Disruptors Report 2019 CHAPTER 1

# THE IMPACT OF ADVANCEMENTS IN BIOTECHNOLOGY ON THE TREATMENT OF DISEASE AND AGING

Can innovations and billions of dollars in research improve the health and longevity of patients?

PRESCOUTER

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*Biotechnology: Driving a Revolution in the Treatment of Disease*

# CONTENTS

The concept of "biotech" encompasses a diverse suite of procedures for modifying living organisms, specifically referring to the use of organisms or biological processes and systems that manufacture products intended to improve the quality of human life[1]. This field emerged in the 1970s. By 1978, Lederberg's projections about the promise of biotechnology proved true with the development of synthetic human insulin; a molecule that was the direct result of recombinant DNA technology. With this dramatic advance, the field rapidly grew into additional applications such as the treatment of rare diseases, cancer, heart disease, and a slew of genetic disorders[2]. For decades, treatment of the diseases of aging and extending the healthy lifespan of patients has seemed part of a distant future. In recent years researchers have shown that something as basic as single gene mutations could extend life in model organisms and that some of the mechanisms these experiments reveal may permit extension of the human lifespan.

This promise is reflected in projected growth; the biotechnology sector is expected to reach 727.1 billion USD by 2025[3]. Some core drivers of this growth include food shortages, the burgeoning field of regenerative medicine, advancements in the microbiome field, and the advanced aging of patients, will spur this sector's growth. The increased investment in this sector and the R+D this investment will support may ultimately lead to treatment of heretofore untreatable diseases of aging and an effective increase in the lifespan of patients.

The medical industry is a key sector in biotechnology. Technological advances in this field have led to the development of medicines which address unmet medical needs and improve the quality of human life. Concurrent advances in our push to identify biomarkers for disease risk and interventions for those disease variants continue to move us closer to the ideal of truly personalized medicine and the development of treatments for some of the root causes of aging-related pathology[4]. Addressing the need for better diagnostic tools to test for and treat, age-related disease, and perhaps even the underlying mechanisms of aging are amongst some of the most complex and persistent issues addressed by biotechnology. For the past four decades, the field of biotechnology has had a remarkable impact on healthcare[5]; and the future impact of biotechnology should continue on this

**Biotechnology sector is expected to reach**


1. *Merriam-Webster - Definition of Biotechnology*
2. *Wikipedia, History of Biotechnology*
3. *Grandview Research, Biotechnology Market Worth $727.1 Billion by 2025*
4. *Nature, Facing up the Global Challenges of Aging*
5. *Health Affairs, The evolution of biotechnology and its impact on health care.*

trajectory, resulting in solutions to population wide needs for improved healthcare. The quest for the fountain of youth by slowing the aging process and extending life will likely accelerate with advanced technologies and innovations in research on precision medicine, leading to novel medicines, revolutionized drug development, and disease modeling.

> *Can advancements in biotechnology extend the healthy lifespan of patients?*

This begs the question: can advancements in biotechnology extend the healthy lifespan of patients? Many scientists and companies are pursuing this goal and a significant percentage believe that soon they will be able to extend life "well beyond 120"[6]. Tracking the life cycles of mice and other model organisms from birth to death has revealed a number of potential biomarkers of aging. The presence of these biomarkers may predict aging-related morbidity. The further study of these biomarkers will help us understand diseases that lead to death which may in turn produce a myriad of scientific innovations and new treatments.

One of the current barriers facing biotechnology moving forward is purely logistical; a number of steps in the research process face delaying logistical hurdles which have yet to be overcome by the development of novel processes. Beyond the field of medicine, research in biotechnology has focused on improving crop and animal yield through genetic engineering. Innovations in this space including the development of novel high efficiency gene editing technologies and the inclusion of advancements in fields like nanotechnology into the biotechnology toolkit may overcome logistic hurdles facing the development of new treatments in the medical biotechnology field. These advancements are paving the way for the rapid creation of new therapies including novel biologics and regenerative medicine methods. As the field of biotechnology incorporates these new advancements, the improved rate of discovery and the lower barrier to entry facing new researchers may bring about new treatments for diseases of aging and ultimately extended healthy lifespans for patients.

*Biotechnology uses organisms and biological processes to manufacture products intended to improve life.*
***Image Source:*** *Tutorialspoint*

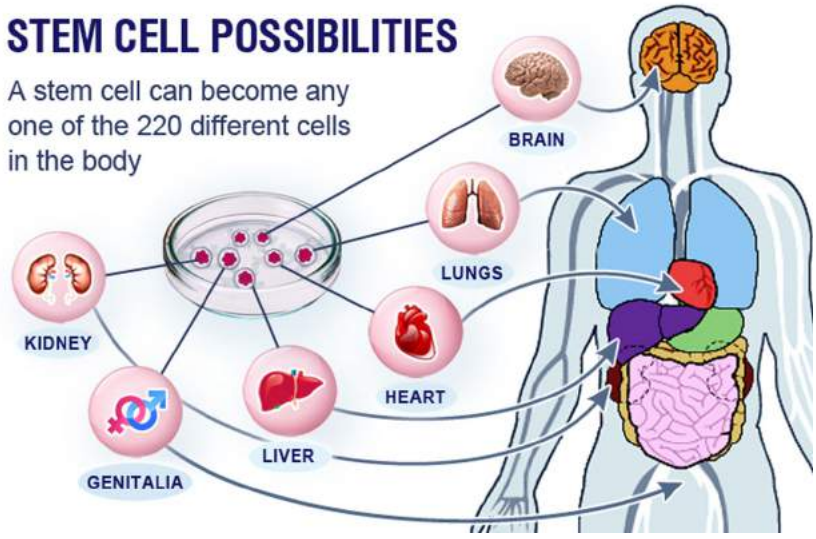
*6. The Observer, Live Forever: Scientists Say They'll Extend Life "Well Beyond 120"*

# CAN WE SLOW DOWN THE AGING PROCESS AND CURE DISEASE?

# CELL THERAPIES: A POTENTIAL PANACEA FOR DISEASE

Cellular therapy can be broadly described as the transplantation of human cells to replace or repair damaged tissue[7]. New technologies, innovative products, and different cell types may be used to treat major trauma and diseases which have proved resistant to treatment thus far. Because of the potential of engineered cells to incorporate into damaged or dysfunctional tissue, advances in this field are a major driver in the regenerative medicine space[8].

The primary component of most cell therapy, stem cells, are undifferentiated cells which have the unique ability to make endless copies of themselves and/or differentiate into specialized cell types depending on their environment[9]. Stem cells have become an essential reagent in regenerative medicine because of these properties. As our ability to control the differentiation of stem cells improves, they have great potential to revolutionize healthcare and aging. Because advances in the stem cell market will open up diseases which have very few treatment options, the market for stem cell therapy is projected to reach 297 billion by 2022 with a compound annual growth rate (CAGR) of 25.5%[10].




*Stem cell possibilities.*

***Image Source:*** *Stem Cell Genetic Med*

7. *Advancing Transfusion and Cellular Therapies Worldwide - Facts about Cellular Therapies*
8. *Advancing Transfusion and Cellular Therapies Worldwide - Regenerative Medicine*
9. *Wikipedia - Stem Cells*
10. *Market Watch - Stem Cell Market Projected to be $297 Billion by 2022*

Stem cells originate from two main sources: adult body tissues and embryos. Research into stem cells helps us understand more about development, aging, and disease. The discoveries made by researchers on stem cell functions have been used to help patients, with the ultimate goal of regenerative medicine. There are three important features of stem cells based on their classification:

- Unlimited self-renewal capabilities
- Non-differentiated cells with unspecialized functions
- Differentiation into specific cell types under the right conditions

> *Scientists have determined that stem cells in the brain can control how quickly our bodies age, and they have found that by introducing fresh stem cells into the body, part of the aging process could be slowed down and even reversed.*

Some forms of adult stem cell therapy such as bone marrow transplantation[11] have been standard in medical practice for a long time. Stem cells can also be grown in culture and differentiated (or transformed) into specialized cell types with the characteristics consistent with the specific cells of various tissues of interest[12]. Recently, scientists have determined that stem cells in the brain may influence how quickly our bodies age. Recent research has also indicated that introducing fresh stem cells into the body may slow down or even reverse elements of the aging process. Researchers from Albert Einstein College of Medicine recently investigated how stem cells found in a region of our brain called the hypothalamus may play a key role in how quickly we age[13]. These stem cells are thought to release tiny fatty bubbles (exosomes) filled with microRNAs (small non-coding molecules of nucleic acids) which then influence the behavior of cells elsewhere in the body. As these cells die out as part of the aging process, the lab found a decrease in muscle, skin, and brain functions of mice. When neuronal stem cells were transplanted from young mice into middle-aged ones, scientists were able to slow the onset of elements of aging. Another team of researchers at the University of Oklahoma Health Sciences Center, led by Professor Mujib Ullah, have demonstrated that stem cells and anti-aging genes, such as the Klotho, play key roles in slowing down the aging process[14,15]. The interplay of stem cells and anti-aging genes may most likely receive and neutralize most of the signaling effects of premature aging. With our current knowledge of stem cells, the feasibility of designing interventions that can either delay aging or improve the human lifespan has increased, but there is still some ways to go to move these discoveries from the lab to the clinic.

*11. Journal of Stem Cells, Hematopoietic stem cells: potential new applications for translational medicine*
*12. NIH - Stem Cell Basics*
*13. Nature, Stem Cells and Aging*
*14. Stem Cell Research and Therapy, Stem Cells and Aging*
*15. The Korean Journal of Internal Medicine, Klotho and the Aging Process*

## TIMELINE OF KEY STEM CELLS BREAKTHROUGHS

**1963**

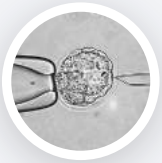
Discovery of renewing cells in bone marrow

**1968**

Bone marrow transplantation between two siblings

**1981**

Embryonic stem cells isolated from mouse blastocysts (Nobel prize)

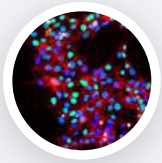


**1992**

Adult stem cells identified in human brain

**2001**

Mouse embryonic stem cells created using nuclear transfer technique



**2006**

Discovery of induced pluripotent stem cells (Nobel prize)

**2010**

Medical treatment using human embryonic stem cells for spinal injury

**2014**

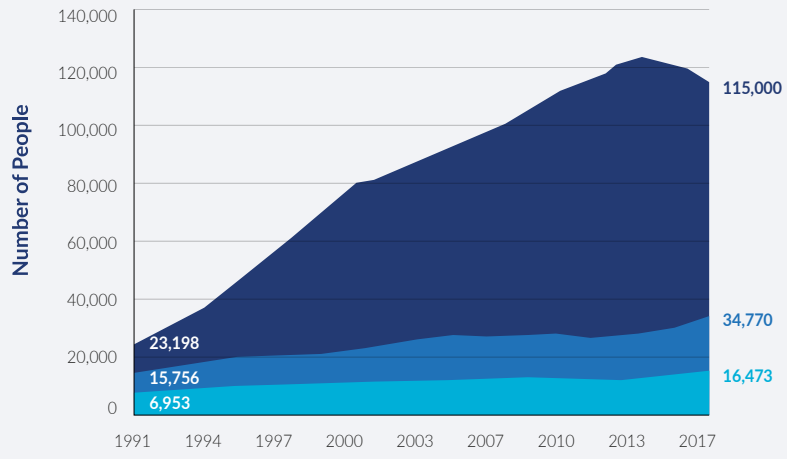
Embryonic stem cells from adult stem cells (Insulin producing Beta cells generated from skin cells)

*Stem cell research dates back to the 1960s.*

***Image Source:*** *Sigma Aldrich*

Since the discovery of induced pluripotent stem cells in 2006, our understanding of stem cell biology and development have been transformed[16]. This technology enables the creation of cell therapies which have the potential to cure diseases that have traditionally only been "managed". With the advent of new techniques, one of the most important current applications of human stem cells is the generation of cells and tissues that may be used in cell-based therapies. Once this sector matures, it would be able to address the chronic shortage of organs which are currently used to treat patients.

