CLINICAL APPLICATION

Clinical application of Rebirthel's technology

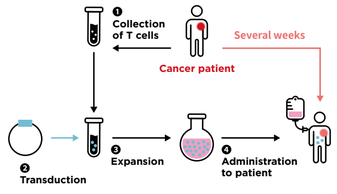
Rebirthel's technology solves immunotherapy challenges

Therapies using autologous T cells have been developed and used around the world. For instance, CD19-CAR-T cell therapy is applied for certain types of leukemia as a standard treatment and is confirmed as effective. However, issues with autologous T cells therapies include “time-consuming”, “costly”, and “heterogeneous in quality” (see upper diagram below).

With Rebirthel's technology, iPS cells can be used as a material to produce, and T allogeneic cells can be mass-produced and cryopreserved. Thus, it will be possible to provide “applicable to anyone = super-universal,” “rapid = off-the-shelf,” “low cost,” and "high-quality" therapeutic T cells (see lower diagram below).

Issues of current adoptive immunotherapy

Ongoing “autologous” T cell therapy



Issues

- **Time-consuming**

Cells need to be collected from patients and cultured after transduction. This can take up to several weeks.

- **Costly**

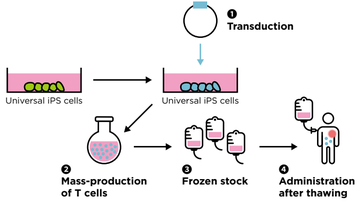
T cells are collected and cultured for every individual patient. The process is made-to-order and thus can be costly.

- **Heterogeneous in quality**

The quality depends upon the condition and the caliber of the T cells collected from the patients.

Advantages of highly universal T cell preparation

Rebirthel’s T cell therapy



Advantages

- **Rapid**

Using frozen cell preparations makes it possible to administer immediately.

- **Low cost**

As regenerated T cells have been mass-cultured in advance, there is no need to collect and culture T cells.

- **High quality**

By utilize iPS cells as a source material, we can guarantee high function and quality T cells.

COMPANY PROFILE

Company Information

Name	Rebirthel Co., Ltd.
Address	Room 311, Creation Core Kyoto Mikuruma, 448-5, Kajii-cho, Kamigyo-ku, Kyoto 602-0841 Japan
Established	October 1st, 2019
Capital stock	30,000,000 JPY
President	Masunori Kajikawa
Director	Toshio Kitamura
Aim	Development and operationalization of cell-based cancer immunotherapies
Shareholders	NISSAY CAPITAL CO.,Ltd. FUJIFILM Corporation Japan Science and Technology Agency SCREEN Holdings Co., Ltd. KAGAWA Securities Co., Ltd TOHO HOLDINGS CO.,LTD Chushin Venture Capital co, Ltd. Future Venture Capital Co.,Ltd

https://rebirthel.com/

Rebirthel

Rebirthel Co., Ltd.

We are pioneering a new era for treating diseases through the transfusion of T cell preparations! Rebirthel provides a novel treatment through a super-universal T cell preparation.

Rebirthel was founded in October 2019 with the aim of providing novel treatments against cancer, infectious diseases, and other immune-related maladies. Our strategy is based upon the technology of killer T cell regeneration from pluripotent stem cells, which was pioneered by Professor Hiroshi Kawamoto, Director of the Institute for Life and Medical Sciences at Kyoto University.

Cancer is the leading cause of death in the world with over 20 million new cases diagnosed annually (over one million in Japan alone). Sixty percent of these cases are treatable via current protocols; however, the other forty percent are presently almost completely untreatable.

Immunotherapies such as immune checkpoint blockade or CAR-T cell therapy have shown high therapeutic efficacy against some cancers. Moreover, the mRNA vaccine developed for SARS-CoV-2 has shown remarkable success in protection against the novel coronavirus infection. Attention is increasingly being focused on the natural disease fighting systems all human beings are born with, including immunotherapy and immune functions.

Rebirthel is a leading company in the field of immunotherapy and has multiple globally patented technologies. These technologies enable us to produce a novel immunotherapy utilizing killer T cells that are regenerated from pluripotent stem cells, which can be used to treat immune-related disorders such as cancer, infectious diseases, autoimmune diseases, and allergies.

In addition to our development pipeline, we also promote business and public-private-academic partnerships. We believe these collaborations contribute to the development of immune therapies throughout the entire industry, helping us to treat patients using T cell preparations as soon as possible.

We are pioneering a new era for treating diseases through the transfusion of T cell preparations! Rebirthel is making every effort to further develop and realize novel immunotherapies. I would like to express my sincere gratitude for your continued support and encouragement.

Masunori Kajikawa
President and CEO
Rebirthel Co., Ltd.

Rebirthel

Rebirthel is a combination of the words "Rebirth" and "Cell"

Our logo represents the self-renewal and differentiation of a stem cell. The two gray circles connected by the gray curved line on the left express an image of a self-renewing stem cell. The green and blue curved lines connecting the green and blue circles on the right represent a developmental pathway from a stem cell to a T cell via a progenitor cell.

Hiroshi Kawamoto
Professor
Director of the Institute
For Life and Medical Science
Kyoto University

Founder, CTO
Rebirthel Co.,LTD.

The image on the right was created by Professor Kawamoto, a founder of Rebirthel. It shows the process of differentiation as well as the architecture of immune system cells. In our body, different cells are produced, stimulated, and highly controlled. It is critical that these cells function in their proper place and achieve their potential via strict cellular selection. The human body can be thought of as a precise factory that produces high quality functional cells.

