Sujet traité : La révolution biotechnologique : l'innovation à l'œuvre! (Partie 2) / The Biotech Revolution : Innovation Unleashed! (Part 2)

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INNOVATION THEMES & STRATEGY

August 28, 2024

The Biotech Revolution: Innovation Unleashed! (Part II)

Last week, in Part I of our biotech series, we examined how AI is turbocharging biotech innovation.[1] Specifically, we discussed the implications of leading AI-powered biotechnologies including next-generation diagnostic screening, predictive analytics, robotic surgery, and AI-powered drug discovery/development. We argued that biotech is ushering healthcare into its most transformative era in history.

This week, we are taking a deep dive into genomics, regenerative medicine, and will conclude with our biotech investment considerations. Genomics and regenerative medicine are at the forefront of biotech solutions that directly enhance human longevity.

In This Report

Breakthroughs across both genomics and regenerative medicine are already treating once untreatable diseases or are restoring once-lost functions. Both fields represent the cutting edge of biotech and are collectively pioneering treatment solutions for addressing both rare and common diseases that currently lack effective clinical treatments.

"Genomics has not only become a crucial clinical tool, but we're at the point of complementing it and addressing patient needs in ways that, 20 years ago, would have been inconceivable. Now, we need to move beyond prolonging life and toward developing cures."

- Gianrico Farrugia, M.D.,
president and CEO of Mayo Clinic

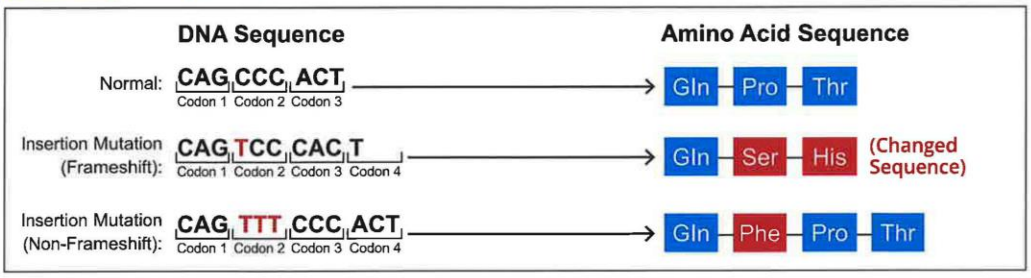
Genomic Mutations And Epigenetic Changes

Both genomics and regenerative medicine are centered around the human genome. The genome contains 3.2 billion DNA base pairs, which constitute our entire set of genetic instructions, akin to our "genetic software." When DNA base pairs become mutated, the "software" becomes compromised and begins to produce incorrect proteins. The result is faulty gene expression: the process of making proteins using the instructions from genes. Genetic mutations are classified into two buckets: inherited mutations from parents present at birth or a mutation that forms later during an individual's life from flawed gene expression.

Aside from genetic mutations directly to DNA strands that result in incorrect protein manufacturing, epigenetic changes are the other main

1 Alpine Macro *Innovation Themes & Strategy* "The Biotech Revolution: Innovation Unleashed!" (August 21, 2024).

Chart 1 **Consequences Of Mutations**



contributor to causing genetic disorders. Unlike genetic mutations that alter the DNA sequence itself, epigenetic changes hinder the body's ability to accurately read and act on DNA instructions. While sections of DNA strictly dictate gene expression, other sections provide the guidance to where in the body a protein is made, when it is made, and how much is made.

Epigenetic changes cripple the body's ability to turn genes "on" and "off". This causes genes to either produce too much or too little protein, or to do so at the wrong times or in the wrong place. This is highly significant, as epigenetics determines cellular function. For instance, since all cells have the same DNA, epigenetic errors can cause cells to develop incorrectly as heart cells instead of kidney cells. Until recently, genetic disorders stemming from either mutations or epigenetic factors have lacked effective treatment or prevention offerings.

