



April 2016

On the edge of a biological cusp

'Imagine being a table to re-writ the genetic kode of any organism including tumans.'

This sentence obviously makes no sense. Now imagine these spelling mistakes occurred in your genetic code (genome). Your genome is made up of a four letter alphabet, consists of three billion letters and resides in every one of the cells in your body. It defines who you are. To put this in perspective, the *Complete Works of William Shakespeare* is based on a 26 letter alphabet and has about six million letters. Of the three billion letters in your genome, roughly 10 million can change between individuals. These changes can have no apparent effect, result in different eye color, for example, or cause disease. There can be additions and deletions to these three billion that can also cause disease. Now imagine trying to find and fix these typos in your 500 copies of Shakespeare. Hard enough with a 26 letter alphabet; near impossible with a four letter alphabet.

The fly in the ointment

For several years now we have been able to 'speed read' genomes at a reasonable cost. This has allowed us to characterize many of the differences between individuals and the differences associated with disease. However, we had no ability to fix the mistakes. We did try. Severe combined immunodeficiency (SCID) is a rare disease where children are born without an active immune system due to errors in their genome. We tried to put in a correct copy of the letters but they went into the wrong location. This made part of the genome, like the first sentence, nonsensical. The result of this disruption was cancer. Recent attempts to treat SCID and other genetic diseases have been to add a 'footnote' to the genome. This consists of delivering a good copy of the sequence to the genome but not actually inserting it. It works but is not as effective as replacing the defective letters. Clearly we need tools that can replace the error and only the error, in all locations of that error. We now have them.

The power of the solution

They go by exotic names like Zinc Fingers, TALENS or CRISPR but each genome editing tool operates by the same principle. Each is able to find a specific sequence of letters out of the three billion and replace it with another sequence of letters. We can do this in plants, animals and humans. Of course we have been selecting desirable characteristics and cross breeding plants and animals for years. But this is a slow process that risks diluting out one desirable characteristic for another. Like everything else in this age, genome editing tools allow us to do it quicker and more

precisely. For example, three letters have been changed in the pig genome to allow the pig to survive an infection that causes African swine fever.

Despite the name, there have been outbreaks in Eastern Europe. Sticking with pigs, Chinese researchers knocked out a growth hormone receptor in Bama pigs to make smaller 'micropigs' for research purposes. However, they proved to be so 'cute' that the real demand is for them as pets. Sticking with China, researchers modified pre-implantation human embryos to fix the gene responsible for B-thalassemia, a potentially fatal blood disorder. While the attempt was not 100% successful, the fact is they tried. You can see the slippery slope we have just stepped onto. The technology is disruptive but it comes with a lot of moral strings attached.

By its very nature, disruptive technology is impactful. It is the job of Altrinsic to identify and understand the disruptive technology, to decide if and when an investment should be made and, perhaps most importantly, to identify the impact on existing holdings and companies within the value chain.

Now, imagine being able to re-write the genetic code of any organism including humans.

Next generation sequencing is affecting Altrinsic's investment decisions today and will continue to do so into the future.

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