The need for transplantable organs far outweighs the current supply. According to the U.S. Department of Human Health and Disease, the number of people on waiting lists continues to grow at rates faster than the number of donors[17]. As of April 2018, there are greater than 114,000 candidates waiting for transplants on the U.S. national waiting list. With the advent of stem cells that can be directed to differentiate into specific chosen cell types in concert, the possibility of a renewable foundation for replacement tissues and organs starts to become a reality. For example, in 2016, scientists from Stanford University, led by lead researcher Gary K. Steinberg, conducted a clinical trial involving stroke victims and the use of stem cells to boost patients' ability to restore brain function[18]. In this trial, the researchers injected modified stem cells into the brains of patients. This treatment led to considerable improvements in motor function. One of the trial participants even regained control of their limbs and left their wheelchair behind. While the advances in stem cells thus far have been dramatic, there is a possible market growth in the hundreds of billions as new applications of this science move from the bench to the clinic.




*The number of people waiting for transplants vastly outnumbers the available transplants.*

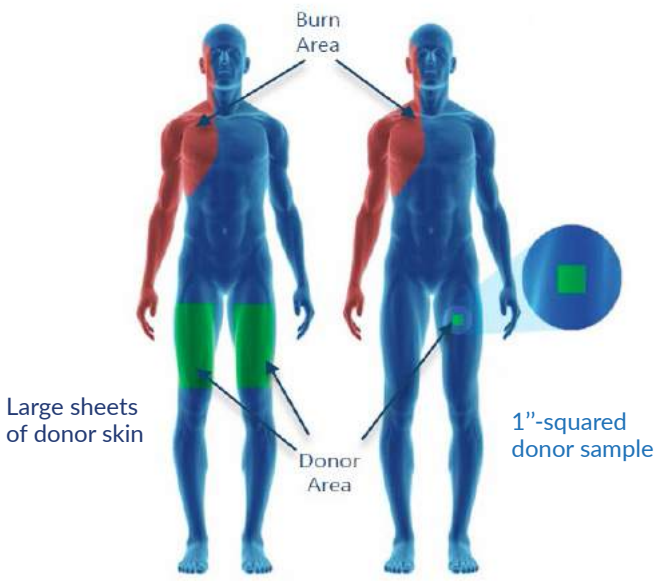
***Image Source:*** *U.S. Department of Health and Human Services*

*16. Cell, Induction of Pluripotent Stem Cells*
*17. U.S Department of Health and Human Services*
*18. Stroke, Clinical Outcomes of Transplanted Modified Bone Marrow–Derived Mesenchymal Stem Cells in Stroke*

## CLINICAL USE OF STEM CELL THERAPIES TO TREAT WOUNDS?

RenovaCare, a stem cell company, is attempting to disrupt the wound care industry with a scalable and easy to apply stem cell therapy. Their technology applies a patient's own stem cells onto severe burns, helping them leave the hospital after only a few days, rather than the weeks required after traditional grafting. The autologous skin repair system, created by the University of Pittsburgh professor, Dr. Jörg Gerlach, was the first of its kind to result in scar free healing. This technology harnesses the power of stem cells. Before they can be utilized, they must be isolated from a skin biopsy and suspended in liquid. This liquid suspension is inserted into the RenovaCare's patented SkinGun, that sprays the suspension onto the wound evenly and gently. Presently, the entire process from cell harvesting to clinical application takes about 2 hours. The benefits of this technology are two-fold: faster healing, and the reduced need to harvest healthy skin for grafting. RenovaCare's technology can use one square centimeter of healthy cells to treat up to 100 square centimeters of burned skin[19]. Traditional grafting techniques require almost 110 squared centimeters of donor skin to treat the same coverage area.

**Skin Grafting** | **CellMist™**




**CellMist™ uses postage stamp-sized sample.**

**Traditional skin grafts require large sheets of surgically removed skin.**

*RenovaCare's system is an investigational treatment for processing and spraying a patient's own stem cells onto wounds.*

***Image Source:*** *RenovaCare*

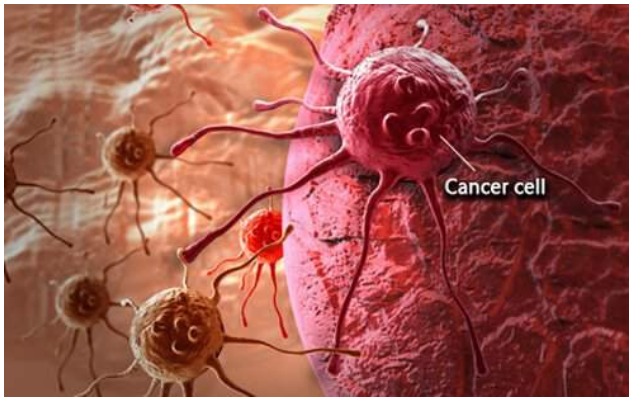
## CAR-T: A NOVEL CELL THERAPY TOOL IN THE FIGHT AGAINST CANCER

While stem cell technology is powering incredible developments in the basic science space and in regenerative medicine, it is also proving to be an incredible resource in the fight against cancer[20]. For example, Chimeric Antigen Receptor T-cell therapy (CAR-T) is being hailed as a powerful new weapon in the fight against cancer. Essentially, CAR-T therapy revolves around enhancing the immune system's ability to

19. *RenovaCare, New SkinGun*
20. *NIH, Definition of Car-T Cell Therapy*

> *Two CAR-T therapies, Novartis' Kymriah and Gilead's Yescarta, have recently been approved for lymphomas, the first of their kind to get FDA approval in the United States.*

target and kill cancer cells by isolating, enhancing, and then introducing them into the patient. Two CAR-T therapies, Novartis' Kymriah and Gilead's Yescarta, have recently been approved for lymphomas, the first of their kind to get FDA approval in the United States[21,22]. With these therapies obtaining FDA approval, the field is thriving with ever increasing numbers of CAR-T clinical trials. While this is exciting, the FDA approved CAR-T therapies which are only used in patients with adult B-cell non-Hodgkins lymphoma or childhood acute lymphoblastic leukemia and these patients need to have previously been through two unsuccessful standard treatments to be considered. Ongoing clinical trials are evaluating CAR-T as first or second lines of defense for these cancer types[23]. CAR-T therapies use a patient's T-cells (a white blood cell produced or processed by the thymus gland and involved in the immune response) which are changed in the laboratory so they can recognize and attack cancer cells. A special receptor (the chimeric antigen receptor) is bound to the T-cell so that it can bind to the proteins found in cancer cells and destroy them. These mutated CAR-T cells are presented to the patient by infusion. Treatments using chemotherapy typically require at least 6 months or more, however, CAR-T therapy can be theoretically finished in a single infusion that usually requires only two weeks of inpatient care[24]. The benefit of CAR-T cell therapies can also last much longer than chemotherapy, since the treatment relies on T cells that can persevere long-term in the body and continue to attack cancer cells. The treatment has also shown remarkable remission rates of up to 94%[25]. These results have significantly improved prospects for patients, investors, and companies alike. Companies like Novartis and Gilead were the first companies to bring CAR-T to market, but many competitors are



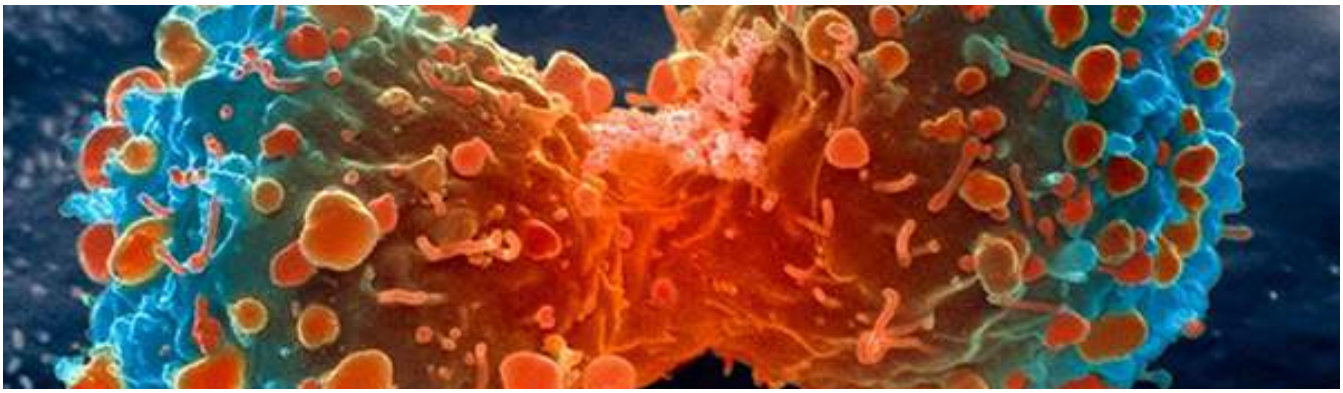

*Cancer refers to cells that grow out-of-control and invade other tissues.*
***Image Source:*** *Onhealth*

21. *Novartis, FDA approval*
22. *FDA, Yescarta*
23. *MD Anderson Cancer Center, 9 things to know about CAR T-cell therapy*
24. *MD Anderson Cancer Center, 9 things to know about CAR T-cell therapy*
25. *LabBiotech, Cancer: World Best Ever CAR-T Results have Just been Disclosed*

growing fast and catching up. For example, companies such as Allogene are developing "off the shelf" or allogeneic CAR-T therapies that do not require the cells to be harvested from patients. Allogene's CAR-T therapy has advantages over first-generation CAR-T therapies[26]:

- ✔ Faster speed to patient
- ✔ Enhanced cell potency
- ✔ Higher efficiency
- ✔ A larger portion of eligible patients since T-cell are not harvested from critically ill patients

Allogene's goal is to improve on the biological processes of the first generation autologous CAR-T therapies and deliver the same benefits, with the advantage of eliminating the need for a



*A dividing lung cancer cell.*
***Image Source:*** *The National Institutes of Health*

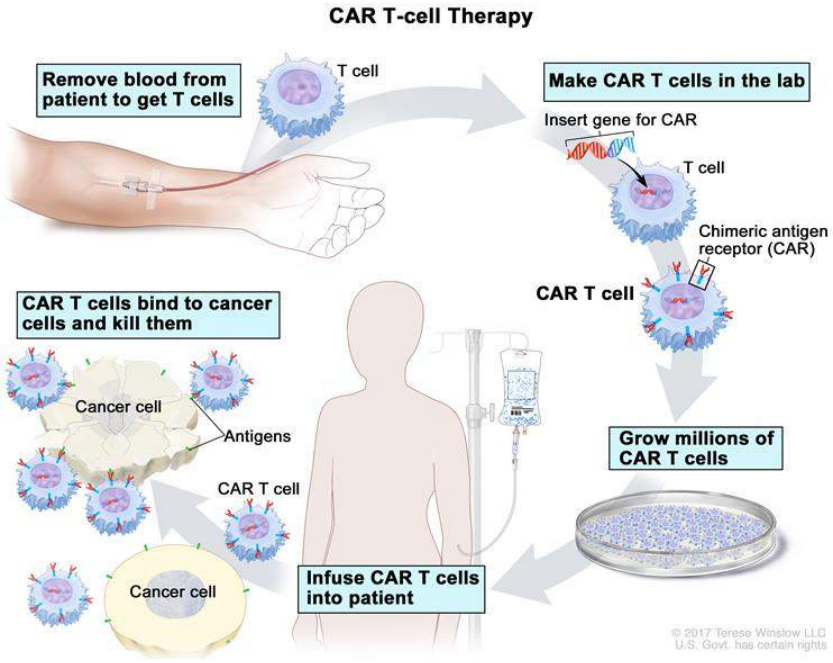
## GENE EDITING: Dramatic Improvements in Precision and their Clinical Implications

Gene editing is a type of genetic engineering in which DNA is inserted, deleted, replaced or modified in the genome of a living organism. Gene editing mediated by CRISPR represents the future of gene therapies, being more efficient and specific than traditional methods. This specificity may in turn lead to the development of permanent cures for genetic diseases. However, precise engineering and delivery options present obstacles to the development of gene editing therapies[27].