Genetic Disorders

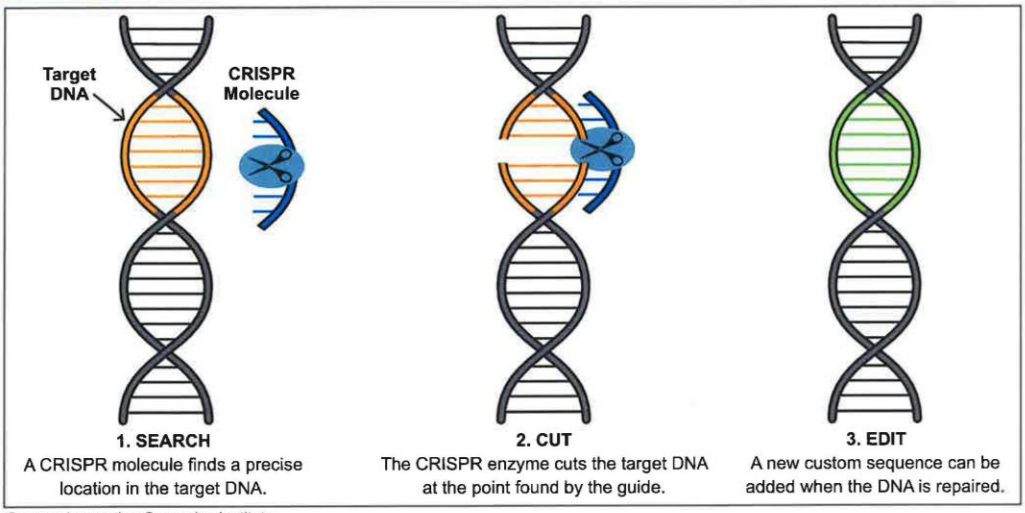
There are an estimated 10,000 different types of single-gene diseases alone, loosely designated as rare diseases. Currently, about 10% of Americans have a rare disease, of which 72% are caused by genetic mutations. While 70% of these mutations are already present at birth, like Sickle Cell, many develop later in life from mutations or epigenetic factors.

For example, 90%+ of all cancers form after birth, meaning only about 5-10% of cancer gene mutations are present at birth. Both genetic mutations and epigenetic changes can occur randomly from a myriad of factors. Mutations caused by inserting or deleting a base in DNA can be particularly harmful. This is because DNA is read in triplets during synthesis, so a shift in a single reading frame leaves the rest totally scrambled. The earlier in the sequence the deletion or insertion occurs, the more altered the protein. This type of mutation, known as a frameshift mutation, is apparent in severe genetic diseases and increases susceptibility to certain cancers (Chart 1).

The Genomics' Revolution

The falling cost of decoding the genome is producing a treasure-trove of genetic data. This data is propelling innovation across genetic therapeutics and novel delivery mechanisms. Not only are therapeutics emerging for diseases that were once thought of as incurable, but novel targeting delivery mechanisms are also overcoming obstacles that have hindered progress.

Chart 2 **CRISPR's Genetic Scissors**



Source: Innovative Genomics Institute

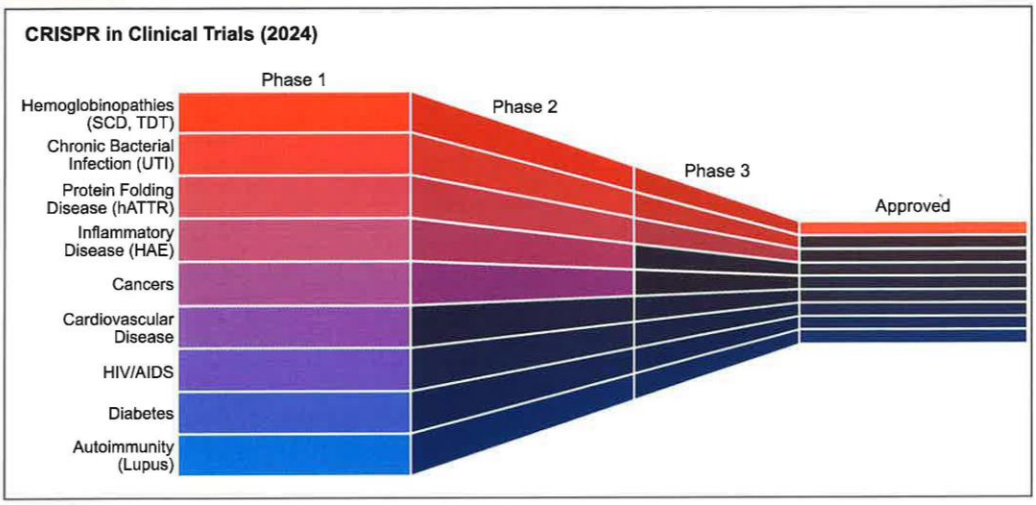
In December 2023, the FDA approved Casgevy, a gene-editing therapy for sickle cell disease. This was a groundbreaking moment for the biotech sector, marking the first FDA approval of a CRISPR-based gene editing therapy. Casgevy went from the lab to an approved therapy in just 11 years, underscoring the pace of biotech's disruptive potential for novel therapeutic development.

