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A Virtual Think Tank Executive Summary

Gene Editing: Clearing Roadblocks to a New Class of Therapeutics

By: Christi Bird, *Principal Consultant, Transformational Health,* Frost & Sullivan

Frost & Sullivan recently invited academic and industry leaders in gene editing to participate in a new and unique thought leadership forum, our Virtual Think Tank series. This forum brought together leading minds in this emerging field to discuss the current state of gene editing, the implications of research and development occurring today, key challenges, and expectations for future applications of gene editing in the clinical space.

Key opinion leaders who contributed to the discussion include:

- **Chengzu Long, Ph.D.,** *Assistant Professor*, New York University School of Medicine
- **Fyodor Urnov, Ph.D.,** *Associate Director,* Altius Institute for Biomedical Sciences
- **YannJouvenot, Ph.D.,** *Senior Manager,* Gene Expression at Bio-Rad Laboratories
- **Kristian Laursen, Ph.D.,** *Instructor, Molecular Genetics,* Cornell University
- **Max Mamonkin, Ph.D.,** *Instructor, Pathology & Immunology Center for Cell and Gene Therapy,* Baylor College of Medicine
- **Adam Hoppe, Ph.D.,** *Associate Professor,* Department of Chemistry and Biochemistry, South Dakota State University

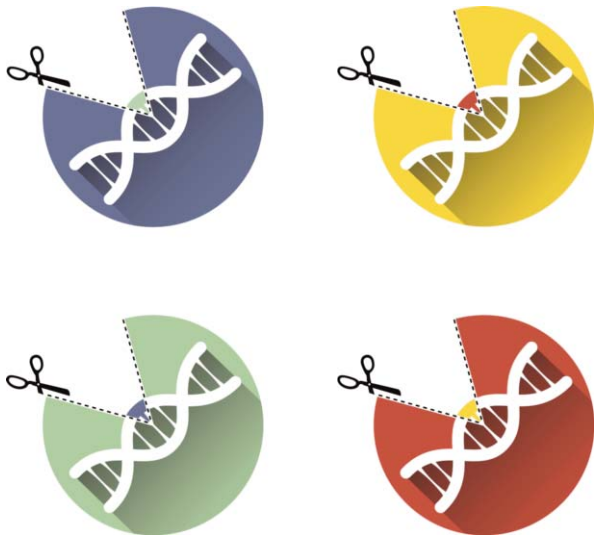
Gene Editing: Clearing Roadblocks to a New Class of Therapeutics

Gene editing allows researchers to alter an organism's phenotype. A phenotype is simply defined as the set of observable characteristics of an individual resulting from the interaction of its genotype with the environment. Using tools such as zinc finger nucleases (ZFNs), TALENs, and CRISPR-Cas9, nucleotides can be added, deleted, or altered at genetic loci of interest, such as those associated with disease.

Thousands of diseases have an underlying genetic basis. Some result from a single gene mutation (i.e., cystic fibrosis, sickle cell disease, hemophilia), while others are more complex. Many of the existing drugs and therapeutic regimens for these diseases primarily treat symptoms or target the disease along its progression. Gene editing techniques enable new approaches to treat disease, in most cases, at the genetic source. In theory, gene editing can target the genetic source of the disease and eliminate it completely from the patient's genome. Researchers are also developing *ex vivo* gene editing techniques that can modify a patient's extracted stem or progenitor cells using CRISPR/Cas9 for subsequent transplantation back into the patient. Thus, genome editing can contribute significantly to various genetic diseases and in some cases offer a cure, or at the very least an effective treatment.

Gene editing can also be used to target non-genetic diseases. One such approach involves enhancing the body's ability to fight diseases. Researchers continue to develop new techniques and spur the development of new technologies to utilize the full potential of gene editing.

Regardless of the methodology taken, gene editing techniques are making global headlines as new discoveries are finally translating into clinical trials. This makes now the right time to bring together thought leaders to talk about gene editing, its progress, its challenges, and how we expect the field to progress.



MAJOR PROGRESS IN GENE EDITING

The experts who joined Frost & Sullivan's Virtual Think Tank on Gene Editing are studying diseases such as Duchenne muscular dystrophy, spinal muscular atrophy, HIV, sickle cell diseases, and kidney cancer. While the field continues to make discoveries attributed to gene editing techniques across various diseases, a few targets have entered clinical trials, and most importantly, some of the first gene editing therapies are being used to treat patients. Dr. Adam Hoppe, *M.D., Associate Professor* at South Dakota State University, outlined that the largest strides have been made in inmonogenic diseases of the blood where there is a clear path forward with sickle cell disease. Also promising are approaches where genetic modification of the liver can take the place of current enzyme replacement therapies.