*26. Allogene*
*27. Acta Pharmacologica Sinica, Therapeutic Gene Editing*

In recent years, gene-editing has emerged as a revolutionary breakthrough tool with potential uses in curing disease. These recent innovations are based on the past 20 years of incremental advances in genome editing technologies using nucleases combined with targeting of specific DNA binding domains. Currently, there are four nuclease-based gene-editing systems:

- **Meganucleases:** enzymes that have a large recognition site that can be used as highly specific tools in genome editing [28].
- **Zinc finger nucleases (ZfNs):** artificial restriction enzymes (enzymes that cleave DNA into fragments at the restriction site) spawned by the fusion of a structural motif to a DNA cleavage domain. These are engineered to target specific DNA sequences[29].
- **Transcription activator-like effector-based nucleases (TALENs):** restriction enzymes engineered to target and cut specific DNA sequences. These are also generated by the fusion of a specific structural motif to a DNA cleavage domain[30].
- **CRISPR/Cas9:** CRISPR is a family of DNA sequences that are derived from DNA fragments from viruses used to detect and eliminate DNA. Cas9 is an enzyme that uses CRISPR sequences to direct, identify, and cut specific strands of DNA that are complementary to the CRISPR sequence[31].




*How CAR-T therapy works illustrating the process of making CAR-T cells for a patient.*
***Image Source:*** *National Cancer Institute*

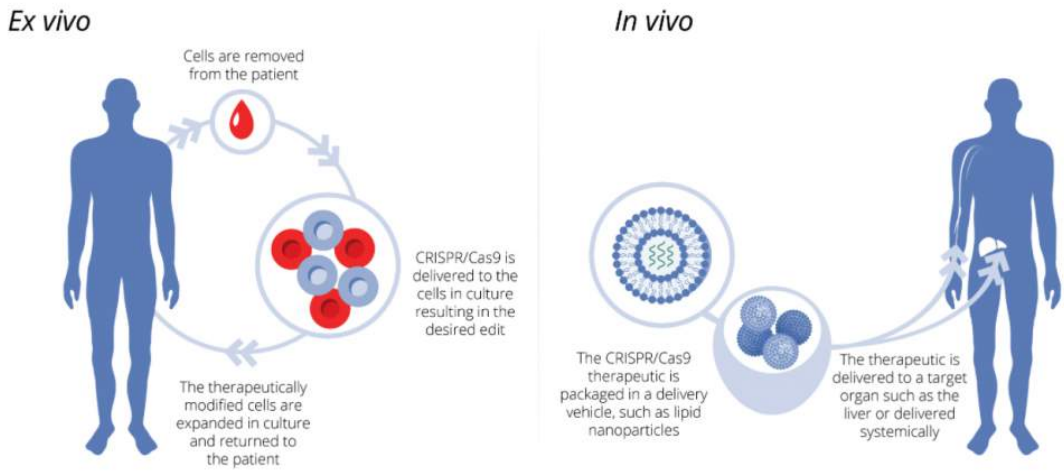
*28. Nature, Meganuclease*
*29. Genetics, Zinc finger Nucleases*
*30. Nature Reviews Molecular Cell Biology, Transcription Activator-Like Effector-Based Nucleases*
*31. Genetics Home Reference, CRISPR/Cas9*

## HOW IS GENE EDITING USED AS A GENE THERAPY?

Gene therapy is a general term used to describe the process for curing and/or treating disease by modifying, supplying, or blocking genes or gene products. There are several kinds of strategies currently employed, including viral methods, which suffer from multiple drawbacks such as transient gene expression and immune mediated destruction of the vector. Recently, a new delivery system for presenting gene editing technologies into cells has emerged. The system developed by KAUST scientists, led by Associate Professor Niveen Khashab, is the first to use sponge-like ensembles of metal ions and organic molecules to coat the molecular components of the precision DNA-editing technology (like CRISPR) leading to an efficient release of the genome-editing machinery inside of the cell[32].

## WHAT IS CRISPR?

As scientists continue to enhance their tools for deleting, replacing, and editing DNA, one particular technology has gained increasing popularity. CRISPR, or Clustered Regularly Interspaced Short Palindromic Repeats, has already been recognized as a key scientific discovery of the 21st century. In 2015, CRISPR took *Science's* 2015 Breakthrough of the Year award[33]. Since then, the potential applications of CRISPR has captivated the world, since it's easier, cheaper, and more efficient than previous gene-editing technologies. CRISPR is a family of DNA sequences originating from immune systems in bacterial and archaea to counter phage invasions. Applications of CRISPR have been tailored for influencing a broad range of living organisms, with specific applications in medicine and crop seed enhancement. In this




*Cells can be edited ex vivo (outside the body) or in vivo (inside the body).*
***Image Source:*** *CRISPR Therapeutics.*

*32. Phys.org, A delivery platform for gene-editing technology*
*33. Science, Breakthrough of the Year award*

> *CRISPR, or Clustered Regularly Interspaced Short Palindromic Repeats, has already been recognized as a key scientific discovery of the 21st century*

arena, one of CRISPR's more striking examples include creation of a "gene drive" that could eliminate pests and/or the diseases they carry[34], and the first deliberate editing of DNA of human embryos[35].

Currently, the CRISPR market is valued at about $350 million and will reach $5.2 billion by the end of 2025 with a CAGR of 40%[36]. A flurry of startup companies are entering the market, such as CRISPR Therapeutics or eGenesis. These companies are using the new technology for "editing" defective genes that have raised hopes for a future generation of medical treatments. They focus on the development of transformative medicines using their proprietary CRISPR/Cas9 gene-editing platform. The CRISPR system delivers unparalleled control over genes in many species, leading to new experiments and investigations into new, more specific, forms of this protein and what greater advancements this technology can enable moving forward.

There are limitations to this new technology. For example, there are a great number of genes to study, the technology is still new, and there are ethical implications. The National Institutes of Health, due to the unknown safety issues and ethics, will not fund studies that use human embryos[37]. This, however, has not stopped some groups from using CRISPR to remove a cardiac disease-causing mutation from a human embryo. Despite these limitations and ethical issues, CRISPR is set to advance our ability to eliminate disease.

*Could the CRISPR revolutionize medicine?*
***Image Source:*** *Bioethics*

*34. Nature, 'Gene drive' mosquitoes engineered to fight malaria*
*35. Nature, Correction of a pathogenic gene mutation in human embryos*
*36. Market Watch, CRISPR And CRISPR-Associated (Cas) Genes Market 2018 Forecast To 2023*
*37. NIH, Statement on NIH funding of research using gene-editing technologies in human embryos*

## CRISPR TIMELINE

**1987**

First report of CRISPR clustered repeats

*Ishino et al.*

**2000**

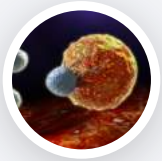
Recognition that CRISPR families are present throughout prokaryotes

*Mojica et al.*


**2002**

Coined “CRISPR” name, defined signature Cas genes

*Jansen et al.*



**2005**

Identified foreign origins of spacers, proposed adaptive immunity function

*Pourcel et al. Mojica et al.*

Identified PAM

*Bolotin et al.*

**2007**

First experimental evidence for CRISPR adaptive immunity

*Barrangou et al.*

**2008**

CRISPR acts upon DNA targets

*Marrafini et al.*

Spacers are converted into mature crRNAs that act as small guide RNAs

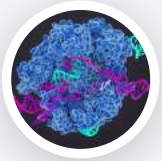
*Brouns et al.*

**2009**

Type III-B Cmr CRISPR complexes cleave RNA

*Hale et al.*

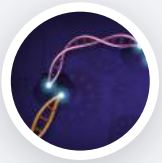
*CRISPR timeline.*
***Image Source:*** *Development and Applications of CRISPR-Cas9 for Genome Engineering*



## 2010

Cas9 is guided by spacer sequences and cleaves target DNA via DSBs

*Garneau et al.*



## 2011

tracrRNA forms a duplex structure with crRNA in association with Cas9

*Deltcheva et*

Type II CRISPR systems are modular and can be heterologously expressed in other organisms

*Sapranauskas et al.*

## 2012

In vitro characterization of DNA targeting by Cas9

*Jinek et al.* *Gasiunas et al.*

## 2013

First demonstration of Cas9 genome engineering in eukaryotic cells

*Cong et al.* *Mali et al.*

## 2014

Genome wide functional screening with Cas9

*Wang et al.* *Shalem et al.*

Crystal structure of apo-Cas9

*Jinek et al.*

Crystal structure of Cas9 in complex with guide RNA and target DNA

*Nishimasu et al.*

*CRISPR timeline.*
***Image Source:*** *Development and Applications of CRISPR-Cas9 for Genome Engineering*

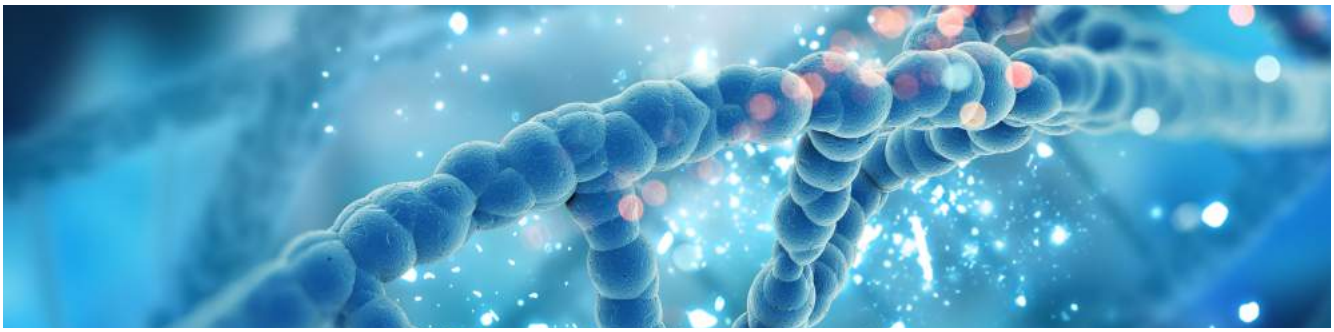
## IS CRISPR TOO GOOD TO BE TRUE?

