Category

Best Startup

Product/Solution Name

Gene Writing™ technology / Tessera

Date of Approval

N/A

Indications

Tessera Therapeutics has not publicly declared initial indications.

Therapeutic Categories

Genetic medicine, genome engineering

Attached Files:

- Tessera_Cotta_2023_ASGCT_FINAL.pdf
- Tessera Presentation JPM 2023_vFinal.pdf

Background information and need for solution/product

The overwhelming majority of human health outcomes, from wellness to serious illness, are driven by underlying variability in our DNA, the code that serves as a unique blueprint to every living thing. The sequencing of the first human genome approximately twenty years ago illuminated the vast landscape of seemingly small errors that can have a monumental impact on health and disease. As a result of these errors, or mutations, millions of people suffer from a wide range of diseases worldwide, from cancer, rare genetic diseases, and common illnesses, many of which are without effective treatment options beyond symptom mitigation.

In the twenty years since, scientists have identified tens of thousands of genetic sequences that directly cause, predispose, or prevent disease. This understanding opens up the possibility of providing cures where none were possible before: the chance for patients to no longer be defined by their disease, or simply to not be patients at all. The ability to address the underlying genetic drivers of disease has been a long-standing goal of the biomedical research community. Despite many attempts, the field has been faced with two key limitations: effective tissue targeting and safe and specific additions or modifications of existing nucleic acid sequences. The ideal genetic medicine can safely make any change to the genome in any cell in the body with a readily manufacturable composition of matter.

Like any therapy, genetic medicines are only effective if they can be delivered safely and effectively. Historically, viral vectors have been the delivery vehicle of choice, harnessing certain viruses' natural ability to effectively deliver their DNA cargo to specific cells. However, viruses are recognized as foreign by the immune system, which mounts a robust response to these vectors that can make initial treatment challenging and preclude re-treatment should it be needed. Lipid nanoparticles (LNPs) have emerged as an efficient delivery vehicle with potential to overcome these limitations. In addition,

LNPs are highly scalable and readily manufacturable as evidenced by their ability to deliver more than a billion doses of mRNA-based COVID vaccines.

Once at its prespecified location, the genetic alteration effected must be precise, safe and durable. Gene therapies introduce functional DNA into a cell as an episome, but over time as the cells divide, the gene therapy materials are diluted along with the therapeutic effect – limiting the durability of this approach. Altering the DNA itself proved to be much more durable, but could it be safe and precise? The discovery of the CRISPR/Cas system a decade ago opened the door for direct human genome editing. CRISPR is a wonderful pair of molecular scissors that can make a double stranded DNA break at a programmable location. Once the DNA is cut, the cell's endogenous repair machinery is required to repair the break, and it will often do so in an error-prone manner, leading to a functional knock-out of the gene in question. This capability follows logically from CRISPR/Cas systems' function in nature - as a bacterial immune system that evolved to destroy DNA - and has made CRISPR/Cas a terrific tool to knock-out a gene that is malfunctioning.

While knocking a gene out can be beneficial in some disease contexts, making precise corrections of mutations or writing healthy genes into the genome could unlock far greater therapeutic potential.

A definitive technology that can safely deliver a therapy to tissues beyond the liver and make a multitude of targeted genetic alterations would reimagine the possibilities for medicine as we know it today and transform the way diseases are treated.

History of the development of the solution/product

What if Nature evolved a safer and more precise way to alter genomes?

This was the question that a team at Flagship Labs including Geoffrey von Maltzahn, Jacob Rubens, and Rob Citorik began exploring to address the limitations of gene therapy and gene editing. They sought to identify systems that - in contrast to CRISPR/Cas - naturally evolved to write DNA rather than to break It. They hypothesized that such systems could be harnessed to write and rewrite DNA in a versatile manner, going beyond the limitations of CRISPR/Cas, and potentially revolutionize the field. Their explorations led them to mobile genetic elements (MGEs), a diverse class of genetic sequences that self-replicate by writing their own genetic sequence from one place to another within a genome. Often dubbed as "jumping genes", MGEs are nature's greatest genomic architects and in fact make up as much as 50% of the human genome. While MGEs were discovered several decades ago by Barbara McClintock (who won a Nobel Prize for that work), there had been few dedicated efforts to leverage these technologies for genetic engineering. The team at Flagship Labs created Tessera Therapeutics, a company dedicated to pioneering a new category of genome engineering technology called Gene Writing™, built on the foundation of MGE biology. Gene Writing can write new sequences or rewrite existing sequences into the human genome creating new possibilities for patients with genetically driven diseases.

Tessera's scientific team has analyzed over 11 trillion base pairs of genetic sequence data from across the tree of life, and from this identified and evaluated over 100,000 potential Gene Writer candidates. Tessera has engineered and optimized Gene Writers for distinct capabilities: Rewriting the genome (e.g., correcting pathogenic mutations) or Writing whole genes or exons (e.g., introducing a functional copy of a deficient sequence). Together, these enable the full spectrum of alteration outcomes - those as precise as rewriting a single nucleotide or as vast as writing in entire new genes. Tessera has also

demonstrated that these technologies can be combined to Write and Rewrite simultaneously, which can be used to reprogram immune cells for anti-tumor applications.

