

With its outstanding expertise and best in class technologies, **Throne Biotechnologies** delivers stem cell innovations for the practical cure of type 1 diabetes and autoimmune diseases

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Diabetes is basically a condition in which there is too much of glucose in the blood. If treatment is not done for the same, high glucose levels can severely damage the body's organs. Possible long-term effects include damage to macrovascular and microvascular blood vessels leading to stroke, heart attack, and problems with gums, eyes, feet, nerves, and kidneys. The good news is that people can reduce the risk of these complications by keeping the cholesterol, blood pressure, and blood glucose levels under the recommended ranges. Patients can also reduce the risk by eating healthy, reducing alcohol intake, and maintaining healthy body weight.

Globally there are various companies delivering excellent treatment for diabetes, but Throne Biotechnologies (Throne) stands out from the rest. To address these two key issues (autoimmunity and shortage of islet beta cells) in type 1 diabetes (T1D), Throne has developed a unique and novel procedure designated the Stem Cell Educator™ therapy, based on the immune education by cord-blood-derived multipotent stem cells (CB-SC). With this patented technology, a patient's blood is circulated through a blood cell separator,

wherein the patient's immune cells (mononuclear cells) are co-cultured with adherent CB-SC in vitro, after which CB-SC-“educated” immune cells (designated Gleukocell™) are returned to the patient's circulation through infusion. This is a one-time, dialysis-like treatment that fundamentally “re-educates” the defective immune system back to health. Over the last 10 years, this technology has been evaluated through international multi-center clinical studies, which have demonstrated its clinical safety and efficacy in T1D and other autoimmune diseases.

In conversation with Yong Zhao, CEO and President of Throne Biotechnologies

What was the motivation behind starting Throne Biotechnologies?

Type 1 diabetes (T1D), an autoimmune disease that affects millions of Americans, requires life-long management with daily glucose monitoring and insulin injections that do not fully control the broad range of long-term adverse health effects that can include

heart disease, nerve damage, and blindness. The hallmark of T1D is the autoimmune destruction of islet beta cells, leading to the shortage of insulin production. Over the last 40 years, the failures of most clinical trials have highlighted the limits of conventional immunotherapy in T1D and underscore the need for novel treatments that overcome multiple immune dysfunctions and help restore islet beta-cell function.

What are safety test conducted to move forward with the stem cell therapy?

To date, the safety of Stem Cell Educator therapy has been well demonstrated by the international multicenter clinical trials in T1D, type 2 diabetes (T2D), and alopecia areata (AA) in the United States, China, and Spain. The procedures were well accepted in all patients aged from 3 to 70 years old, without any significant adverse events and safety concerns during the treatment. Stem Cell Educator therapy modifies rather than destroys immune cells responsible for autoimmunity without increasing the chances of infection and tumor formation, as demonstrated by the long-term (4 years) follow-up study of Stem Cell Educator therapy.

There are a number of researches that need to be done on cell therapy that would establish that it can be used as a form of treatment line. Tell us about your efforts in the research segment.

Most conventional immune therapies for T1D have failed over the past 40 years, which included the clinical trial of mesenchymal stem cells (MSC). Over the last 10 years, our Stem Cell Educator technology has been evaluated through international multi-center clinical studies, which have demonstrated its clinical safety and efficacy in T1D and other autoimmune diseases. Mechanistic studies revealed that Stem Cell Educator therapy could fundamentally correct the autoimmunity and induce immune tolerance through multiple molecular and cellular mechanisms such as the expression of a master transcriptional factor autoimmune regulator (AIRE) in CB-SC for T-cell modulation, an expression of Galectin-9 on CB-SC to suppress activated B cells, and secretion of CB-SC-derived exosomes to polarize human blood monocytes/macrophages into type 2 macrophages. Stem Cell Educator therapy is the leading immunotherapy to date to safely

and efficiently correct autoimmunity and restores β cell function in T1D patients.

Tell us in brief about your Optimization and Pre-Clinical Tests.

Regulatory T cells (Tregs) play a crucial role in maintaining immune tolerance through releasing immunosuppressive cytokines interleukin-10 (IL-10) and/or transforming growth factor-beta 1 (TGF-beta 1). Increasing evidence demonstrates that defects of Tregs, either in cell number or in function, contribute to the initiation and progression of T1D patients. Therefore, targeting Tregs for the treatment of T1D is an attractive approach. Using the autoimmune-caused non-obese diabetic (NOD) mouse model, we showed that treatment with the purified CB-SC-modulated CD4+CD62L+ Tregs (modulated CD4CD62L Tregs) could reverse overt diabetes and result in a marked reduction of insulinitis, restored Th1/Th2 cytokine balance in peripheral blood, and induced apoptosis of infiltrated T cells in pancreatic islets. Notably, pancreatic histological studies established the proliferation of residual islet beta cells with a high percentage of Ki67+insulin+ beta cells in the

modulated CD4CD62L Tregs-treated diabetic mice, relative to that of CB-SC-unmodulated CD4CD62L Tregs group. In line with these animal studies, we demonstrated the restoration of islet beta cell function in T1D patients after receiving Stem Cell Educator therapy.

What does the future hold for your company and its customers? Are exciting things on the way?

To date, Stem Cell Educator therapy has gained three phases 2 clinical trial approvals by the FDA for T1D treatment (IND19247), alopecia areata (IND 19246), and severe COVID-19 patients (IND 19679). As a global-leading technology in the field of T1D treatment (JDCA, 2021, New York), it is highly expected that Stem Cell Educator therapy will achieve an expedited FDA approval under the designation of Regenerative Medicine Advanced Therapy (RMAT) due to an unmet medical need for T1D and alopecia patients. Collectively, Stem Cell Educator therapy has the potential to revolutionize the treatment of T1D and eliminate the need for lifelong insulin therapy without the safety and ethical concerns associated with conventional immune and/or stem cell-based approaches. SR

Meet the leader behind the success of Throne Biotechnologies

Dr. Yong Zhao is the **CEO** and **President** of Throne Biotechnologies. He is an internationally-acclaimed scientist and doctor who specializes in immunology and stem cell biology. He is the first scientist to discover the CB-SC stem cells from human cord blood and is the inventor of Stem Cell Educator therapy to treat type 1 diabetes and other autoimmune diseases. He has held scientist and professorship positions at Hackensack Meridian Health and the University of Illinois at Chicago. He holds 9 patents and 60 publications and received his post-doctoral training from the University of Chicago. He has been featured on CNN, USA Today, CBS, and additional major international news networks. As a former physician, Dr. Zhao aims to bring non-invasive and sustainable cures to people with type 1 diabetes, autoimmune diseases, and other life-threatening diseases.

