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The Disruptive Dozen

12 GCT breakthroughs that are revolutionizing healthcare

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Key Takeaways

- Gene and cell therapy (GCT) is widely recognized as a transformational opportunity in medicine, with the potential to stop or slow the effects of disease by targeting it at the genetic level.
- The “Disruptive Dozen” identifies 12 emerging GCT technologies with the greatest potential to transform healthcare over the next several years
- These breakthroughs range from restoration of sight and increasing the supply of donor organs, to treating brain cancer, hearing loss and autoimmune diseases that currently lack few or any treatment alternatives.

Gene and cell therapy (GCT) technologies are transforming medicine and the approach to severe diseases like cancer, hereditary conditions including Huntington Disease and Sickle Cell, as well as rare disorders that currently have no treatment alternatives.

GCT has the potential to stop or slow the effects of disease by targeting it at the genetic level, either replacing, inactivating or modifying the genetic material or by transferring live or intact cells into a patient to treat or cure disease. Even in cases where the GCT approach does not fully cure a condition, GCT has the potential to be life changing. This is because GCT treatments are often “one and done,” only requiring a single administration, which may enable a patient to manage their disease without onerous ongoing treatment cycles.

While some of the first GCT applications were focused on rare and orphan diseases, recent advancements show tremendous potential opportunity for use cases with more broad applications. Beyond the messenger ribonucleic acid or mRNA vaccines that protect against infectious disease including COVID-19, GCT technologies exhibit promise to address prevalent chronic diseases such as diabetes and hearing loss, as well as central nervous system (CNS) disorders and Alzheimer’s.

This week, Bank of America joined Mass General Brigham to present the World Medical Innovation Forum in Boston, where over 1,000 clinical experts, industry leaders and investors explored how to advance GCT technologies that may lead to breakthrough medical advancements and solutions. We highlight the twelve emerging GCT technologies - the "Disruptive Dozen" - with the greatest potential to impact and transform healthcare in the next several years. These breakthroughs range from restoration of sight and increasing the supply of donor organs, to treating brain cancer, hearing loss and autoimmune diseases.

Restoring sight by mending broken genes

Roughly 200 genes are directly linked to vision disorders. In the last several years, groundbreaking new gene therapies have emerged that can compensate for faulty genes in the eye by adding new, healthy copies — a molecular fix that promises to restore sight to those who have lost it. The approach, known as CRISPR-Cas-9 gene editing, could open the door to treating genetic forms of vision loss that are not suited to conventional gene therapy, and a host of other medical conditions. A clinical trial is now underway to evaluate a CRISPR-Cas 9 gene-editing therapy for a severe form of childhood blindness for which there currently are no treatments. Although this treatment is still experimental, it is already historic — it is the first medicine based on CRISPR-Cas-9 to be delivered in vivo, or inside a patient’s body. Similar gene-editing therapies are also under development that correct genes within blood cells.

A gene editing solution to increase the supply of donor organs

In the U.S. alone, more than 100,000 people need a life-saving organ transplant. But the supply of donor organs is quite limited, and every day, patients die waiting for a donor organ. One way to address this crisis is xenotransplantation — harvesting organs from animals and placing them into human patients. Advances in gene editing technology make it possible to remove, insert, or replace genes with relative ease and precision. This molecular engineering can sidestep the human immune system, which is highly adept at recognizing foreign tissues and triggering rejection. Over the last 20 years, scientists have been working to devise successful gene editing strategies that will render pig organs compatible with humans. The field has taken another major step forward in the past year: transplanting gene-edited pig organs, including the heart and kidney, into humans. While extensive clinical testing is needed before xenotransplantation becomes a reality, that future now seems within reach.

Cell therapies to conquer common forms of blindness

The eye has been a proving ground for pioneering gene therapies and is also fueling new cell-based therapies than can restore sight, offering a functional cure by replacing critical cells that have been lost or injured. One approach involves stem cells from the retina that can give rise to light-sensitive cells, called photoreceptors, which are required for healthy vision. Scientists are harnessing retinal stem cells to develop treatments for incurable eye diseases, including retinitis pigmentosa. Because the immune system doesn't patrol the eye as aggressively as other parts of the body, retinal stem cells from unrelated, healthy donors can be transplanted into patients with vision disorders. Other progress includes cell therapies that harness patients' own cells, for example, from blood or skin, that can be converted into almost any cell type in the body, including retinal cells. Another novel treatment being tested utilizes stem cells from a patient's healthy eye to repair the affected cornea of the other eye.

