Biozipcode, Ltd.

We lead the industry by pursuing cures, not symptomatic treatment.

Biozipcode, Inc.

Ver. 2026/06/18

Diabetes is an incurable disease, and the reason why it is incurable was unknown. This time, we discovered pathological stem cells that cause diabetes and named them "diabetes stem cells."

Whereas, it has been reported in the past that the cause of incurable cancer is pathological stem cells called "cancer stem cells."

Therefore, in both cases, pathological stem cells are at the root of the disease, and as long as the patient lives, they will remain lurking in the body forever as stem cells that cause incurable diseases.

This treatment is the world's first attempt using Biozipcode™ to cure these incurable disease by targeting and removing these pathological stem cells.

Technology Introduction

Overview of Kyan Medical Co., Ltd.'s Technology

01 From Symptom Management to Complete Remission
Marketing of Diabetes Complete Cure Medicine & Treatment of Diabetes Cure

The preclinical study on the combination of HDAC inhibitors and insulin for curing diabetes has been completed. Clinical trials to obtain FDA approval are planned.

A separate trial using 5-ALA, which has similar functions to HDAC inhibitors and effectively corrects epigenomic abnormalities, ***has progressed to Phase IIa and demonstrated statistically significant results****. However, since the trial was not originally designed to pursue a "complete cure" for diabetes, a new trial will be required.*

02 Biozipcode™ (Cell Targeting Technology)
Utilization of "Biozipcode™"

Acquire "Biozipcode" for diabetic stem cells and common cancer markers to **develop diagnostic tools** and **side-effect-free cures for diabetes**, as well as **side-effect-free cancer treatments**.

Seek research collaborators and business partners to expand the applications of Biozipcode.

< Technology 1 > Discovery of Diabetes Stem Cells

Our research team discovered abnormal cells in hematopoietic stem cell fractions that cause diabetes and its complications, exhibit refractory characteristics.

< Technology 2 > Cell-Targeting Technology (Biozipcode™)

Aiming to develop cell-targeted drugs as a new drug delivery method for the next generation, beyond the current era of molecular-targeted drugs.

01

Marketing of Diabetes Complete Cure Medicine & Treatment of Diabetes Cure

From Symptom Management to Complete Remission

Technology Overview

1999

2003

2023

2026

October

The day Dr. Hideto Kojima start

On October 1999, Dr. Hideto Kojima **planned a gene therapy targeting the liver** at Baylor College of Medicine, **based on mechanisms of pancreatic islet development**. Using transcription factors involved in pancreatic development (Pdx-1, Ngn3, NeuroD1), islets were regenerated in the liver of mouse, aiming for a cure for diabetes.

1999

2003

2023

2026

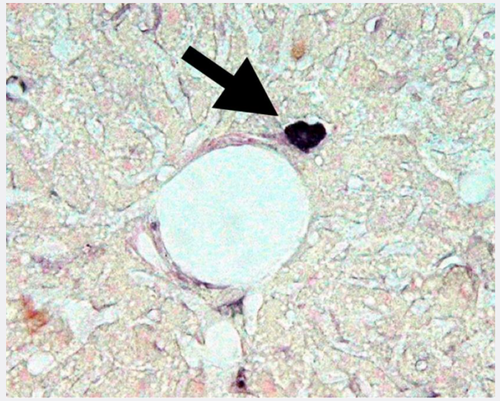
May

Encounter with Diabetes Stem Cells

The paper **“NeuroD-betacellulin gene therapy induces islet neogenesis in the liver and reverses diabetes in mice” (Nature Med, 2003)** was completed.

This research successfully recreated islets in the liver using NeuroD1. However, one unresolved question remained. **Strange cells producing proinsulin were found in the liver of untreated diabetic mice** used as controls for gene therapy.

These cells were located right next to the portal vein capillaries in the liver of hyperglycemic mice. In 2003, a paper including microscopic images of these strange proinsulin-positive cells was accepted.



Strange Cells Producing Proinsulin

"After that, a 20-year battle with strange cells begins."

1999

2003

2023

2026

June

Discovery and Impact of Diabetes Stem Cells

The paper **“Complete remission of diabetes with a transient HDAC inhibitor and insulin in streptozotocin mice” (Com Bio, 2023)** was completed.