CRISPR, or Clustered Regularly Interspaced Short Palindromic Repeats, brings a Cas protein to a specific location on the DNA helix and functions as a genetic pair of "scissors" (Chart 2). In short, CRISPR facilitates replacing an existing (problematic) segment of code with a new (corrected) sequence by adding, removing, or changing letters using a customizable template.

Casgevy's success has ushered in a wave of optimism towards CRISPR-based therapeutics and many are in the development pipeline. For example, therapeutics for cancers, inflammatory disease, protein folding disease, and UITs are in phase 2 trails or further, with therapeutics for cardiovascular disease and lupos amongst others in phase one (Chart 3). Importantly, these therapeutics are positioned to "reverse" or prevent diseases entirely; the "holy grail" of biotech innovation.

While emerging CRISPR and other gene-editing therapies hold immense promise, it's essential to note that several hurdles must be overcome before such treatments realize economic viability. For example, high costs are currently the largest inhibiting factor to growing access to genetic therapies. For example, Casgevy is priced at around $2 million per patient. An analysis conducted by the think-tank The Aspen Institute forecast that by 2031, America may spend $30bn a year on gene and cell therapies that only cover 550,000 people. This equates to roughly ten

Chart 3 **CRISPR Therapy Pipeline**



Note: Colored cells denote phase completion; source: Peter H. Diamandis

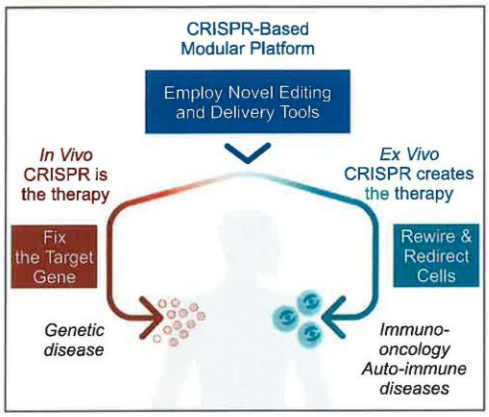
times the average cost per patient of an American currently using available prescription drugs. Yet, regulatory shifts and new therapeutic approaches are converging and this could exponentially reduce cost and increase access.

Draft guidance from the FDA through the proposed Platform Technology Designation Program is poised to shorten and smoothen the path for gene-editing genetic therapies to enter the market. In a nutshell, the program strives to accelerate development and clinical review timelines. For CRISPR and other gene-editing platforms, this means companies could streamline the regulatory process and thus accelerate the development of genetic medicines. Platform status is a necessary catalyst to lower the cost of genetic therapies. For example, the cost of developing monoclonal antibodies declined almost 50-fold in 20 years following its emergence as a key platform for drug development.

Transitioning therapies from ex vivo (where cells are removed from the body, edited and quality-checked in a specialized lab, and then reintroduced after the patient has undergone intensive chemotherapy) to in vivo is another necessary change to reduce costs. In short, in vivo delivers genetic material directly to targeted cells to treat affected organs or instruct cells and tissues to produce specific proteins that help combat diseases (**Chart 4**).