During his tenure at Sangamo Therapeutics, our panelist Fyodor Urnov, now *Associate Director* at Altius Institute for Biomedical Sciences, coined the term "gene editing" in 2005 with colleagues Philip Gregory, Michael Holmes, and Edward Rebar. His team at Sangamo was the first to move a gene editing therapy to a clinical trial in 2009 with a zinc-finger nuclease (ZFN)-based therapeutic, SB-728-T for HIV. Most recently, Urnov led research on the BCL11A erythroid enhancer as a potential treatment for hemoglobinopathies, such as β-thalassemia and sickle cell disease. These indications are now in preclinical testing as collaborations between Sangamo and Bioverativ (recently acquired by Sanofi). Vertex Pharmaceuticals and CRISPR Therapeutics have their own co-developed gene editing therapy forβ-thalassemia and sickle cell disease, CTX001, expected to enter Phase 1/2 clinical trials in Europe and the US in 2018. Should any of these treatments be found to be safe and effective, within the next decade patients with β-thalassemia or sickle cell disease can anticipate a therapy that will substantially improve their quality of life.

Sangamo Therapeutics also announced in November 2017 that it had treated the first patient with an *in vivo* zinc finger nuclease (ZFN) gene editing therapy, SB-913, in its seminal Phase 1/2 clinical trial for mucopolysaccharidosis type II (MPS II), or Hunter syndrome. Even with regular weekly enzyme replacement therapy (ERT), the current treatment method, many patients with MPS II die before the age of 20 from complications of the disease. Sangamo is using gene editing to introduce a corrective gene into the DNA of liver cells of patients with MPS II that enables the liver to produce the enzymes made deficient by the disease. In two additional clinical trials, the company is targeting hemophilia B and MPS I with similar therapies that restore the function of enzymes involved in those diseases. Should these therapies be commercialized, not only will they offer cures for these diseases, but they may reduce healthcare costs over the life of patients given the elimination of weekly ERT infusions.

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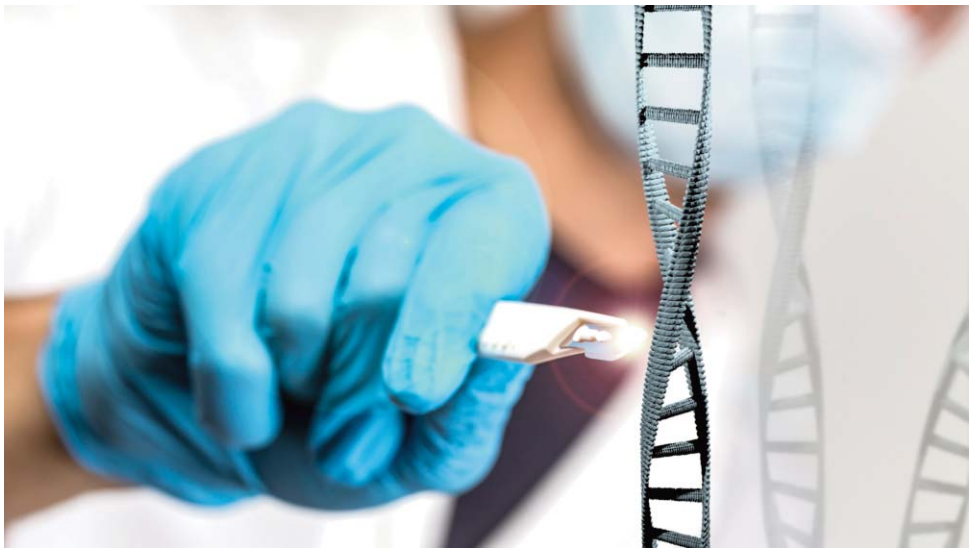
Another promising gene editing approach Dr. Hoppe and the panel discussed was what he termed the"weaponization of chimeric antigen receptor T (CAR-T) cells," cells that already exist in the patient's body. In fact, in August 2017, the Food and Drug Administration (FDA) approved the first gene therapy in the U.S., a drug called Kymriah from Novartis, for B cell acute lymphoblastic leukemia (ALL). This CAR-T cell therapy removes T cells from the patient's blood and introduces a gene that expresses the chimeric antigen receptor (CAR) protein that directs T cells to target and destroy leukemia cells once re-infused. While the therapy carries a hefty $475,000 price tag, Novartis has instituted an outcome-based pricing model, meaning the company will only receive payment if a patient responds to treatment within the first month of usage. Meanwhile, Cellectis is developing its own gene edited off-the shelf CAR-T cells, which the company claims will dramatically reduce costs of this type of immunotherapy. Instead of using the patient's own T cells, this therapy will utilize CAR-T cells manufactured on a large scale to bring down costs.