Diabetes is a chronic progressive disease that does not heal naturally. Its cause is linked to genetics, lifestyle, and autoimmunity, but the details are unclear.

Professor Kojima's team discovered abnormal cells in the hematopoietic stem cell fraction that create a refractory nature for diabetes and its complications. These cells persist even when blood sugar levels are normalized, maintaining their disease stem cell properties.

The removal of these cells, termed **"diabetic stem cells,"** showed potential for curing diabetes and its complications. **Combining insulin with HDAC inhibitors for a certain period removed the "diabetic stem cells," leading to complete remission of diabetes.**

1999

2003

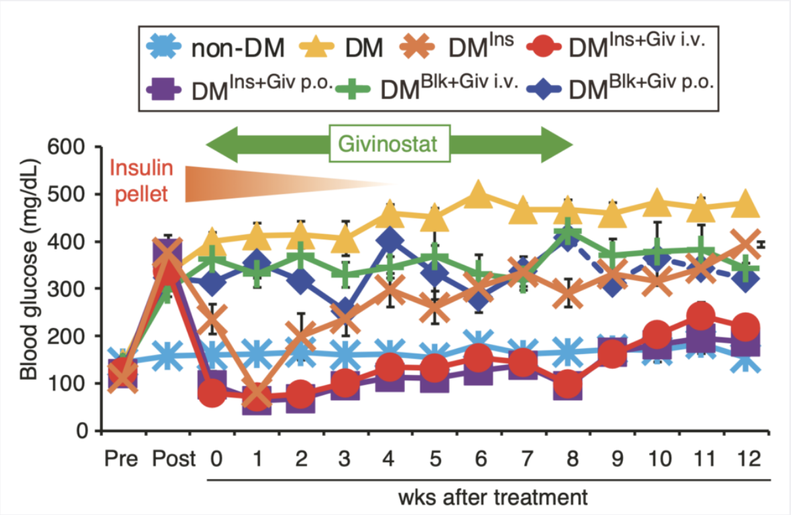
2023

2026

June

Insulin and Histone Deacetylase (HDAC) Inhibitors

Experimental results was that , diabetic mice implanted with insulin pellets were given Givinostat for 8 weeks, which maintained glycemic control and maintained normoglycemia after the insulin pellets were removed, and for an additional 4 weeks after Givinostat treatment was stopped.



Complete remission with sustained euglycemia with insulin + Givinostat combination therapy

Patents pending (some approved): PCT/JP2020/039044, PCT/JP2020/039045, PCT/JP2022/008036, PCT/JP2022/008036

1999

2003

2023

2026

April

Discovery and Impact of Diabetes Stem Cells

Since 2015, Studio Makyu Co., Ltd. has been conducting joint research with Shiga University of Medical Science, establishing a research base and supporting in vivo and in vitro experiments, bioinformatics, proprietary software development, and in silico research using GPGPU-based large-scale computation. **In 2022, Biozipcode, Inc. was established to take over and further develop these research activities, and a joint research laboratory for regenerative medicine was set up within Shiga University of Medical Science.** Since then, the company has advanced research on therapeutic technologies using the cell-targeting peptide “Biozipcode™” to address diabetes and other intractable diseases.

From 2026, these research activities will be further developed through the establishment of the Industry-Academia Joint Research Course, **“Department of Biocommunication Development,” at Kyoto University Graduate School of Medicine and Faculty of Medicine**, with the research theme of “Development of Cell-Targeted Therapy.” Through collaboration with Kyoto University, Biozipcode Inc. will accelerate the development of cell-targeted therapies based on Biozipcode™ technology and promote future medical implementation and partnerships with pharmaceutical companies and research institutions in Japan and overseas.

KYOTO UNIVERSITY KYOTO JAPAN FOUNDED 1897

Biozipcode, Inc.

