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KADIMASTEM
stem cells to cure diseases

Restorative therapeutics for ALS and diabetes

Applying a unique approach, Kadimastem is developing stem-cell-based therapies for life-threatening diseases.

Bodily systems are highly complex and delicately balanced, so when something goes wrong—through cell malfunction, for example—consequences can be catastrophic. Israel-based Kadimastem specializes in developing restorative therapeutics from human pluripotent stem cells (hPSCs) for such disorders. hPSCs can give rise to all tissues in the body, and Kadimastem's technology enables their accurate differentiation into a range of functional types, including insulin-producing cells to treat diabetes and neuron-supporting glial cells to treat neurodegenerative diseases.

Michel Revel, Kadimastem's CSO, cofounded the company in 2009 after 40 years at the Weizmann Institute, where his work led to the multiple sclerosis blockbusters Rebif and Avonex (both based on interferon-β1a). "There we used cells to produce drugs, but now the cells themselves are the drug," he said. "The functional cells we produce at Kadimastem have the potential to restore critical activities that are lost in tissues damaged by diseases."

Healthy astrocyte production

Kadimastem has two major programs, the most advanced of which is AstroRx for treating amyotrophic lateral sclerosis (ALS). Also known as Lou Gehrig's disease, ALS is a devastating, progressive disorder in which motor neurons in the brain and spinal cord degenerate and die, blocking signals to muscles, which gradually weaken and fail. There is no cure or effective treatment for ALS, which affects around 150,000 people worldwide, most of whom do not survive beyond five years after disease onset.

The exact cause of ALS is unknown, but malfunctioning astrocytes—cells in the central nervous system that support neurons—are thought to have a key role. Normally, astrocytes help keep neurons healthy by secreting neurotrophic factors and removing toxic compounds, such as excess glutamate, from their microenvironment. Defective ALS astrocytes fail to do this, causing the motor neurons to die.

Using its innovative stem cell technology, Kadimastem produces healthy, young human astrocytes that slow disease progression by compensating for the damage caused by unhealthy astrocytes (**Fig. 1**). Clinical-grade hPSCs are expanded under good manufacturing practice (GMP) conditions and, through a stepwise process, accurately differentiated into astrocytes. Differentiation takes about eight weeks and results in healthy cells that can be frozen in ampoules and stored indefinitely as an off-the-shelf product suitable for all patients with ALS. When required, the cells are thawed and injected under local anesthesia into the patient's cerebrospinal fluid, and from there the cells are able to travel to where they are needed. Because cerebrospinal fluid is immune privileged, no immunosuppressants are used.

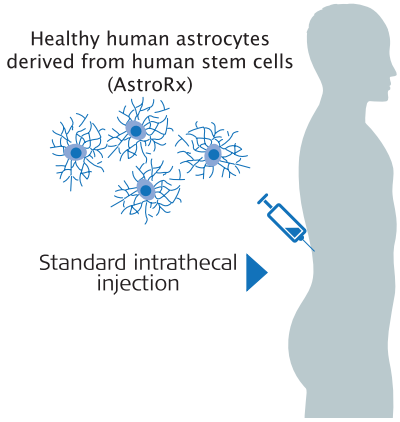

Figure 1: Healthy, young human astrocytes (AstroRx) produced by Kadimastem are injected into ALS patients to slow disease progression.

Preclinical tests in a rodent ALS model showed that the cells reduce glutamate and secrete neurotrophic factors *in vitro* and significantly improve motor function *in vivo*, delaying disease onset and prolonging survival by 20%. "Astrocyte-like cells produced from mesenchymal stem cells only secrete neurotrophic factors, but our astrocytes produce neurotrophic factor and also remove toxic glutamate," said Yossi Ben-Yossef, CEO and cofounder. "Additionally, *in vitro* studies show that our cells also significantly reduce oxidative stress, which is very high in ALS patients."

Diabetes cell therapy

Kadimastem also uses its novel approach to help the millions of people with diabetes, a group of diseases characterized by excessive levels of blood sugar. Some patients are unable to produce insulin because their pancreatic beta cells are damaged or destroyed (type 1), whereas others are unable to use insulin properly or produce it sufficiently (type 2). The resulting excessive blood glucose level causes cumulative damage throughout the body, increasing the risk of fatal complications. Although many patients can manage their diabetes by injecting insulin, blood sugar levels are difficult to maintain and monitor properly, and insulin injections do not prevent the disease's long-term cumulative effects. Donated beta cells from cadavers can be transplanted into some patients; however, this requires lifelong immunosuppression, and there is a shortage of organ donations.

Again, using an innovative stepwise process, Kadimastem accurately differentiates glucose-sensitive, insulin-secreting islet-like clusters from clinical-grade hPSCs. It takes about a month to form the clusters, which contain insulin-producing beta cells and glucagon-producing alpha cells.

Cleverly, the cells will be encapsulated in a nanochemical sheath that still allows glucose sensing and insulin secretion. As well as preventing immune rejection once inside the patient, encapsulation ensures that the cells cannot move around the body, enabling their retrieval at a later date. "This is another advantage over islets from cadavers, which are infused into the portal vein and may escape in the body," said Revel.

It is expected that, once transplanted into a patient (either subcutaneously or intraperitoneally), the cells will sense blood glucose and release insulin and glucagon as necessary, restoring homeostasis. Preclinical results in diabetic mice are encouraging, with therapeutic levels of insulin secreted in the blood about two weeks after implantation and continuing for many months.

"Our stem-cell-based treatment obviates the need for insulin injections and monitoring blood sugar levels and should reduce the life-threatening consequences of diabetes," said Ben-Yossef. "It is suitable for treating patients with type 1 diabetes and the 30% of those with type 2 disease who require insulin injections—some 150 million people worldwide."

Partnering with Kadimastem

Kadimastem will apply for orphan drug status for AstroRx and plans to start clinical trials by mid-2017, whereas its diabetes cell therapy is currently in preclinical trials. Kadimastem is interested in biopharmaceutical and biotech partners that can quickly progress either product to and/or through the clinic. The company is particularly interested in partnering with organizations in Japan, where new legislation aimed at accelerating the development of cell-based treatments allows patients to be treated with products with a positive phase 1 safety profile.

"We are able to accurately differentiate both embryonic and induced pluripotent stem cells and have large-scale GMP-grade production capabilities," said Revel. "We believe our unique approach to regenerative medicine will be transformative for people suffering from diabetes or neurodegenerative diseases such as ALS."

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