These examples are just a few of the key gene editing initiatives in advanced stages that may offer diseased patients a cure, or at the very least, improve their quality of life in the near future. Should several gene editing treatments successfully advance through clinical trials and FDA approval, these outcomes will bring even greater attention and investment to the field.

ISSUES IN COSTS AND ACCESSIBILITY

While the industry, physicians, and patients have anxiously anticipated the first gene editing treatments, issues of costs and accessibility remain top concerns. While treatment cost may appear steep at first glance, many expect the one-time cost for gene editing therapies to pale in comparison to current lifetime treatment cost estimations. If a gene therapy works, the payer trades a lifetime of conventional treatments, plus their complications, for a single one-time cost. Chengzu Long, *Assistant Professor* at New York University School of Medicine said, for gene therapy, "the cost is hundreds of thousands in general, but for these patients, if you want to really take care of them for a lifetime, that is also going to be quite expensive." This becomes even more glaring when the gene editing therapy is used as the first line of defense, or treats a disease that strikes early in life. Kristian Laursen, *Ph.D., Instructor, Molecular Genetics* at Cornell University, added, "For terminal cases of cancer, there's really no choice. Those patients don't really have any options. As these therapies become more widespread, the pricing will be less elevated. They might move to the frontline therapies and then a lot of these questions [around cost] will disappear." This is true of gene editing therapies that target more prevalent diseases, as larger volumes and the necessity for greater efficiencies in manufacturing and delivery will bring costs down. In addition, the panel reasons that one cannot put a price on a saved life or better quality of life.



In terms of insurance coverage in the U.S., given the nascency of this class of therapies, debates still surround how these costs will be covered. Besides the outcome-based pricing model, the industry is actively discussing the possibility of price comparisons between the gene therapy and 10 years of the current treatment model. If the one-time cost is less than the 10 years of treatment of the chronic disease, then insurance would pay for it. Each proposed system is not without its concerns. What if a patient fails to return to the doctor to test for remission? What if the patient switches insurance companies? As more gene therapies reach the market and patients demand them, particularly when the therapy offers a cure, industry stakeholders (i.e. physicians, researchers, pharmaceutical companies, insurance companies, lawmakers, bioethicists, and patient advocacy groups) must come to the table to find solutions to allow for widespread access to the cure.

From a cost perspective, anidealgene therapy will be one that provides a cure in a one-time dose and actually reduces the lifetime patient healthcare costs related to the disease. If a pharmaceutical company can make that case, it becomes an unequivocal decision for patients to undergo such treatment and for insurance companies to provide coverage.

Ultimately, gene editing provides hope for millions of people suffering from diseases with insufficient or no treatment options.

THE CALL FOR MORE DISCOVERY RESEARCH AND NEW TOOLS

While major strides have been made in gene editing in a short period of time, basic discovery research will need to continue, particularly research focused on the long-term effects of gene editing. Dr. Hoppe expanded, "I believe for anything that manipulates the genome, there is a need to be able to ascertain that no off-target effects will occur and that is probably one question for anybody doing gene editing. That is one of the main concerns. We do have, I believe, a wide variety of tools that help us with this, especially with the development and expansion of next-generation sequencing." While researchers are certainly studying off-target effects of gene editing in the lab with a growing number of tools available to them, Dr. Hoppe suggests that continued monitoring of patients over lifetimes will better elucidate any unanticipated health impacts.

Dr. Hoppe added, "This calls into question the regulatory guidance on gene editing and what level of risk can be accepted for these therapies." For instance, what if a gene therapy cures an immunodeficiency which greatly increases quality of life for the patient, but long-term could cause a form of cancer linked to the therapy? Does the risk outweigh the benefit? Current regulatory guidance by the FDA classifies gene editing for therapeutic purposes under its existing framework for biological products handled by the FDA's Center for Biologics Evaluation and Research (CBER). In its official blog, the FDA states its awareness of the potential for off-target effects as a key industry concern. Questions like this highlight the need for continued discovery and clinical research to assess risks associated with gene therapyas well as the development of new tools to aid such research.