BUSINESS OVERVIEW

Business development with an eye on the future

Rebirthel's Business overview

Rebirthel's business consists of two main components: i) in-house research, where we promote our own proprietary R&D and ii) licensing, where we license our specialized technologies to other firms which are currently using patient-derived adoptive immunotherapy.

Rebirthel's in-house research has two priority pipeline projects: targeting WT1 antigens and regenerating tumor-infiltrating T lymphocytes.

-In the project targeting WT1 antigens, regenerative T cells are generated using TCR genes, which has already been proven to be safe and effective in clinical trials (development for acute myeloid leukemia clinical trials are currently underway at Kyoto University Hospital, and investigator-initiated clinical trials are scheduled to be conducted in 2024).

-We believe our regenerating tumor-infiltrating T lymphocytes project to be the ultimate immunotherapy; as such, we are constantly striving to develop new technologies utilizing it.

Regarding licensing, we have concluded research agreements and commercial agreements with a variety of pharmaceutical companies. They have successfully adopted Rebirthel's technologies to their business plans, where they have been developing T cell therapies using patient-derived cells for autologous T cell transplantation systems and exploiting new therapeutic methods through synergy effects.

Rebirthel's Strengths

We believe that we have four advantages that other companies do not.

01.

World's first iPS cell-derived killer T cell therapy

We realize high quality and rapid treatment by combining differentiation induction and mass culture technologies based on iPS cell technology.

02.

Patented technology platform that enables xenotransplantation

We have already obtained several patents in Japan and overseas, including for the TCR-iPS cell method, which solves the problem of current adoptive immunotherapy (autologous transplantation).

03.

Generalized technology that controls rejection (as well as transplant rejection)

Disabling HLA enables "super-universal" to suppress immune rejection associated with transplantation therapy.

04.

As a platform technology, it can be utilized for various infectious diseases and autoimmune diseases in addition to cancer treatment

This hybrid of allogeneic transplantation + personalized medicine, which utilizes immune cells as drugs, can be applied to a variety of infectious diseases including the novel coronavirus infection.

TECHNOLOGY

Pioneering technology

Rebirthel's outstanding technical capabilities and strong cooperative network with Kyoto University

Rebirthel's strengths to carry out both in-house research and licensed business piplines lies in the fact that our technology has a patented platform which is ahead of its competitors, which enables us to create and develop a wide range of applications based on our own in-house resources.

Rebirthel's various patented technologies are based upon the research of its founder Professor Hiroshi Kawamoto, Kyoto University. Prof. Kawamoto and his team are leading the research field of immunotherapy in the world, including being the first to successfully regenerate antigen-specific T cells from pluripotent stem cell.

Rebirthel enjoys a strong, well established cooperative framework with Kyoto University. It allows us to conduct cutting-edge research and develop next-generation technologies, grant exclusive worldwide licensing rights in a series of superior technologies, and to collaborate on investigator-initiated clinical trials. We are building comprehensive cooperative systems not only for R&D, but also for commercialization, POC acquisition, clinical application, and delivery to patients.

Major patented technologies for which Rebirthel has exclusive licenses

01. **TCR-iPSC method** - [PRODUCTION METHOD FOR PLURIPOTENT STEM CELLS HAVING ANTIGEN- SPECIFIC T CELL RECEPTOR GENE]
- Applied 2014 : PCT/JP2015/070623 WO 2016010154 A1 - Patented in EU, AU and JP

This method efficiently transfers the target TCR or CAR gene into pluripotent stem cells and has been patented in Japan and other countries.

Various types of immunotherapies using T cells have been proposed in the past, but most of them are autologous transplantation systems using the patient's own cells (or conditions that are considered autologous transplantation). Some allogeneic systems have also been proposed, but they are cell populations with a large number of T cell clones (and a large number of TCRs), and the risk of graft-versus-host disease (GVHD) cannot be avoided. Thus, immunotherapy by T-cell xenotransplantation has been considered contrary to common sense.With the invention of the TCR-iPS method, material cells that produce T cells with a single antigen specificity can easily be induced to differentiate and thus be used for allogeneic transplantation without the risk of causing GVHD.

02. **DP separation method (method to induce high quality CTL)** - [METHOD FOR INDUCING CD8+ T CELLS]
- Applied 2016 : PCT/JP2017/015358 WO2017179720 A1 - Patented in EU, JP and US

This method of inducing CD8+ T cells from pluripotent stem cells has been patented in Japan and other countries.

It is known that high-quality killer T cells require CD8αβ heterodimers, but conventional methods cannot efficiently induce differentiation.The invention of the DP isolation method makes it possible to induce high-quality killer T cells of the CD8αβ type with high cytotoxic activity. The T cells induced by this method can be used as foundation cells for the development of CAR-T cells in other types, making this technology highly versatile for the development of other immunotherapies.

03. **TCR-cassette method** - [METHOD FOR PRODUCING FOREIGN ANTIGEN RECEPTOR GENE-INTRODUCED CELL]
- Applied in 2018: PCT/JP2019/029537 WO2020022512

This method is an evolution of the TCR-iPS cell method, in which a deck-like sequence is inserted at the TCR gene locus, and the desired TCR or CAR being replaced like a cassette tape deck.

Gene transfer methods using lentiviruses and other methods have the disadvantages of i) random insertion of TCR genes into the genome, and ii) unstable expression levels, which carry the risk of genome damage.With the invention of the TCR cassette method, the TCR gene can be inserted at the native TCR locus and gene expression can be regulated by endogenous enhancers, making it possible to express the TCR at a fixed, specific location and with controlled expression levels. This is a highly versatile technology that allows the desired TCR or CAR to be inserted simply and safely, just like changing a cassette tape.