Harnessing the power of RNA to treat brain cancer

RNA is widely known for its helper functions, carrying messages from one part of a cell to another to make proteins. But scientists now recognize that RNA plays a more central role in biology and are tapping its hidden potential to create potent new therapies for a range of diseases, including a devastating form of brain cancer called glioblastoma. This cancer is extremely challenging to treat and highly adaptable. New approaches that either target RNA or mimic its activity could hold promise, including an intriguing class of RNA molecules called microRNAs. One team identified a trio of microRNAs that plays important roles in healthy neurons but is lost when brain cancer develops. These microRNAs can be stitched together into a single unit and delivered into the brain using a virus. Initial studies in mice reveal that this therapeutic can render tumors more vulnerable to existing treatments, including chemotherapy. Another team is also exploring a microRNA called miR-10b. Blocking its activity causes tumor cells to die. Now, scientists are working to develop a targeted therapeutic against miR-10b that can be tested in clinical trials.

Realizing the promise of gene therapy for brain disorders

Gene therapy holds enormous promise for serious and currently untreatable diseases, including those of the brain and central nervous system. But some big obstacles remain. For example, a commonly-used vehicle for gene therapy — a virus called AAV — cannot penetrate a major biological roadblock, the blood-brain barrier. Now, researchers are engineering new versions of AAV that can cross the blood-brain barrier. Using various molecular strategies, a handful of teams have modified the protein shell that surrounds the virus so it can gain entry and become broadly distributed within the brain. These modified viral vectors are now under development and could begin clinical testing within a few years. Scientists are also tinkering with the inner machinery of AAV to sidestep potential toxicities. With a safe, effective method for accessing the brain, researchers will be able to devise gene therapies for a range of neurological conditions, including neurodegenerative diseases, cancers, and devastating rare diseases that lack any treatment.

A flexible, programmable approach to fighting viruses

The COVID-19 pandemic has laid bare the tremendous need for rapidly deployable therapies to counteract emerging viruses. Scientists are now developing a novel form of anti-viral therapy that can be programmed to target a range of different viruses — from well-known human pathogens, such as hepatitis C, to those less familiar, such as the novel coronavirus SARS-CoV-2. This new approach harnesses a popular family of gene editing tools, known as CRISPR-Cas. While CRISPR-based systems have gained attention for their capacity to modify human genes, their original purpose in nature was to defend bacteria from viral infections. As a throwback to these early roots, scientists are now adapting CRISPR tools to tackle a variety of viruses that infect humans. Researchers are studying the potential of these programmable anti-viral agents in the context of several different viruses, including ones that pose significant threats to global health, such as SARS-CoV-2, hepatitis C, and HIV.

On the move: Cell therapies to restore gut motility

The human digestive tract — or "gut" — has its own nervous system. This second brain, known as the enteric nervous system, is comprised of neurons and support cells that carry out critical tasks, like moving food through the gut. When enteric neurons are missing or injured, gut motility can be impaired. Now, scientists are developing an innovative cell replacement therapy to treat diseases of gut motility. Donor cells can be isolated from a patient's own gut or from a more readily available source, such as subcutaneous fat. These cells are then cultivated in the laboratory and coaxed to form the progenitors that give rise to enteric neurons. Researchers are also devising "off-the-shelf" approaches, which could create a supply of donor cells that are shielded from the immune system and can therefore be transplanted universally across different patients. Early research shows that transplanted enteric neurons can also take up residence in the brain. That means these forays in cell therapy for the gut could also help pave a path toward cell therapies for the brain and spinal cord.