The discovery of CRISPR stimulated the medical research community and is being heralded as a potential way to treat diseases like cancer; however, this has come into question recently. German researchers recently published in Nature Medicine that 96% of the people in their study had a pre-existing immunity to Cas9[38]. They also found that 85% of people had antibodies against it. This may prove to be an important barrier to using CRISPR to power genetic therapy in patients.

CRISPR's gene editing platform is built on the use of the bacterial protein Cas9. Scientists get this protein from either *Staphylococcus aureus* or *Streptococcus pyogenes*. *S. aureus*, which can cause staph infections[39] while S. pyogenes causes strep throat[40]. What does this mean for CRISPR? For now, scientist may need to find alternative methods to perform CRISPR mediated gene therapy for those with an immunity to CRISPR based proteins.

## WHAT COMES AFTER CRISPR?

Is CRISPR the final frontier of gene editing? This may not be the case, as there is a new gene-editing tool on the rise, MAGESTIC, which stands for "**M**ultiplexed **A**ccurate **G**enome **E**diting with **S**hort, **T**rackable, **I**ntegrated **C**ellular barcodes"[41]. MAGESTIC exploits the CRISPR/Cas9 technology but increases CRISPR's typical DNA-cutting function by adding a couple of key linchpins: the active recruitment of "donor" DNA to the cut site and a genomic barcode. Normally after CRISPR edits the DNA, other helper molecules are required to stitch the nucleotides (the parts that make up DNA) back together, a highly inefficient process. The MAGESTIC concept is different: the strands of DNA are cut, and then with the help of an engineered protein, replacement DNA is recruited to repair the severed strand. What makes MAGESTIC unique is its ability to track the edits reliably using a genome-integrated barcode. This allows millions of yeast cells to undergo distinct edits all at once. While this



*The CRISPR/Cas9 genome-editing technique is setting the molecular biology field on fire.*
***Image Source:*** *CNN*

*38. Nature Medicine, High prevalence of Streptococcus pyogenesCas9-reactive T cells within the adult human population*
*39. CDC, Group A Streptococcal (GAS) Disease*
*40. CDC, S. aureus in Healthcare Settings*
*41. Nature, Multiplexed precision genome editing with trackable genomic barcodes in yeast*

technique has thus far only been tested in yeast, its ability to prevent or minimize unintended edits could provide us with a tenable way to move forward in our quest of editing defective genes and eliminate some diseases altogether.

In addition to MAGESTIC, Precision Biosciences is working on a next-generation genome editing platform derived from a natural genome editing enzyme called a homing endonuclease[42]. Meganucleases are an example of a homing endonuclease. Homing endonucleases are nature's gene editing system. Precision Biosciences technology, ARCUS, uses what they call an ARC nuclease - a fully synthetic enzyme similar to the homing endonuclease but considerably improved in order to operate as a therapeutic grade genome editing platform. ARC nucleases are created using, in part, *in silico* techniques[43]. While very similar to the homing endonucleases, ARC nucleases more easily recognize specific DNA sequences and have advanced into the arena of custom gene editing tools.

| PROPERTY | CRISPR | ZFN | TALEN | MEGANUCLEASE |
|---|---|---|---|---|
| **Specificity (off-target)** | Relatively non-specific | Relatively non-specific | Specific | Very specific |
| **Biasing events (repair)** | NHEJ | NHEJ | HDR | HDR |
| **Design & targeting constraints** | PAM requirement (NGG for SpCas9) | Context-dependent assembly of ZFs; GC rich targets preferred | Assembly of TALE repeats; 5' targeted base is T | Re-design of protein-DNA interface; central 4 bases intolerant to change |
| **Dimerization required** | No | Yes | Yes | No |
| **Coding sequence** | Long | Short | Long and repetitive | Short |
| **Therapeutic delivery** | Easy | Moderate | Moderate | Easy |
| **Vector packaging** | Moderate | Difficult | Difficult | Easy |
| **Multiplex potential** | High | Low | Low | High |
| **Cost-effective** | Yes | No | Moderate | No |

**NHEJ, non-homologous end joining; HDR, homology-directed repair.**

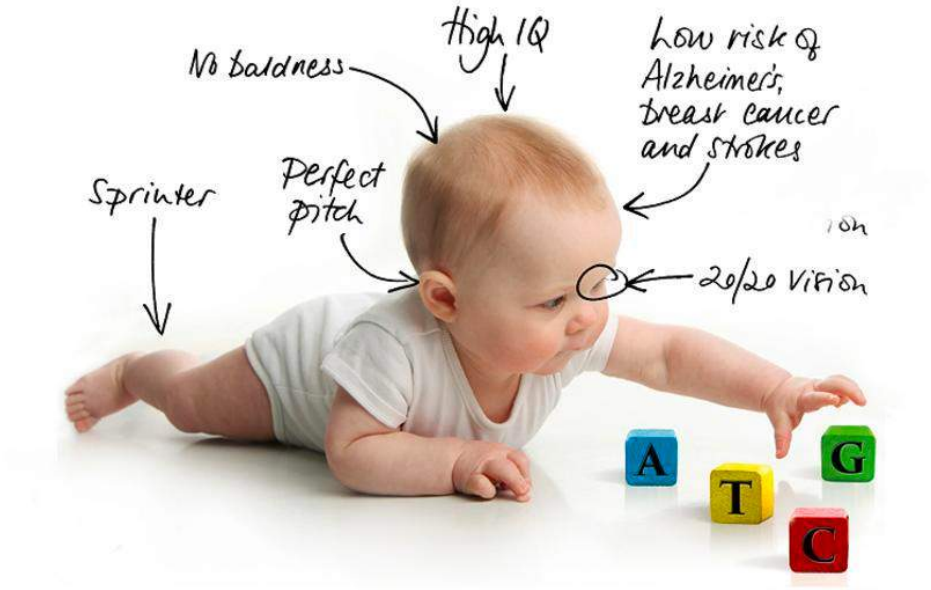
*Comparison of the different methods of gene-editing.*
***Image Source:*** *Applications of Alternative Nucleases in the Age of CRISPR/Cas9.*

*42. Current Gene Therapy, Meganucleases and Other Tools for Targeted Genome Engineering: Perspectives and Challenges for Gene Therapy*
*43. Cell-based Immunotherapies in the News*

## GENE EDITING ON HEALTH AND DISEASE - WHAT DOES THIS MEAN FOR THE FUTURE?

It made news last year when scientists in Oregon successfully modified the DNA of human embryos, renewing worry that babies will one day be designed[44]. The team corrected a gene causing an inherited disease called hypertrophic cardiomyopathy (HCM). Many babies born with the defect in MYBPC3, which could lead to a failing heart with thickened walls. There is currently no treatment for this disease. The team removed the underlying mutation with the use of CRISPR, successfully creating viable embryos. While CRISPR could modify DNA in human embryos, the bigger and ethical question is should we? The Nuffield Council on Bioethics, says changing the DNA of a human embryo could be considered morally permissible if it's in the child's best interest. Of course, this comes with criticism, with groups suggesting the Bioethics[45] group is opening the door to an unrestricted use of heritable genetic engineering leading to an era of the genetic have and have-nots.

> *While CRISPR could modify DNA in human embryos, the bigger and ethical question is should we?*




*What does a future with CRISPR look like?*
***Image Source:*** *The Economist*

*44. Nature, Correction of a pathogenic gene mutation in human embryos*
*45. The Nuffield Council on Bioethics*

## DESIGNER BABIES:THE CONTROVERSY

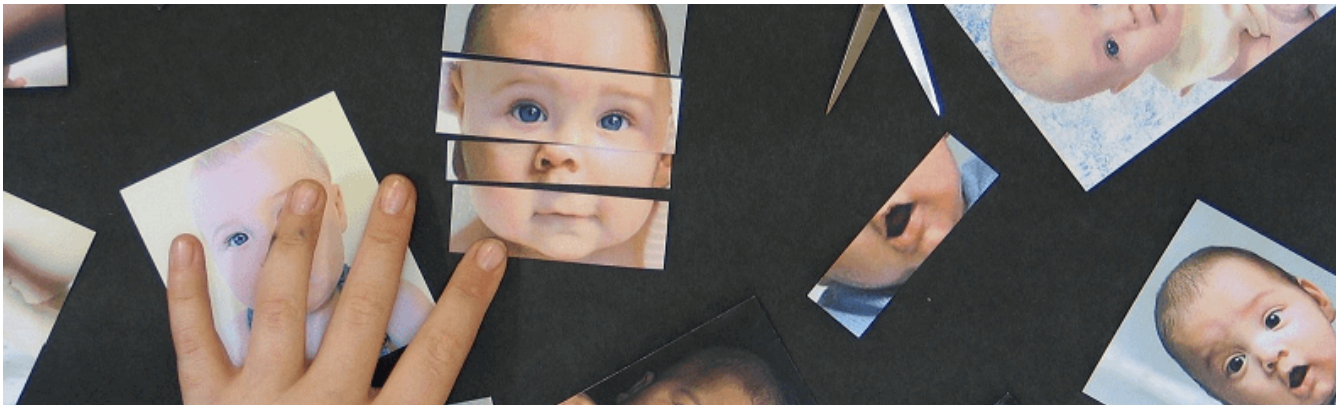
Late last year, scientist He Jiankui, of the University of Science and Technology in Shenzhen, China announced details of an experiment permanently altering the DNA of humans. Dr. He claims to have used CRISPR to create the world's first genetically edited babies: a set of twin girls, preventing these babies from contracting HIV. He has confirmed that there is a third potential CRISPR baby on the way.

His work, which was announced in November 2018, has not been verified as of the writing of this report.

The news of the first gene-edited babies was met with international condemnation, including the criticism of Dr. Jennifer Doudna, co-creator of the CRISPR/Cas 9 platform. In fact, Dr. Doudna issued a statement reminding the public that this work has yet to be peer-reviewed, without which the veracity of his claim cannot be evaluated. This work also strengthens the need to limit the use of gene-editing in human embryos to cases where there is no other viable option, as suggested by the National Academy of Sciences[46]. In addition to Dr. Doudna's statement, Dr. Francis Collins, Director of the National Institutes of Health, called the experiment a misadventure that crossed every line, scientifically and ethically[47].