Gene Writers are composed of an RNA template and a Gene Writer protein that can both be delivered as RNA to make precise and programmable alterations in the DNA of a cell. Gene Writers use a mechanism called Target Prime Reverse Transcription (TPRT), the same mechanism used by a major category of MGEs in nature to move themselves around the genome. The fact that the composition of matter is entirely RNA allows Gene Writers to be delivered non-virally, with LNPs, to reach the exact cell or tissue requiring this alteration.

LNPs can safely and effectively deliver nucleic acids to cells without eliciting a robust immune response as is common with viral delivery vectors. LNP delivery has been validated as being safe and effective in several contexts - in particular for delivering CRISPR/Cas systems to the human liver. Tessera is seeking to deploy its Gene Writing technology to cure liver diseases, but to truly unlock its full potential, Tessera has been innovating novel LNPs that have the potential to deliver RNA cargoes to tissues beyond the liver.

In January 2023, Tessera shared proof of concept data that demonstrated the potential of its Gene Writers to write therapeutic messages in the genome of non-human primates (NHPs), to generate clinically relevant rewriting at the genetic locus responsible for the rare disease phenylketonuria (PKU) and to generate tumor-clearing chimeric antigen receptor (CAR)-T cells by all-RNA delivery. The technology was also shown to be capable of targeting non-viral delivery systems to hematopoietic stem cells (HSCs) and T cells in NHPs. Notably, success in NHP models is highly predictive of success in human studies for non-viral genetic medicines. Tessera presented additional data at ASGCT 2023 including improved efficiencies of its RNA Gene Writers in animal models of PKU and sickle cell disease, as well as correction of a point mutation responsible for the genetic disease alpha-1 antitrypsin deficiency (AATD) and the ability to multiplex alterations - making simultaneous edits to knock in a gene while knocking out another without causing translocations. This last technological advance supports the development of highly engineered cell therapies for oncology. Looking ahead, Gene Writing in cells and tissues such as T-cells and HSCs as well as the liver, the lungs and the eye holds immense potential to offer a durable therapeutic solution for millions of patients worldwide. Under the leadership of Michael Severino, physician and biopharma industry veteran who previously served as Vice Chairman and President of AbbVie, the company is building on this momentum and advancing its lead programs towards the clinic while continuing to innovate its core Gene Writing and LNP Delivery technologies.

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Why this solution/product is innovative, the broad implications for future research, and/or how it will improve the human condition

Tessera's goal is to make any genomic alteration needed (from a single nucleotide change to a whole-gene insertion), in the specific cells where it is needed, to address diseases of high unmet need. Tessera's hope is that in the future, a child born with a severe genetic disease may receive a single administration of a potentially curative Gene Writer and grow up without ever learning the name of the disease they were born with; that cancer patients can receive a single IV Infusion that engineers

their T cells in vivo - within their own body - to target and eradicate their tumor cells; and that patients who are predisposed to serious common diseases have the option to rewrite their genome to remove the mutations that predispose them to these conditions.

Tessera's Gene Writing™ platform is a groundbreaking technology that has the potential to transform the landscape of medicine and revolutionize the management of numerous diseases by moving beyond symptom control to effective treatments and, in some cases, full cures. What sets Tessera's technology apart is the sheer breadth of therapeutic alterations that can be achieved with its genome engineering toolkit: from a single letter change to writing an entire functional gene. Since its creation in 2018, Tessera has been the first to demonstrate efficient TPRT-based gene editing in the liver of mice and NHPs as well as human HSCs and T cells, the first to show integration of a full-length gene by delivering instructions as all RNA components, and the most efficient at delivering RNA-encoded genetic instructions to HSCs and T cells of mice and NHPs. Tessera is innovating with dizzying speed in the genome engineering space to bring treatments and cures to patients in need.

The ability of Gene Writers to make highly specific alterations to the genome opens extraordinary therapeutic possibilities not only across a plethora of diseases – including inborn errors of metabolism, rare genetic diseases, and various cancers - but also to introduce protective mutations that preclude common diseases from occurring. This specificity circumvents the limitations that other gene editing technologies, such as CRISPR, have been facing. For example, CRISPR is not always efficient, and inaccuracies can lead to off-target effects. Conversely, Tessera's technology is capable of making alterations at a single nucleotide level with unparalleled precision. This specificity not only reduces the risk of adverse side effects but also makes it possible to target previously untreatable genetic diseases. Coupled with LNP delivery that can target tissues beyond the liver, Gene Writing is rewriting the playbook on genomic engineering – a single treatment that can offer a wide range of genomic alterations to cure diseases across tissue types and perhaps even prevent or alter disease development in the future.

The potential impact of Tessera's technology on the human condition is tremendous. If successful, the ability to cure a wide range of diseases will rewrite outcomes for numerous patients. For those with PKU, a metabolic disease managed primarily by dietary restrictions due to lack of curative options that can cause severe neurological impairments including seizures, as well as delays in growth and maturation, a single faulty letter of code in their DNA defines their story. What if we could rewrite their stories? And the stories of millions of other patients battling diseases with a genetic basis? And beyond an existing illness, what if we could get ahead of disease with preventive genomic alterations and revolutionize our collective experience of health and wellness?

The potential of Gene Writing to touch the lives of people is near limitless. At Tessera, we are working diligently to write the next chapter of medicine and shape healthy stories for all.

Please provide appropriate references (ie Pubmed links)

See reference presentations uploaded here.

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