Signal From Noise

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CRISPR — Improving Our Original Recipes

"DNA is like a computer program but far, far more advanced than any software ever created."

— Bill Gates

In 2020, Drs. Jennifer Doudna and Emmanuelle Charpentier won the Nobel Prize in Chemistry for developing the gene-editing tool known as CRISPR. In the words of the Nobel committee that honored Drs. Charpentier and Doudna, CRISPR has "reshaped the life sciences," with almost endless examples of how CRISPR-Cas9 could be used …"

The promise recognized by the Nobel Committee just five years ago is now bearing fruit, and the rate of harvest appears to be accelerating. On March 24, 2025, Verve Therapeutic ($VERV) announced regulatory approval for clinical trials of its CRISPR-based treatment for heterozygous familial hypercholesterolemia (HeFH), an inherited condition that causes elevated blood concentration of low-density lipoprotein (LDL) cholesterol (aka "bad" cholesterol) and is associated with premature coronary artery disease. The company hopes tests will show that a single dose of its VERVE-102 treatment can turn off the gene that causes HeFH.

Charpentier and Doudna's discovery built on decades of research into a defense mechanism used by the *Streptococcus pyogenes* bacteria to fight off viral infections. In essence, the bacteria use RNA to copy and record snippets of the genetic codes of viruses that they encounter. When re-exposed to one of those viruses, the bacteria can use this guide RNA to quickly recognize it and bind a DNA-slicing enzyme – a protein known as Cas9, to those genetic snippets – thus severing the viruses' genetic code and rendering them unable to replicate.

CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) mimics that process, creating "guide RNAs" to target specific gene sequences on a DNA double-helix and bind Cas proteins to them. If the Cas protein used is Cas9, this essentially allows scientists to snip our genes with precision, and either nullify or replace them. The CRISPR process is superior to previous methods of gene editing in that it eliminates the need to laboriously and slowly engineer a new, unique protein for each gene to be targeted.

Source: Freepik

As the Nobel Committee suggested: "Biochemists and cell biologists can now easily investigate the functions of different genes and their possible role in the progression of disease. In plant breeding, researchers can give plants specific characteristics, such as the ability to withstand drought in a warmer climate. In medicine, this gene editor is contributing to new cancer therapies and the first studies attempting to cure inherited diseases."

(*Note: For those who would like a refresher on basic terminology and concepts regarding genetics, we suggest resources provided by the CDC, the National Human Genome Research Institute, and the University of Utah.*)

CRISPR and disease

Perhaps understandably, the potential to use CRISPR to cure diseases captured the immediate attention of scientists and the public. In late 2023, the FDA approved the first CRISPR-based treatment, Casgevy. Multiple drug regulators around the world followed suit, and last fall, the first non-trial patients began receiving the treatment. Casgevy was developed by Vertex Pharmaceuticals ($VRTX) in partnership with CRISPR Therapeutics ($CRSP). It uses Cas9 to target the gene that causes sickle-cell anemia.

An explanation on the Casgevy process serves to illustrate how CRISPR treatments can work. The process begins with bone-marrow stem cells being collected from a patient, which are then cultured and modified in a lab, using the gene-editing technology to produce red blood cells with normal hemoglobin. The patient then undergoes intensive chemotherapy to kill existing bone-marrow cells in their body, after which the modified cells are introduced into the bloodstream to replace them.

Though the treatment has proven effective in clinical trials, the required chemotherapy – which is unavoidably harsh, toxic, and thus, risky – has sparked efforts to develop a so-called "in-vivo" treatment in which the gene-editing takes place within the patient's body. **Editas Medicine ($EDIT)** is working on one such possible in-vivo sickle-cell treatment. This approach, viewed as significantly more challenging from a technological perspective, is still in the early preclinical stages of development.

In addition to treating sickle-cell anemia and high cholesterol, researchers are developing CRISPR-based treatments for other diseases and conditions.

- **Caribou Biosciences ($CRBU)** has multiple treatment candidates in clinical trials that could treat aggressive lymphomas, blood cancers, and lupus.
- **CRISPR Therapeutics** has multiple candidates in clinical-stage trials that might become effective treatments for various blood cancers and Type I diabetes.
- **Intellia Therapeutics ($NTLA)** has clinical-stage candidates for gene-editing treatments of Hereditary Angioedema (HAE) and Transthyretin Amyloidosis, and Hemophilia B.

CRISPR and diagnostics

In addition to the potential to treat numerous diseases and conditions, the gene-editing technology can be used in medical diagnostics. CRISPR-based assays offer the advantage of high speed and sensitivity, and in many cases can deliver results at the point-of-care, making them less resource-intensive.

In general, such diagnostics rely on using guide RNA to detect a specific DNA or RNA sequence (such as might be created by specific pathogens during infection, for instance), and then binding them to a Cas enzyme that creates a detectable effect – typically taking the form of a visible line on a lateral flow strip. Existing CRISPR diagnostics as of this writing can be used to test for:

- COVID-19
- Human Papillomavirus (HPV)
- Zika
- Dengue
- Tuberculosis
- Malaria

Researchers are also working on tests for fungal pneumonia and some types of lung and ovarian cancer, as well as over-the-counter tests to detect chlamydia and gonorrhea.

As of this writing, the two main CRISPR-diagnostic platforms are SHERLOCK (Specific High sensitivity Enzymatic Reporter UnLOCKing), the technology of Cambridge, Massachusetts- based Sherlock Biosciences; and DETECTR (DNA Endonuclease Targeted CRISPR Trans Reporter), owned by Brisbane, California-based Mammoth Biosciences. SHERLOCK and DETECTR operate on similar principles, pairing guide RNA with Cas13 and Cas12 enzymes, respectively.