Continuing on the topic of new tools, Dr. Laursen spoke of the need for better delivery tools, particularly around CRISPR-based cancer therapies where all cancer cells need to be targeted to prevent relapse. Furthermore, the panel discussed the need for better tools and more structured standard operating procedures (SOPs) to improve clinical trial guidance, manufacturing practices, and long-term monitoring of efficacy. Thus, while the industry continues to make great strides using gene editing for therapeutic applications, and make major headlines along the way, there is a continued call for more discovery research and improved tools to feed pipelines, help solve issues of off-gene effects, and develop SOPs to navigate the FDA process.

THE FUTURE FOR GENE EDITING

Gene editing applications are already expanding rapidly as tools get cheaper and easier to use. Looking to the future, our panel touched on both the good and the bad that could stem from gene editing.

Certainly the more gene therapies move to the clinic, the more basic research is needed to feed the pipeline. Max Mamonkin, *Instructor* at the Pathology & Immunology Center for Cell and Gene Therapy at Baylor College of Medicine, commented, "As with any technology that's as revolutionary as gene editing, as it becomes more and more accessible to labs around the world, I'm sure there will be a lot of demand, as one can only imagine the countless applications of these technologies." Dr. Mamonkin continued, "This technology really allows us to build a cell that we need. It's kind of like Lego blocks. You can customize a cell for a particular application. You can remove genes. You can add genes and you can remove genes that potentially cause toxicity, case in point for CAR-Tcell. So you can customize the cells to switch off some genes that are responsible for cell rejection or add some safety switch."

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In this manner, the panel discussed the possible creation of modified cells with a custom set of genes created through gene editing that could be inserted into a patient to target their particular disease. After testing for safety and efficacy and going through the required approval process, these "custom" cells could then be utilized as an off-the-shelf therapy, like the Cellectis CAR-T cells. This means instead of deriving cells from a patient and performing gene editing on the cells before restoring them into that patient, the cells can be prepared in bulk like any other drug and provided to any patient. Dr. Mamonkin envisioned a cell incapable of malignant transformation and uncontrollable division that would deliver the required therapeutic effect and could be injected into the patient as needed. These off-the-shelf therapies manufactured in bulk would significantly bring down the cost of gene therapy compared to utilizing cells derived from each patient.

While our Virtual Think Tank panel provided many examples of success stories and the future promise expected from gene editing therapies, they cautioned that multiple negative cases, such as fatal outcomes of clinical trials or stories of unethical usage of the technology could derail the field. Yann Jouvenot, *Senior Manager,* Gene Expression at Bio-Rad Laboratories pointed to physical enhancements for competitive athletes as a likely alternate use of gene editing technology in the future. Dr. Chengzu mentioned muscle enhancements, or changing hair, eye, or even skin color as additional unethical uses of the technology that should be avoided. Dr. Hoppe summarized, "I think as the technology gets better and you can begin to apply it more readily to treat more and more diseases that the question becomes, where do you transition from treating a disease to providing an enhancement or competitive benefit, and I think that's where ethics questions come in."

While our experts felt it was not far-fetched to start thinking and talking about these possible unintended uses of gene editing, they also cautioned about over-regulation of a field in its infancy. Dr. Jouve not expanded, "We've started to actually draft a lot of regulations before a lot of the research has actually been done. So, while I do say let's keep an eye open and be mindful of what can happen, we also have to make sure that we don't start painting some super apocalyptic scenario that then starts hindering big actual progress of research."

CONCLUSION

Ultimately, gene editing provides hope for millions of people suffering from diseases with insufficient or no treatment options. The industry, patients, insurers, and policymakers will watch anxiously as more therapies navigate through clinical trials with the hope of moving this revolutionary technology from bench to bedside for patients that so desperately need better treatment options.

Gene editing technology and its applications are evolving at an unprecedented pace, and our attitude toward it is warming as well. As with many novel, scientific technologies, gene editing has its own set of challenges ranging from delivery, safety, and patient access to public opinion and future unintended applications. With continued collaboration between key stakeholders and careful, safe advancement of early gene editing therapies, potential roadblocks can be thwarted.

Frost & Sullivan would like to thank the gene editing thought leaders who joined our Virtual Think Tank for their time and valuable insights into this promising field. We hope that this discussion spurs new ideas and fosters additional exchanges in this burgeoning area.