Intellia Therapeutics, cofounded by Jennifer Doudna and Nessan Bermingham (awarded the 2020 Nobel Prize in Chemistry for their pioneering work in CRISPR), is a global leader in developing in vivo therapies. The company currently has four in vivo CRISPR therapies in the clinical pipeline, with two others in the preclinical phase. Beam Therapeutics is another leader in the in vivo space, with four in vivo therapies in clinical trials.

Chart 4 *In Vivo* Versus *Ex Vivo*



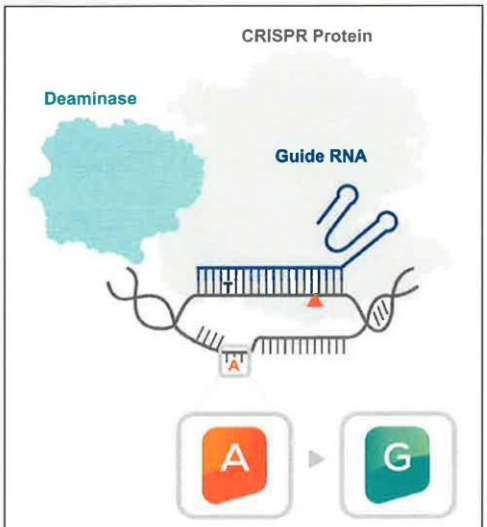
Note: Colored cells denote phase completion
Source: Intellia Therapeutics

Safety And Efficacy Improvements

The most significant technical challenge for gene-editing treatments remains accurately targeting and modifying only the intended areas on DNA or cellular targets. However, large strides are being made to improve therapeutic delivery to prevent the risk of negative externalities. While CRISPR-based gene therapies remain the most proven to date, new less invasive CRISPR-supported delivery mechanisms are coming down the pipeline. Specifically, new methods negate CRISPR's need to completely "cut" both strands in a DNA helix, minimizing the risks of unwanted insertions or deletions. For example, enzymes called CRISPR-Cas9 nickases (nCas9s) only cut one strand of the DNA double helix. They are used in pairs, directly reducing the risk of off-target effects.

Another emerging approach called base editing is highly precise and can chemically alter a single letter in a DNA sequence without requiring any cuts

Chart 5 The Multiple And Highly Versatile Applications Of Base Editing



Name	Description	Programs
Correct Mutations	Repairs the most common type of gene mutation, single base changes	Beam-302, Beam-301
Silence Proteins	Turns off any gene with disease-causing activity	Multiple at Beam and partners
Activate Expression	Turns on genes to restore increase function	Beam-101
Modify Proteins	Changes how proteins bind or signal without disrupting their function	Escape
Multiple Edits	Targets multiple pathways simultaneously with high efficiency	Beam-201

Source: Beam Therapeutics

(Chart 5). Already, the technique is in the clinic and showing promise. A base editing treatment developed by Verve Therapeutics can turn off the PCSK9 gene in the liver by only making a single letter change in the DNA (from A to G), preventing hypercholesterolemia.

Table 1 Benefits Of Prime And Base Editing

Technology	Capabilities	Strengths
Base Editing	• Can make four kinds of DNA substitutions	• Highly efficient • Fairly small (in some cases able to fit into a singular vector) • Advanced farther in animal testing • Currently in six ongoing trials
Prime Editing	• Can make all 12 types of DNA substitutions • Can make insertions (up to ~200 bases) and deletions (>5,000 bases) • Can make large insertions >5,000 base pairs when paired with recombinases	• Versatility (more possible substitutions plus insertions and deletions) • Immune to bystander editing • Doesn't cause spontaneous mutation

Source: Cell and Gene

A new technique called prime editing sits at the forefront of gene-therapy innovation. Prime editing leverages the Cas9 nickase enzyme along with a uniquely designed RNA that both locates and carries a template of the desired change. This ensures the therapy is given precisely and delivers the correctly edited gene. Developments in prime editing are rapidly moving forward. It took only four and a half years to use prime editing in a patient after scientific publication. Prime Medicine, a biotech firm, has already begun to use the technique in clinical trials to treat chronic granulomatous disease (Table 1).