CAR-T cell therapies take aim at autoimmune diseases

CAR-T cells have emerged as powerful treatments for some forms of cancer, especially blood cancers. By harnessing the same underlying concept — rewiring patients' own T cells to endow them with therapeutic properties — scientists are working to develop novel CAR-T therapies for a variety of autoimmune diseases. Several research teams are engineering CAR-T cells so they can seek out and destroy harmful immune cells, such as those that produce auto-antibodies — immune proteins that help coordinate the attack on the body's own tissues. For example, one team is using CAR-T cells to destroy certain immune cells, called B cells, as a potential treatment for lupus, a serious autoimmune disease that mainly affects women. Scientists are also

developing CAR-T therapies that take aim at other rogue members of the immune system. These efforts could yield novel treatments for multiple sclerosis and type 1 diabetes.

Regrowing cells in the inner ear to treat hearing loss

In the U.S. alone, some 37 million people suffer from a hearing deficit. Currently, there are no drugs that can halt, prevent, or even reverse hearing loss. Scientists are working on a novel regenerative approach that could restore the cells in the inner ear required for normal hearing, offering hope to millions of patients who grapple with hearing loss. Healthy hearing requires specialized cells in the inner ear called hair cells, which have fine, hair-like projections. If the cells are damaged or lost, which often happens with age or after repeated exposure to loud sounds, the body cannot repair them. But researchers have discovered a potential workaround that can stimulate existing cells in the ear to proliferate and give rise to new hair cells. Scientists are now working to convert this molecular strategy, which is being studied in animal models, into a therapeutic that is safe and effective for hearing loss patients.

New technologies for delivering gene therapies

A formidable challenge in the field of gene therapy is delivery — getting gene-based therapeutics into the body and into the right target cells. Researchers are exploring the potential of new delivery methods that could expand the reach of gene therapy, including microneedles. When applied to the skin, a microneedle patch can penetrate the outermost layer with minimal pain and discomfort. This novel delivery method can readily access the legion of immune cells that reside in the skin -- important targets for vaccines as well as for the treatment of various diseases, including cancer and autoimmune conditions. Another emerging technology involves an implantable device made of biodegradable materials. When placed inside the body, this device can provide localized, sustained release of therapeutics with few side effects. The approach is now being tested for the first time in cancer patients using standard chemotherapy drugs administered directly at tumor sites. In the future, this method could be customized for the delivery of gene therapy payloads, an advance that could revolutionize cancer treatment, particularly for difficult-to-treat forms like pancreatic cancer.

Engineering cancer-killing cells that target solid tumors

CAR-T cells are a revolutionary form of cell therapy that has yielded some remarkable cures of difficult-to-treat blood cancers. But the outcomes in other cancers have been lackluster. Now, scientists are enhancing this technology to enable new ways of treating solid tumors. One approach involves making CAR-T cells more like computers, relying on simple logic to decide which cells are cancer — and should be destroyed — and which cells are healthy and should be spared. By building several logic gates and combining them together, researchers are hoping to pave the way toward targeting new tumor types. Scientists are also devising other groundbreaking forms of cancer-killing cell therapy, including one that uses cancer cells themselves. This approach exploits a remarkable feature: once disseminated within the body, cancer cells can migrate back to the original tumor. Researchers are now harnessing this rehoming capability and, with the help of gene editing, turning tumor cells into potent cancer killers. An early version of this technology uses patients' own cells. Now, the scientists are developing an off-the-shelf version that can be universally applied to patients.

Reawakening the X-chromosome: a therapeutic strategy for devastating neurodevelopmental diseases

The X chromosome is one of two sex-determining chromosomes in humans, and it carries hundreds of disease-causing genes. These diseases often affect males and females differently. In females, one X chromosome is naturally, and randomly, chosen and rendered inactive. Although X-inactivation was once thought to be permanent, scientists are uncovering ways to reverse it. Scientists are now exploiting this unusual biology to reawaken the dormant X chromosome — a strategy that could yield much-needed treatments for a group of rare, yet devastating neurodevelopmental disorders, which predominantly affect females. This new approach could hold promise for females with Rett syndrome, a severe X-linked disorder. A similar strategy could also hold promise for other serious X-linked disorders, including fragile X syndrome and CDKL5 syndrome.

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