMN US	02/08/16	$55.75	$51.76	-7.16
2U INC	TWOU: US	06/02/17	$33.25	$37.90	13.98

Medical

Company	Ticker	Rec Date	Price Then	Price Now	Gain/ loss %
Intuitive Surgical	ISRG	07/04/16	$ 626.12	$ 735.70	17.5
Terra Tech Corp	TRTC	11/11/16	$0.41	$0.27	-34.47
Autodesk	ADSK	01/11/16	$70.10	$82.94	18.32
Abcam	ABC	07/03/17	913p	913p	0

Moonshot

Company	Ticker	Rec Date	Price Then	Price Now	Gain/ loss %
SolarWindow	WNDW	07/04/16	$3.96	$3.36	-15.15
Alkane Resources Ltd	ALK: AU	05/09/16	AU$ 0.31	AU$ 0.30	-1.64
Mobileye US	MBLY	10/01/17	$39.86	$46.19	15.88
Editas	EDIT: US	07/03/17	$21.02	$21.02	0

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