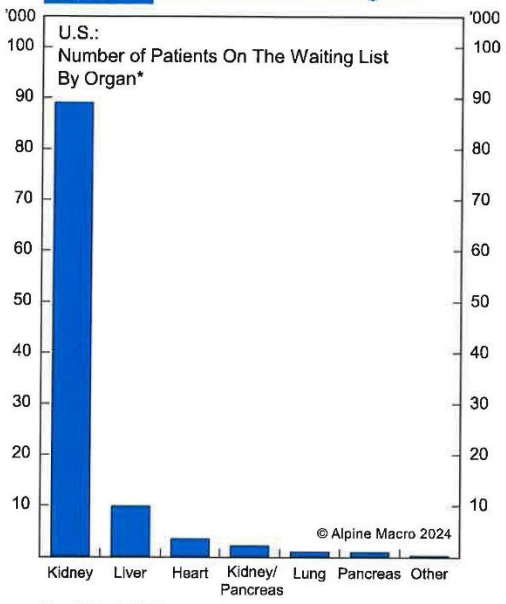
Importantly, prime editing enables larger pieces of the genome to be altered, opening the door for treatments to diseases where errors stretch over a long distance, like Huntington's disease. In addition, it holds the most promise to fix multiple mutations with one correction, meaning it could improve the economics of gene editing and correct almost 90% of disease-causing genetic variations.

Epigenetic Reprogramming

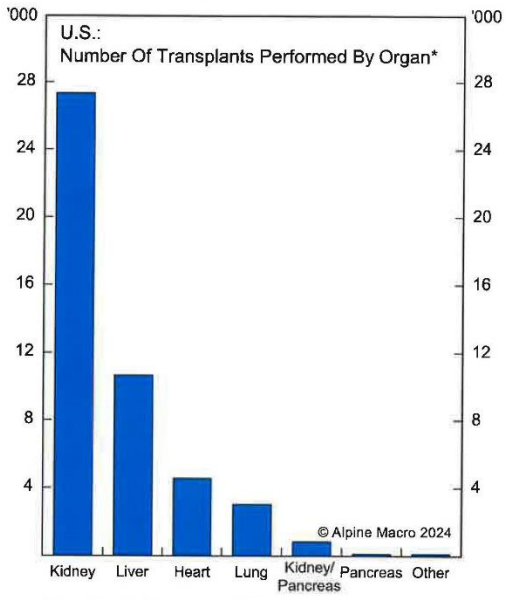
Although the human genome remains unchanged throughout life, the way that our genes are "expressed" or turned on and off does. This is called epigenetics, and is the main factor that causes signs of aging and diseases as we age. The highly nascent field of epigenetic reprogramming is showing that it can "turnback the clock" by reversing aging in tissues, proving neuro-regeneration is possible. A breakthrough from Harvard genetics professor Dr. David Sinclair found that mammalian cells preserve a copy of epigenetic information from earlier in life, which could be used as a blueprint to reverse aging.

Dr. Sinclair's team successfully restored vision in mice with irreversible vision loss using epigenetic reprogramming and has shown that the approach can be applied to the liver, various muscles, the brain, ears and more. While epigenetic reprogramming has not been tried in a human clinical trial to date, Dr. Sinclair's team has begun trials in primates with compelling results. Epigenetic reprogramming

Chart 6 **The Great Need for Organs**



*As of March 2024; source: HRSA



*As of March 2024; source: HRSA

has the potential to reverse the biological clock by tapping into the youthful epigenetic instructions housed inside every cell.

The potential of epigenetic editing or reprogramming is beginning to receive attention from biotechs. For example, Epitor Therapeutics leverages epigenetic influencing from the body's natural mechanisms to influence genes compared to invasive methods like CRISPR to change, edit, or introduce new genes. Epitor has found that the accumulation of damaged RNA cells with compromised software instructions directly leads to disease. By using viral vectors as a delivery method, Epitor is "opening the hood" of one's DNA sequence and "jumpstarting" cells with the uncompromised DNA software instructions to correct or eliminate the target disease.