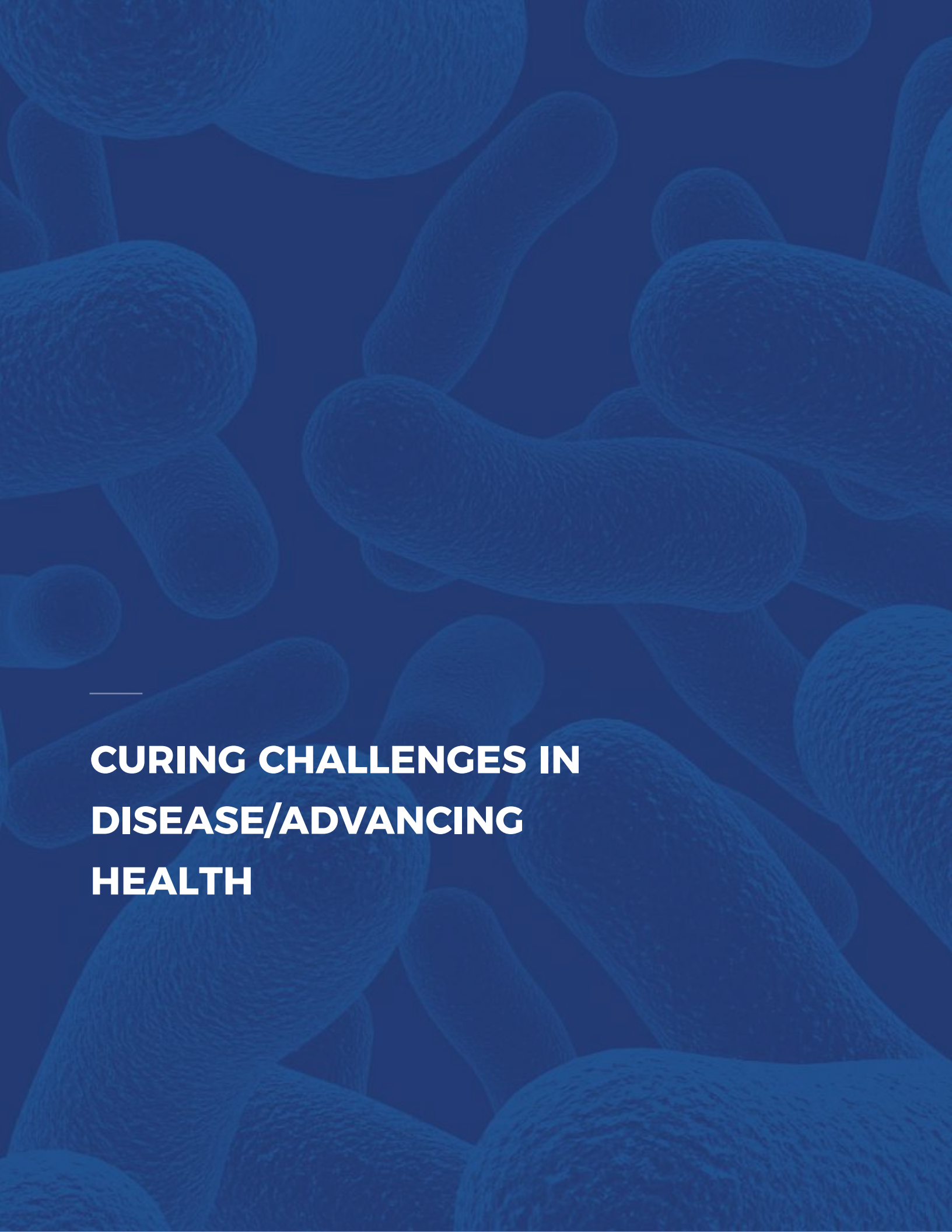
> *Dr. Francis Collins, Director of the National Institutes of Health, called the experiment a misadventure that crossed every line, scientifically and ethically.*

As of the writing of this report, Dr. He is under investigation over whether his experiment broke Chinese law or regulations[48].



*Recently the world was introduced to the first gene-edited babies*
***Image Source:*** *Genetic Literacy Project*

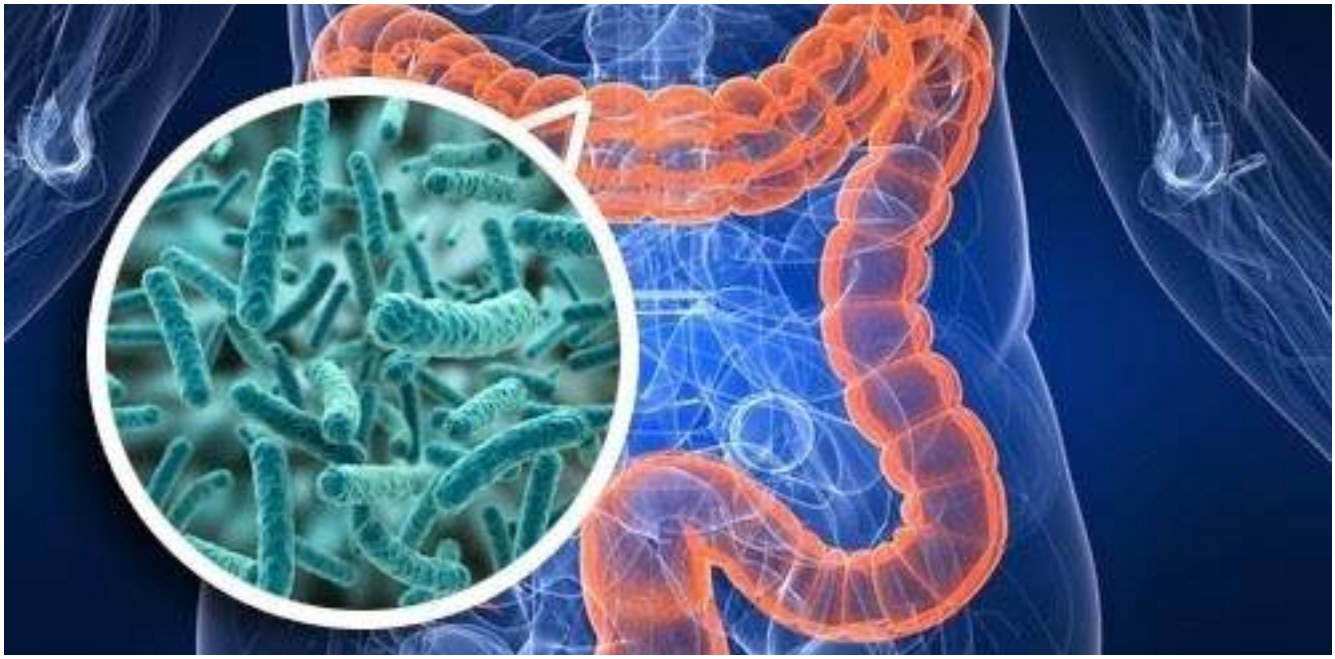
*46. CRISPR co-inventor responds to claim of first genetically edited babies*
*47. Collins responds to He Jiankui CRISPR baby study*
*48. The Chinese scientist who claims he made CRISPR babies is under investigation*



# CURING CHALLENGES IN DISEASE/ADVANCING HEALTH

# THE MICROBIOME: AN ANCIENT PARADIGM

The human microbiome is defined as the collection of bacteria, viruses, and single-cell eukaryotes that dwell in the human body[49] . The human microbiome has recently emerged as a crucial moderator in the different interactions between our body and food. It is increasingly shown that the microbiome can impact our health by influencing a range of diseases including cancer, obesity, and allergies[50]. Modern approaches to this field focus on encouraging the growth of "good bacteria" to prevent "bad bacteria" from establishing itself in the human body. Interestingly, the total number of genes in the microbiome exceeds the number of genes in the entire human genome and the microbiome accounts for up to five pounds of the adult body weight. The microbiome helps digestion, produces vitamins, regulates the immune system, and fights against disease causing bacteria. Current research demonstrates that our microorganisms and their genetic contributions control our health and lives as much as our genes[51]. This is shifting our view on how to target therapies, and the long-term morbidity that could be altered by the gut microbiome.



*The human microbiome has recently emerged as a crucial moderator in the different interactions between our body and food.*
***Image Source:*** *The Development of the Gut Microbiome.*

*49. Baylor College of Medicine, The Human Microbiome*
*50. Frontiers in Genetics, Microbiome Research Is Becoming the Key to Better Understanding Health and Nutrition*
*51. Knect365, Is The Future of Microbiome Research Already Here?*

With new techniques and more access to diagnostic tools, interest in understanding the microbiome is growing exponentially. The Human Microbiome Market is set to be worth $3.2 billion USD by 2024[52]. The composition of the microbiome and its effect on human health and vulnerability to disease hasn't been easy to investigate. Thus far, only a small percentage of the organisms that make up the human microbiome have been identified and of those, even fewer have been studied. Until now, isolating most microbes hasn't been feasible. New technological advances such as multi-omics approaches (which includes metagenomics and metabolomics) have now made it feasible to analyze the entire human microbiome. As of this writing, there are almost 1200 registered clinical trials that are testing whether these microorganisms can help treat diseases, and general research in the field has grown exponentially[53]. The field now has a substantial body of microbiome research focused on different pathologies, such as inflammatory bowel disease. New directions in the field include: reproductive biology, bone health, disorders of the central nervous systems, and antibiotic microbial perturbations[54].


*uBiome's SmartGut is a microbiome screening test that identifies pathogens from your gut.*
***Image Source:*** *uBiome.*

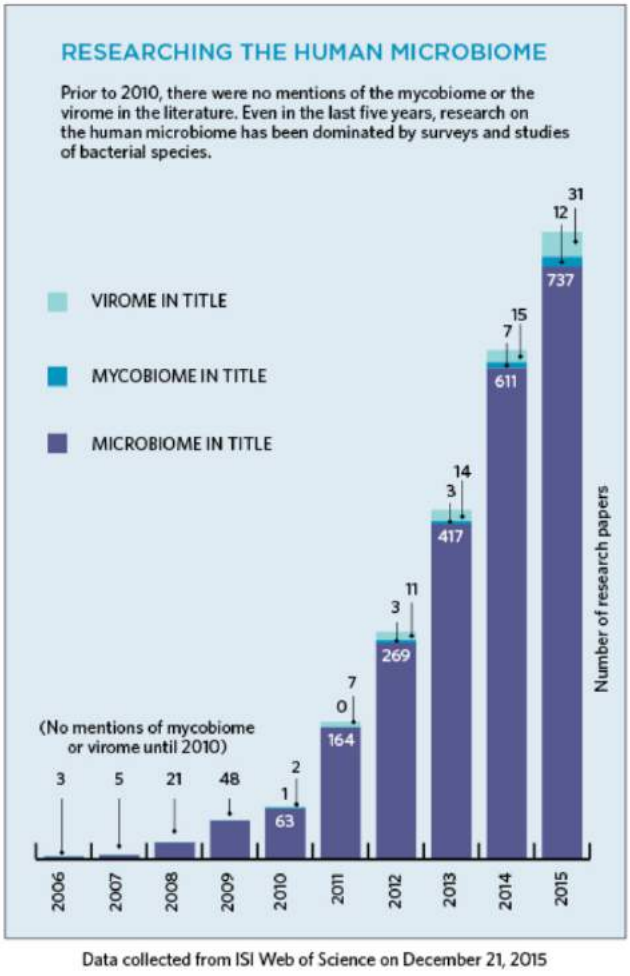
## CAN WE UNDERSTAND OUR PERSONAL MICROBIOMES?