CRISPR and agriculture

This seems like a good time to bring up Norman Borlaug. Dr. Borlaug is often described as "the man who saved a billion lives," and that's neither hyperbole nor a final count. Over several decades, Borlaug developed high-yield varieties of wheat – resistant to disease and harsh weather – that helped double or even triple yields around the world. In doing so, he prevented famines that would have led to as many as a billion people dying from starvation.

Source: Unsplash

Now, CRISPR technology could help scientists accomplish in months what took Dr. Borlaug decades of laborious cross-breeding to accomplish. (That is no disrespect to Dr. Borlaug, who in our view deservedly won the 1970 Nobel Peace Prize, Presidential Medal of Freedom, and Congressional Gold Medal, among many other honors for his efforts.)

The technology is currently being used to develop crops that are more resistant to pests, diseases, and the extreme effects of climate change; crops that require less water or are less reliant on fertilizer, and crops that are more nutritious. Already, American consumers can eat a CRISPR salad – and we make no apologies for that pun. A North Carolina startup named Pairwise used the gene-editing technology to create a mustard green to be less pungently peppery (some describe it as bitter) while still retaining its high nutritional value. The new plant, reportedly comparable in flavor to arugula, has been approved for sale, and Pairwise has partnered with Bayer ($BAYRY) to scale up production and bring it to market.

Bayer has also partnered with Pairwise to create corn with higher yields (more kernels per ear), as well as corn that is more resistant to high winds. Separately, the life-sciences conglomerate is also working with a South Korean biotech startup, G+GLAS, to create Vitamin D-enhanced tomatoes (useful for people in colder climates with less sunlight). Other major companies using CRISPR for crop research include:

- **Corteva ($CTVA)**. The company's Agriscience division is working on multiple projects, both independently and in collaboration with other companies (including Pairwise). They include various disease- and climate change-resistant varieties of corn and rice.
- **Cibus ($CBUS)**. Cibus's projects include rapeseed and canola that can be more easily harvested with machines and whose pods yield more nutritious cooking oil. – developing high-oleic soybeans and other improved crops. It is also using CRISPR to develop herbicide-resistant rice and canola varieties

- **Arcadia Biosciences ($RKDA)**: Arcadia's research includes improving wheat and soybeans, specifically seeking crops with superior nutrition and/or higher tolerance for drought, salinity, and heat. One of its products on the market is GoodWheat products, which claims reduced gluten along with higher fiber and protein content.

CRISPR and computing

As with so much of our world, the promise of CRISPR technology has been greatly enhanced by recent advances in the fields of computing and artificial intelligence. If CRISPR can simplistically be described as a technology that allows scientists to snip strands of DNA with precision, it must be pointed out that scissors are largely useless unless one knows *where* to cut. This is where AI comes in.

AI is being used to analyze genomic datasets, including the human genome. With the help of machine-learning models, such technology will help researchers better identify effective or optimal genetic sequences to target with guide RNA to safely achieve the desired effects and highlight potential unintended consequences (including but not limited to off-target cuts). As it relates to protein synthesis, AI might also help scientists discover new Cas proteins to use to achieve effects other than mere slicing and dicing.

Yet the exchange might go both ways. The Nobel Committee that honored Drs. Doubna and Charpentier was perhaps slightly myopic in limiting their references to the life sciences.

Some computer scientists and engineers believe CRISPR might ultimately prove to be the key to progressing beyond the limits of Moore's Law. As advances in manufacturing ever-smaller computer chips bump up against the limits imposed by the laws of physics, DNA-based computing might ultimately provide a route to further advances.

DNA offers key advantages over the on-off transistors that form the foundation of silicon chips. To begin, it offers data-storage density that is orders of magnitude greater than a standard memory chip – one gram of DNA can theoretically store 215 million GB of data (which, for reference, is enough to store 36 million feature-length movies). DNA computers can also be configured to do parallel processing on a massive scale – allowing for billions or even trillions of calculations simultaneously, making them superior for solving problems involving optimization (the famous travelling salesman problem, for example), search, and pattern-matching.

The difference, obviously, is that rather than electrical currents, DNA computer operations are based on biochemical actions, such as binding single strands of DNA together, joining multiple paired strands, or separating them – and then decoding the answer from the results of those reactions. CRISPR's ability to facilitate the editing and manipulation of DNA has obvious theoretical applications in this field.

DNA computers moved beyond the theoretical in 1994, with Leonard Adelman creating a prototype that solved a Hamiltonian path problem (a combinatorial problem similar to the traveling salesman problem referenced above). Nevertheless, investigation into DNA-based computing applications remains in its earliest stages, with most research being carried out in academia. Companies involved include some familiar names, as well as some that are less well-known.

- **Microsoft ($$MSFT)**
- **IBM ($$IBM)**
- **Twist Bioscience ($TWST)**
- CATALOG (privately held)

Conclusion

As is often the case with companies that work with new technologies – the hoped-for benefits to humanity, and thus, the investment potential, might not be realized. In addition, competing technologies might emerge that end up taking market share and eroding profit potential. The nascent nature of companies working with CRISPR-related technology can be seen in the size of many of the companies involved: Most firmly fall into the small-cap category. Thus, as always, *Signal From Noise* should be used as a source of ideas for further research rather than as a source of investment recommendations.

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