Regenerative Medicine

Regenerative medicine focuses on replacing, engineering or regenerating human cells, tissues, or organs to restore or establish normal function. Recent advancements in this space are making the prospect of "manufacturing" human organs a reality. The need could not be greater. Currently, in the U.S. alone, every eight minutes someone is added to the transplant waiting list which totals over 103,000. Sadly, 17 people die daily waiting in the transplant queue. Today, 35% of all U.S. deaths could be prevented or at a minimum delayed with sufficient organ access (**Chart 6**).

Dr. Dean Kamen, a serial inventor and recipient of the U.S. Medal of Technology and Innovation, has made it his mission to fix this problem. Dr. Kamen creating

the "Silicon Valley" for human-organ manufacturing, dubbed BioFabUSA. BioFabUSA is an offshoot of the Advanced Regenerative Manufacturing Institute (ARMI) that forges public-private partnerships that represent industry, academia, government and nonprofit organizations. The program is creating the world's first tissue manufacturing platform that is scalable, modular, and automated to control critical process parameters and therefore limit variability. BioFabUSA's tissue manufacturing facility houses 200 teams and takes up 50,000 square feet building filled with clean rooms specializing in tissue and organ production.

ARMI partner Organamet Bio has already successfully "manufactured" bioengineered human hearts and intends to make personalized human hearts available within five years. The BioFabUSA campus is also home to United Theraputics, a global leader in organ manufacturing and lung biotechnology. The company has already created the world's most complex 3D-printed object, a human lung scaffold.

Another exciting area of disruption is an offshoot of regenerative medicine known as bioelectric re-programming. Bioelectricity is the electrical currents that flow within living organisms, tissues, and cells. These electrical currents are responsible for many things within the body, including how cells communicate and how humans perceive pain or feeling. Dr. Michael Levin and researchers at Tufts University have created a "bioelectric atlas". The novel tool transcribes these electrical signals outside of the body, allowing researchers to follow numerous disease indicators and their associated connections at the cellular level. By tracking in-cell voltage patterns, Dr. Levin discovered that cells are electrically programmed to create a specific body part. This has unlocked a key roadblock in regenerative medicine by enabling the modification of voltage in cells and tissues that transfer information electronically. Already, this is improving amputation-stump health by increasing an amputee's ability to interface with prosthetics by forging the cellular electrical connection.

Investment Considerations

As evidenced through Part I and II of our biotech series, the sector is an innovation hotbed. Already, several biotech-based offerings are having a disruptive impact. In the short to medium term, our view is that areas in biotech most directly aided by AI and automation will realize increased adoption and use cases. Specifically, technologies like AI-diagnostic screening and predictive analytics tools that boast low upfront implementation cost have proved ability to improve clinical outcomes. In the longer-term, biotech's potential to cure rare diseases or prevent diseases entirely on a widespread basis cannot be dismissed, albeit carrying increased risk. Regardless, the highly fragmented nature of the biotech sector requires a diversified investment approach that encompasses the wide range of emerging technologies.

From a historical perspective, the sector has been a posterchild for mania crazes. As we laid out in Part I, we are in the camp that biotech is at the start of an up-cycle. Yet, these up-cycles often conclude with overshoots. For example, the biotech ETF XBI topped out above $170 when the COVID-19 pandemic pumped funding into the biotech sector and inflated valuations. Overshoots

are also driven by significant lags stemming from years to decades between the initial breakthrough and the point at which that breakthrough achieves economic viability.

As a result, prudent selection of entry points is essential when participating in the sector. Investors should note that biotech will also continue to experience above-average volatility and individual equities that often carry a higher beta than that of other market participants.

We believe wide reaching biotech-focused ETFs including XBI provide investors broad exposure to innovations across the biotech sector. XBI's structure of primarily small and mid-cap securities is aligned with our overarching "broadening out" theme and could outperform under conditions where smaller biotechs perform well. However, investors looking for more targeted exposure to biotech innovation covered in these reports could consider companies like Intuitive Surgical (ISRG), United Therapeutics (UTHR), and Medtronic (MDT).

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