Each individual microbiome is unique, a collection of trillions of microorganisms in and on your body that play a large role in our health and disease. These trillions of microorganisms carry out important work – work that our bodies cannot do on their own. Maintaining a balanced microbiome is essential to maintaining good health. So, how do we do that? By sequencing the DNA of our gut microbes we can identify key pathogens associated with our diet and lifestyle choices that lead to gut conditions, including diseases like Crohn's Disease. With the information provided by sequencing, physicians can gain a better understanding of an individual's

> *Each individual microbiome is unique, a collection of trillions of microorganisms in and on your body that play a large role in our health and disease.*

*52. Transparency Market Research, Human Microbiome Market to be Worth US$3.2 Billion by 2024*
*53. Clinical Trials, Microbiome*
*54. Future Microbiology, The microbiome: current and future view of an ancient paradigm*

steps to rebalance the microbiome to improve overall health. Companies like uBiome are helping scientists better understand the microbiome. uBiome uses machine learning, artificial intelligence, advanced statistical techniques, and sequencing to analyze microbes in a patient's sample. They can even help you track your microbiome over time. uBiome has three products: SmartGut, SmartJane, and Explorer. SmartGut was developed as the world's first sequencing-based clinical microbiome test that provides healthcare providers with actionable insights, and uBiome offers patient's the ability to monitor their personal microbiome. The Explore kits give patients access to tools that help them learn more about their personal microbiome; allowing citizen scientists to develop and execute their own independent easy to use sampling kits in conjunction with the world's largest microbiome database.



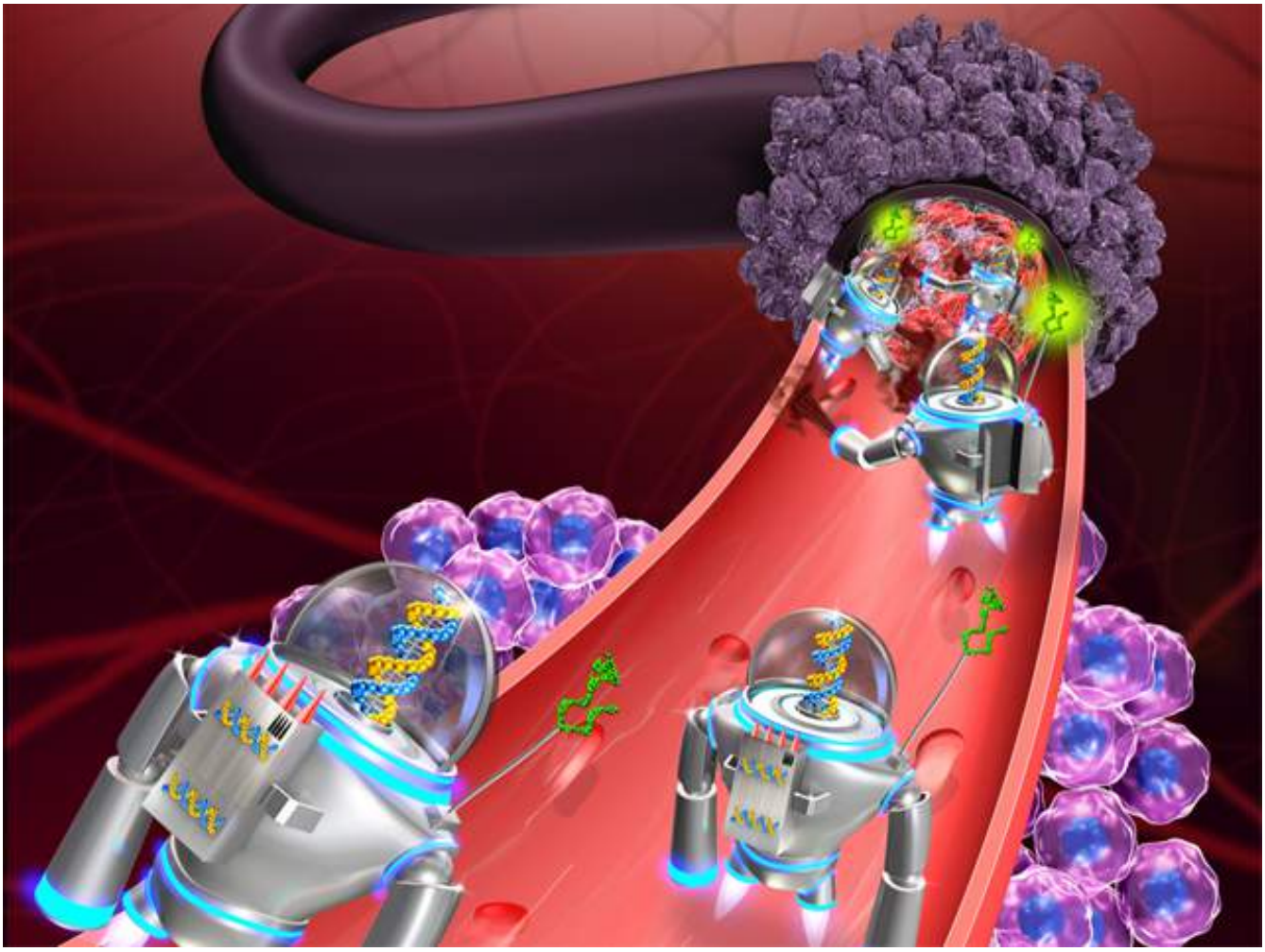

*Studies into the microbiome increased between 2006 to 2015.*
***Image Source:*** *The Scientist*

## CAN WE CREATE CUSTOM MICROBES?

One question that can be asked of next-generation industrial biotech platforms and microbial engineering is, where would we be without organisms? It may not be obvious, but the direction of the research is to create methodology for the development of highly optimized custom microorganisms. Companies such as Ginkgo Bioworks, is leading the way in building organisms and programming genomes. Ginkgo Bioworks, creates custom microbes across multiple markets. They build their factories using microbe engineering through software and hardware automation. Ginkgo's goal is to learn from nature to develop new organisms that replace technology with biology. According to Ginkgo, "in biological engineering, living organisms are the factories that build new products."

## NANO-SCALE THERAPIES: ARE THEY THE FUTURE?

Nanoparticles offer advantages for drug delivery due to their unique physical properties such as; particle size, which influences the circulation time and bioavailability of the drug; larger surface area, which augments the solubility of the drug; tunable surface charge of the particle and possible encapsulation; and the accommodation of a large drug payload[55]. These characteristics make nanoparticle-based drug delivery systems ideal contenders to advance therapeutic effects.



*DNA robots target cancer.*
***Image Source:*** *The Scientist*

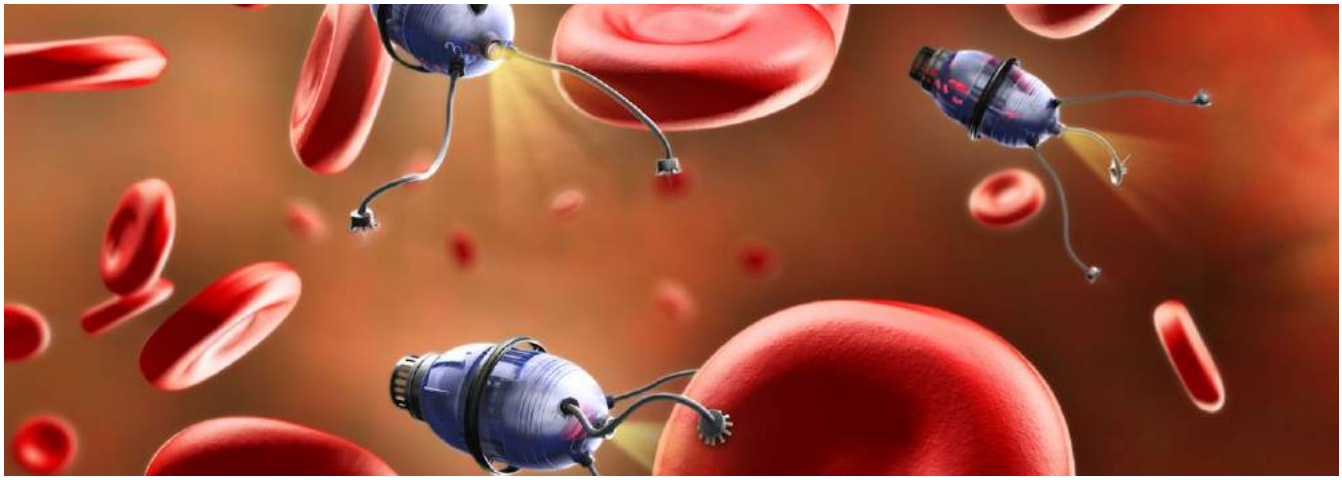
*55. Therapeutic Advances in Infectious Disease, The role of nanotechnology in the treatment of viral infections*

> *Nanoscale robots were successfully programmed to shrink tumors in mice.*

Nanorobotics is the creation of machines and robots at or close to the scale of a nanometer[56]. Essentially, this refers to the manipulation and control of materials from 1 to 100 nanometers, much smaller than a cell. There are many different kinds of nanorobots. To name a few: sperm-inspired microrobots has been developed, that can be controlled through oscillating weak magnetic fields which will be used in targeted therapy tasks[57]; or DNA nanorobots whose key application is to deliver targeted drug therapies to identify and destroy disease.

## MAY NANOBOTS BECOME AN EFFECTIVE TOOL IN THE FIGHT AGAINST CANCER?

Nanoscale robots have the potential to disrupt the drug delivery market by serving as intelligent delivery systems that respond to molecular triggers[58,59]. Using DNA origami, Suping Li of the University of Chinese Academy of Sciences and his colleagues, were able to construct autonomous DNA robots that could be programmed to deliver treatments directly to tumors. These nanoscale robots were successfully programmed to shrink tumors in mice. With this strategy, physicians could target many types of cancer, since all solid tumor-feeding blood vessels are basically the same. The global market for nanobots is expected to reach $100 billion by 2023 with a CAGR of approximately 21%[60].



*Robot armies attack disease.*
***Image Source:*** *Factor*

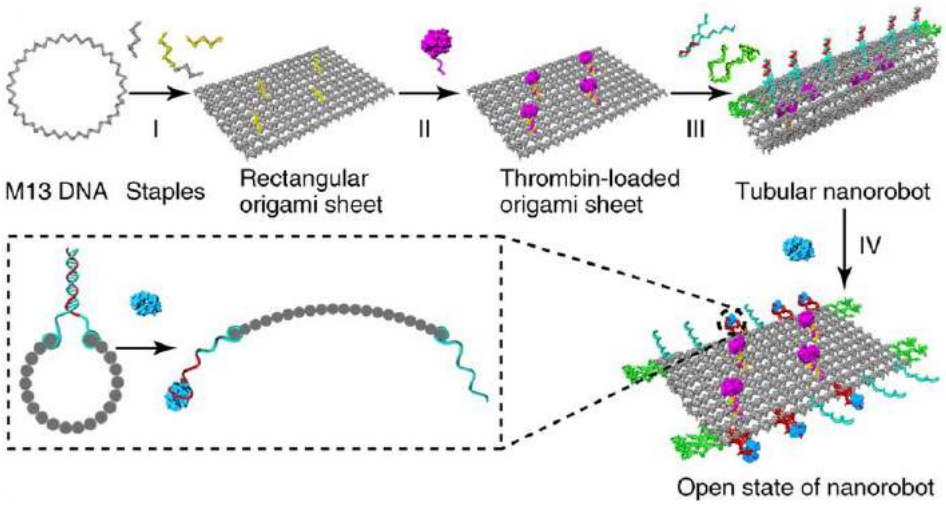

56. *Wikipedia - Nanorobotics*
57. *Applied Physics Letters, MagnetoSperm: A microrobot that navigates using weak magnetic fields*
58. *Nature, A DNA nanorobot functions as a cancer therapeutic in response to a molecular trigger in vivo*
59. *Nature, DNA in a material world*
60. *Market Research Future, Nanobots Market Research Report- Global Forecast To 2023*

## ARE THERE OTHER KINDS OF NANOMEDICINES?

Considered powerful, nanomedicine can improve the efficiency of antiviral drugs, including those problems often associated with issues of solubility and bioavailability[61]. As a result, many of these drugs require high doses and recurrent administration. Therefore, the development of novel treatment strategies is essential. The interaction between nanostructures and microorganisms is quickly disrupting the medical field. According to experts, the activity of antiviral drugs could improve nanomedicine formulations. Additionally, the physicochemical properties of these nanobots can enable their capability to affect specific targets within the viral structure.

Companies like Nanoviricide, Inc., a development stage company, are developing nano-technology based biomimetic anti-viral medicines. Nanoviricides, as the name suggests, are antiviral agents designed to trick a virus into attaching to it in the same way it would to its receptor on a cell.

Once the virus attaches, the nanoviricide wraps itself around the virus to trap it. During this encapsulation, the virus could lose the proteins needed to bind to the cell, leaving the virus effectually destroyed. The nanoviricide is designed to disassemble the viral particle circumventing the need for the immune system to intercede. Viral particles have evolved in such a way to upset the immune response, thus technologies such as these nanomedicines are needed to outwit and thwart the viral particles' plan of defense.




*Design and characterization of thrombin-functionalized DNA nanorobot.*
***Image Source:*** *A DNA nanorobot functions as a cancer therapeutic in response to a molecular trigger in vivo.*

*61. Expert Opinion on Drug Delivery, Nanomedicine formulations for the delivery of antiviral drugs: a promising solution for the treatment of viral infections*

# PERSONALIZED MEDICINE THROUGH MULTIOMICS

The use of biotechnology in medicine aims to help ensure that patients are diagnosed and treated with therapies best suited to their own genetics, conditions, and other health characteristics – in other words, moving in the direction of personalized medicine. The use of biotechnology has offered diagnostic test kits, vaccines, and radio-labeled biological therapeutics to focus directly on the patient and improve human health. Personalized medicine focuses on a medical model that separates patients into different groups, with medical decisions, interventions, and/or practices tailored toward to the individual based on a predicted response[62]. This has spawned some new and innovative therapeutic endeavors.

> *The integration of multiple-omics technologies will allow researchers to gain a more complete picture of the elements involved in disease, and through a better understanding of disease mechanisms and identifying informative markers for disease progression.*

To this end, the integration of multiple-omics technologies will allow researchers to gain a more complete picture of the elements involved in disease, and through a better understanding of disease mechanisms and identifying informative markers for disease progression, provide better treatments for patients and more adequate drugs[63]. These multiomic approaches are starting to play a critical role in complex disease research, more specifically, in cancer research[64].

## WHAT IS MULTIOMICS?

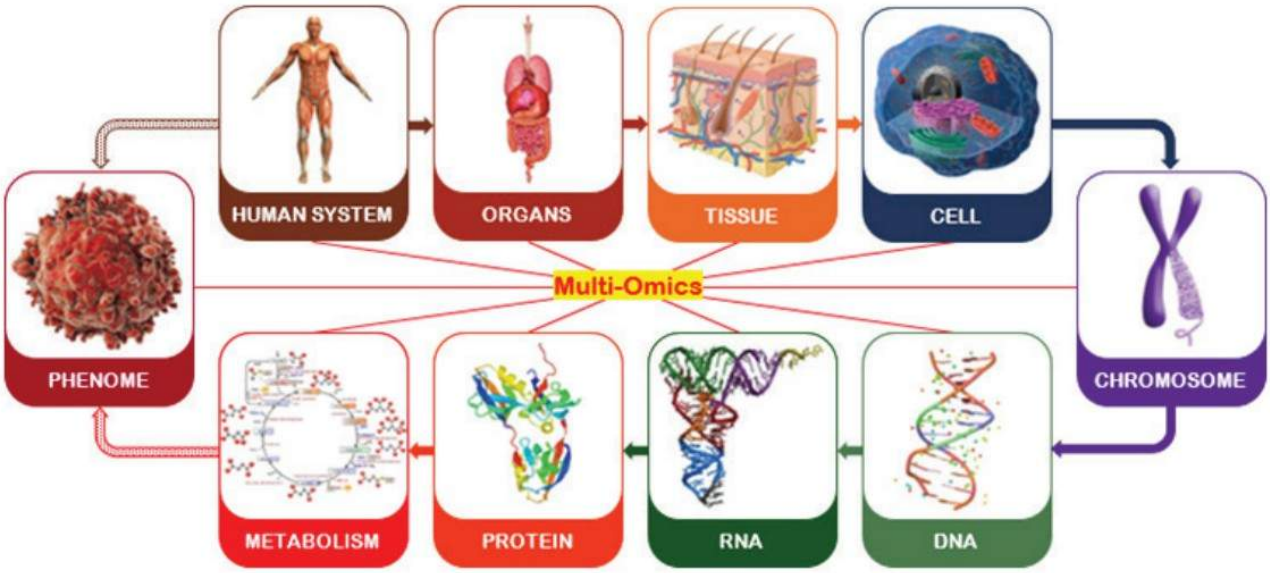
Multiomics represents the biological analysis approach using datasets that are multiple "omes", such as the genome, proteome, transcriptome, epigenome, and microbiome[65]. It's the use of multiple omics technologies, used in conjunction, that will allow us to study life in a concerted way. Technological developments are facilitating larger studies that can rapidly deliver huge quantities of data. Multi-omics approaches will enable scientists to address central biological questions. By combining the different "omics" techniques we are now able to get a complete picture of what is happening in the human body and by extension diseases, while understanding

62. *Wikipedia, Personalized Medicine*
63. *Genome Biology, Multi-omics approaches to disease*
64. *EMPA Journal, The crucial role of multiomic approach in cancer research and clinically relevant outcomes*
65. *Wikipedia, Multiomics*

the functional processes occurring in a system. This emerging field combining different types of "omics" datasets to dissect complex mechanisms of disease is becoming more popular and powerful in precision medicine. However, it faces some headwinds due to a lack of efficient and appropriate ways to integrate the different types of data sets. Collecting and integrating information from these multiple "omes" will ultimately give us a better understanding of complex diseases like cancer.

## WHY IS THIS APPROACH SO IMPORTANT?

The approach of using single omics provides information about the biological processes active among a particular disease group, providing a perspective of the different molecules that make up a cell (or tissue, or organism)[66]. The issue here is that these analyses are limited to a single level of omics data, such as genomic data. These analyses are often limited and may end up identifying differences that are consequential rather than causative. Integrating these "levels" helps generate a view that scientists refer to as a multiomics approach. Using the multiomics approach provides more concrete data for specific biological mechanisms and phenomena, since this approach uses information obtained independently from several omics levels (i.e., proteomics, genomics, or metabolomics)[67].

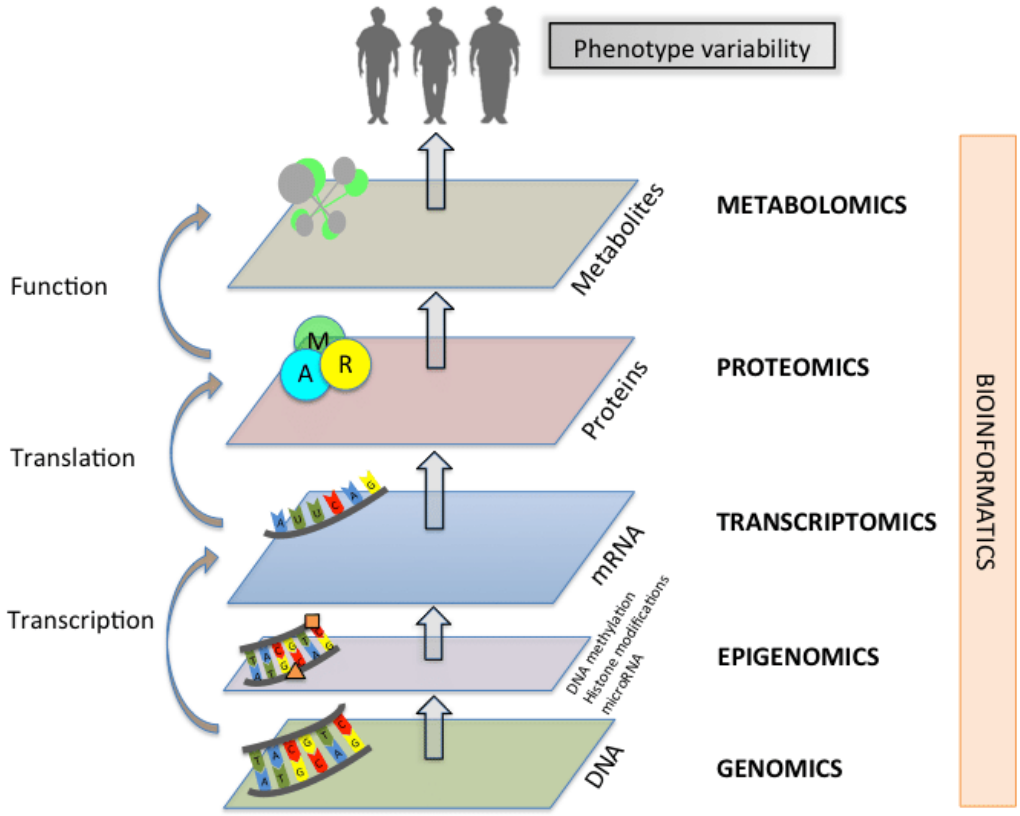



*The power of multi-omics*
***Image Source:*** *Prediction of Potential Lead Molecules through Systematic Integration of Multi-omics Datasets - A Mini-Review.*

66. *Genome Biology, Multi-omics approaches to disease*
67. *Melgen,Multi-Omics: a Revolutionary Approach to Data Analysis*

## ARE THERE DATABASES TO HELP WITH THESE ANALYSES?

The recent advances in the field of omics have created multiple research opportunities, but the current software and database resources are disjointed. Introduce, OMICtools, a manually curated metadatabase that offers an outline of more than 4000 web-accessible tools related to the different omics technologies, accompanied by information and published assessments of tool performance[68]. Data about each tool is curated through the datasets of a diverse set of developers. The combination of studying these "omes" together allows scientists to analyze complex biological data efficiently to find key biomarkers.




*An illustration depicting the perspective data integration through the multi-omics approach.*
***Image Source:*** *The contribution of genetics and environment to obesity*

*68. Database, OMICtools: an informative directory for multi-omic data analysis*

# SPOTLIGHT ON CRISPR

## SPOTLIGHT ON CRISPR

Dr. Trevor Martin
*CEO of Mammoth Biosciences*

Reading through the resume of Dr. Trevor Martin, CEO of Mammoth Biosciences, is no small feat. Educated at top American universities, Dr. Martin is the CEO and co-founder of Mammoth Biosciences. While the medical sciences were advancing, diagnostic tools were not. With an interest in democratizing access to diagnostic tools and Dr. Martin's interest ignited, Mammoth Biosciences was born.

Mammoth Biosciences' mission, as mentioned above, is to democratize access to an endless variety of tests for bio-sensing in healthcare (and other industries) using a CRISPR-based platform on which an unlimited number of tests can be built. To learn more about this interesting venture, we interviewed Dr. Martin to learn more about the direction this disruptive technology is going.

> *By rapidly building and deploying highly accurate and accessible diagnostic tools, our ability to track and control epidemic outbreaks, for example, stands to be improved immensely.*

***Q: How will CRISPR (and other gene-editing platforms) solve difficult health problems?***

**A:** There are a variety of ways that researchers and businesses are seeking to influence the prevention and treatment of diseases and disorders through CRISPR therapeutics.

...We believe the most promising and immediately achievable application of CRISPR technology is in diagnostics. By rapidly building and deploying highly accurate and accessible diagnostic tools, our ability to track and control epidemic outbreaks, for example, stands to be improved immensely.

***Q: How far are we from eradicating disease?***

**A:** New diseases are appearing and evolving all the time; so while there's a long ways to go before we can say we've eliminated the threat of disease entirely, there are steps we can take today to significantly

improve the way we address and manage the spread of disease at scale; the first step -- identify the disease.

***Q: What are some of the challenges facing the field?***

A: Right now, the diagnostics space is struggling to find a system that has the specificity and sensitivity of lab based molecular testing and the low cost, speed, and accessibility of existing over-the-counter testing. We believe CRISPR can offer the best of both worlds.

***Q: What is the current state of the CRISPR industry and whether there is room to attract more customers, introduce new products, sell products or achieve company growth?***

A: We will begin marketing our CRISPR-based platform to both hospitals and consumers alike in the coming years, all the while making sure that the general public is informed about how we use CRISPR and how CRISPR diagnostics in particular works. Excitingly, this field is relatively unexplored, and I think new and novel use cases of CRISPR systems outside of gene editing will continue to be developed.

> *A core value we have as a company is communication and transparency and I think this is a critical value for any CRISPR company or individual leveraging this technology to have.*

***Q: What are your thoughts on the recent paper identifying people with a pre-existing immunity to CRISPR?***

A: CRISPR immunity is an exciting emerging field but there is definitely a lot more work to be done before definitive conclusions can be drawn.

***Q: What are your thoughts on the ethical implications of using gene editing in humans? And what are the future directions it will take?***

A: While CRISPR is perhaps most famous in the therapeutics space, our focus at Mammoth is on diagnostics at this time - applying this powerful tool outside of the body. I can only speak to what is in the foreseeable pipeline for Mammoth. More broadly, a core value we have as a company is communication and transparency and I think this is a critical value for any CRISPR company or individual leveraging this technology to have.  Where are the marketing opportunities for a field like CRISPR?

***Q: What are your thoughts related to claims that the world's first genetically edited babies have been born?***

A: I believe the scientific community is generally in agreement that there is more research to be done and ethical discussions to be had before germline editing of humans should be undertaken. Critically, there is a clear lack of transparency and communication in the work that led to these claims.

***Q: How are the public and government perceiving these technologies?***

A: I think despite the relatively large amounts of press CRISPR has received, most of the public still doesn't understand what CRISPR can do to improve our healthcare system. We are excited to help educate the public on the potential of CRISPR and make sure the science behind it is accessible and easily understood.

***Q: What are the regulatory hurdles for these technologies?***

A: For diagnostic technologies the regulatory hurdles can vary depending on the target disease and format of the test. At Mammoth we're eager to embrace the regulatory process and see it less as hurdles for the technology and more as opportunities to demonstrate the effectiveness of our system.

***Q: What can you tell us about yourself and how you founded Mammoth Biosciences?***

A: I started my career studying biology at Princeton, where I performed research in molecular research for the Storey Lab and conducted independent research in quantitative biology.

After Princeton, I went on to complete my Ph.D. in Biology at Stanford University, where I worked at the intersection of statistics and genetics. At the time, there were major advances in being made in areas like artificial intelligence and therapeutic development, but not as much core innovation in diagnostics. I decided I wanted to focus on democratizing access to powerful diagnostic tools and the important molecular information they provide that can help people live healthier lives. While at Stanford, I met future Mammoth co-founder Ashley Tehranchi, who shared in my vision. Shortly after, we came across Jennifer Doudna, the CRISPR co-inventor, whose lab invented the diagnostic use of Cas13 at UC Berkeley and we were quickly convinced that CRISPR systems were the right technology for us to achieve our goal of democratizing access to powerful diagnostics. So Jennifer and her star graduate students Janice Chen and Lucas Harrington joined us as co-founders.

> *We were quickly convinced that CRISPR systems were the right technology for us to achieve our goal of democratizing access to powerful diagnostics.*

As part of this expanded team we took our vision a step further and founded Mammoth Biosciences with the goal of democratizing disease detection and enabling individuals to better understand their health with the world's first CRISPR-based platform capable of detecting any biomarker or disease containing DNA or RNA.

***Q: There are several CRISPR companies on the market. How is Mammoth Biosciences different from the company?***

A: The majority of companies pursuing CRISPR-based products or services today are focused on therapeutics; editing the genome to generate favorable genetic traits or alleviate disease phenotypes. While we're primarily focused on the healthcare space at this time, we believe the most viable path to applying CRISPR technology to immediately improve lives is through diagnostics. For this reason, we're creating a CRISPR-based platform that serves as a search engine for biology, which can detect and identify any DNA- or RNA-based disease, from common infections to STDs and even cancer.

Furthermore, our platform-based approach can accommodate an unlimited number of tests, both within healthcare and also across industries such as agriculture, oil and gas, and forensics.

***Q: How will your work impact the field? And what is your hope for the field?***

A: Mammoth's platform stands to fundamentally change the way the medical community and consumers interact with the $45 billion global disease detection market, by bringing the power of versatile DNA/RNA testing to the point-of-care in a scalable and universal platform.

> *A core value we have as a company is communication and transparency and I think this is a critical value for any CRISPR company or individual leveraging this technology to have.*

For consumers, this could mean no more doctors visits to check your child for strep before he or she gets on the school bus in the morning; no more waiting at the ER for bronchitis results, and no more disparity between people who can and can't afford checkups at the clinic. With these kinds of tests, our hope is to bring affordable testing to the masses; in effect, people will gain access to knowledge about their own health and ultimately take back control over this costly part of the healthcare system.

Beyond having a personal impact, Mammoth has the potential to change how hospitals and clinics work all around the world. Especially in the developing world, doctors have limited access to advanced medical equipment, as it's often expensive and cumbersome to transport. Contrarily, Mammoth's test won't

require refrigeration or complex instrumentation so doctors can go straight to the point-of-care and diagnose in real-time. This is essential during massive disease outbreaks, like Ebola, where the disease is highly contagious, transmits rapidly before symptoms show, and takes up to 3 days to diagnose in a lab setting. Ultimately, the faster and more accurate the diagnosis, the faster and more effective the treatment response will be, and the closer we are to a healthier world.

***Q: What is the future of biotech and more specifically CRISPR? Where do you see the field going in the next 5-10 years?***

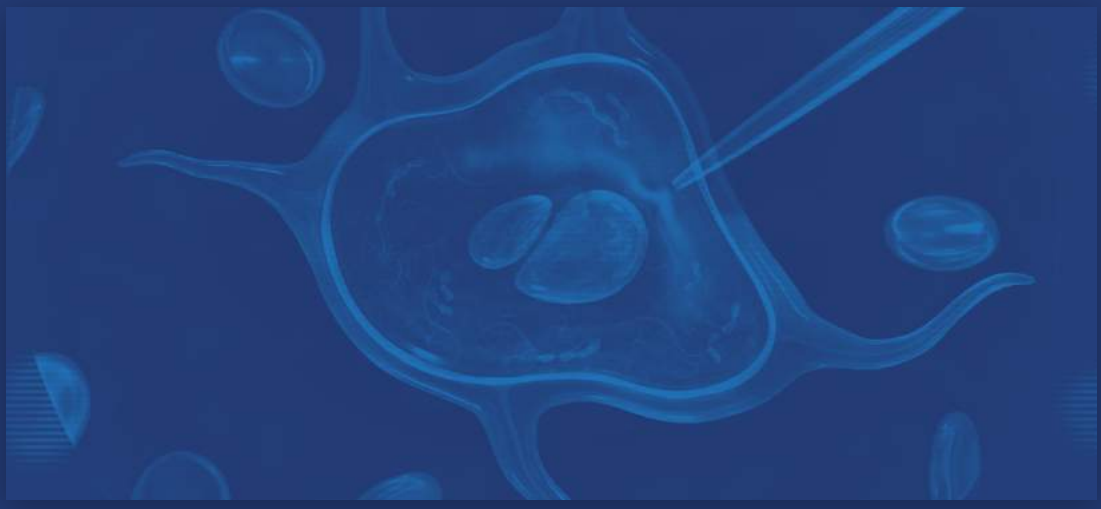
A: Over the next 5-10 years I see CRISPR systems becoming the platform for a wide variety of applications beyond gene editing - anytime a nucleic acid sequence needs to be identified quickly and reliably (e.g. for diagnostics or for turning genes on or off without editing the genome itself) CRISPR can serve as a robust and powerful tool.

*For more information on this company and the CRISPR platform, check out Mammoth Biosciences.*

# LOOKING AHEAD

While still a relatively new field, biotechnology has made progress since its rise in the 1970s. As showcased in this report, much of that progress is the result of advances in diagnosing, curing , and even preventing disease. In this report, we addressed specific emerging and advancing technologies: gene therapies, stem cell treatment, nanomedicine, new treatment delivery systems, data analysis and integration, and of course the delivery systems used.

With the advent of these technologies, the practice of medicine has changed intensely over the years, as it will continue to change. Millions of patients worldwide have benefited from these innovative advancements in therapeutics, for example, look at how synthetic insulin changed the game for diabetes. As companies continue to address unmet medical needs, future advancements in biotechnology research will bring electrifying novel developments to people around the world.



# ABOUT THE AUTHOR


**VIDHYA SIVAKUMARAN, PHD**

*PreScouter*


## PROFESSIONAL SUMMARY:

Vidhya completed her PhD in Biochemistry with a specialization in cardiac membrane biophysics from Virginia Polytechnic Institute and State University. After earning her PhD, Vidhya completed a 3-year cardiology fellowship at The Johns Hopkins Medical Institutions focusing on research in the field of cardiac physiology and heart failure. Vidhya continued her passion for research at Loyola University in Chicago, before exiting academia for a career in industry.

## RESEARCH BACKGROUND:

The focus of Vidhya's research in graduate school was the molecular mechanism of calcium transport in the heart. Vidhya shifted her focus to heart failure and oxidative stress during her fellowship and then back to focusing on structural changes that take place in calcium handling proteins during her last postdoc. Vidhya has expertise in using biochemical and molecular biology techniques, electron paramagnetic resonance spectroscopy, and fluorescence microscopy.

## SCIENTIFIC INTERESTS:

Biotechnology, Life Science Consulting, Scientific Communication, Market Research Analysis, Business Development, and Leadership.

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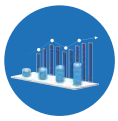
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