Department of
Regenerative Medicine
Shiga University of Medical Science

Reasons Why Diabetes Is Not Curable (1)

Causes found in previous research:

Abnormal Bone Marrow Stem Cells (BMDCs) Inhibiting β-Cell Regeneration

Background

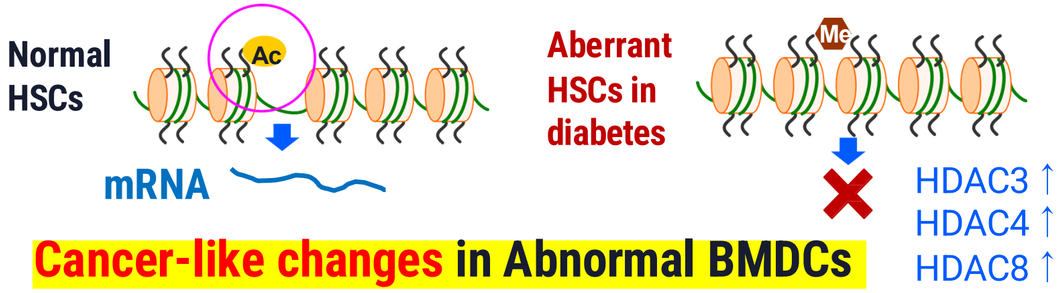
- ✓ Diabetes is increasing globally, necessitating the development of effective treatments.
- ✓ Our research focuses on **why diabetes remains incurable**, emphasizing the regenerative capacity of β-cells.

β-Cell Regenerative Capacity

- ✓ β-cells have regenerative ability, actively regenerating during the perinatal period.
- ✓ They can also regenerate under certain conditions in adults.
- ✓ **In diabetes, this regenerative capacity is likely reduced.**

Discovery of Abnormal BMDCs

- ✓ Abnormal BMDCs play a crucial role in the progression of diabetes.
- ✓ These abnormal cells are generated under hyperglycemic conditions and cannot be eradicated by insulin treatment.
- ✓ **Abnormal BMDCs disrupt normal tissue function and hinder the healing of diabetes.**

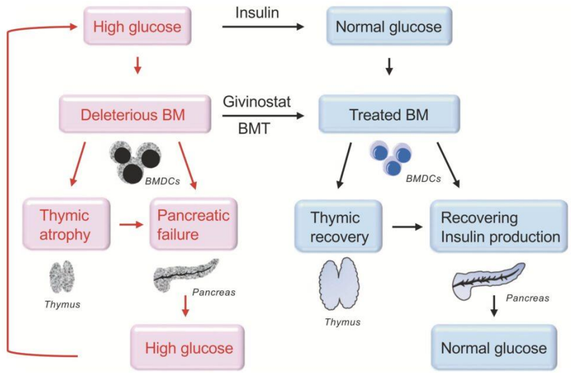


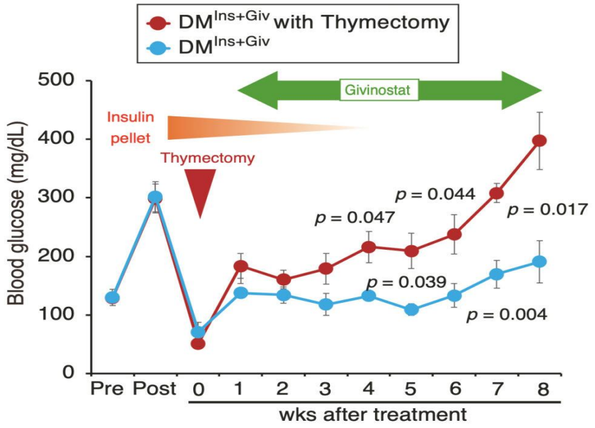
Abnormal expression of HDACs was observed in the HSC cells (LSK) in DM

Reasons Why Diabetes Is Not Curable (2)

From Hypothesis to Proof:

The Path to a Diabetes Cure through Targeting Abnormal BMDCs





Hypothesis and Research Methods

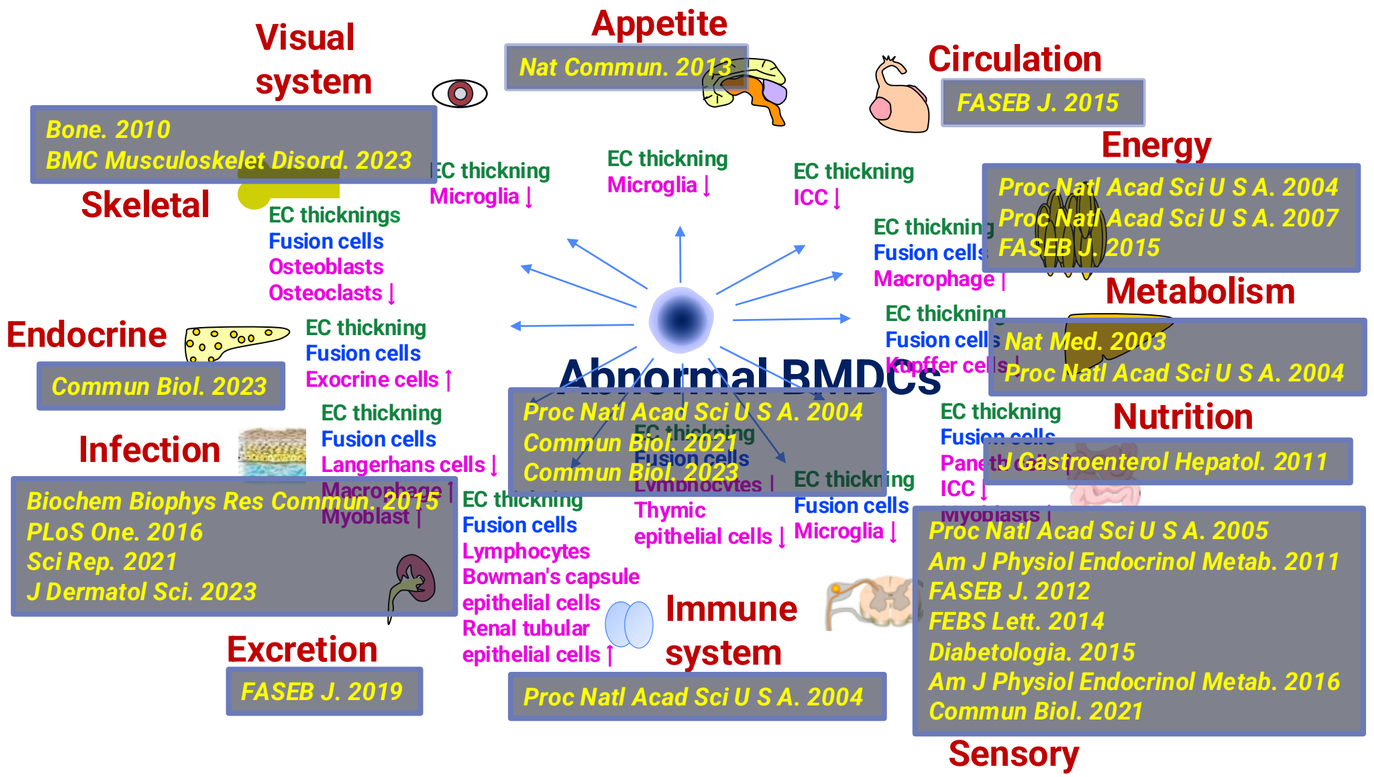
- ✓ **Treating abnormal BMDCs may restore β-cell regenerative capacity and normalize insulin secretion.**
- ✓ Hypothesis tested using streptozotocin (STZ)-induced diabetic model mice.
- ✓ Controlled hyperglycemia with insulin to suppress abnormal BMDCs generation.
- ✓ **Used HDAC inhibitors** to correct epigenetic changes in abnormal BMDCs.

Research Outcomes

- ✓ **Treating abnormal BMDCs enables β-cell regeneration.**
- ✓ Complete remission of diabetes (≈ cure) is expected.
- ✓ Recovery of thymic function **(Regeneration of the T cell system that eliminates abnormal cells, aiding in natural remission)**.
- ✓ Opens new avenues for diabetes treatment.

A Testament to 20+ Years of Research

Our publications on bone marrow-derived cells in diabetes and its complications (2003-2024)



Research-Based Truths

We present over 20 years of research on **abnormalities in bone marrow-derived cells and organ damage in diabetes,** summarized by organ.

Each paper explains how these abnormalities are related to diabetes.

List of Achievements

Shiga University of Medical Science, Department of Regenerative Medicine Development*

https://biozipcode.org/lab/achievement

*The Department of Regenerative Medicine is currently integrated with the Department of Life Information Science, led by Professor Kojima, and is conducting joint research.

SOLUTION

International Patents from Basic to Application

01 **Diabetes Therapy Targeting Abnormal Stem Cells**

02 **Therapy for Diabetes Using Stem Cell Migration Agent**

03 **Methods and Agents for Novel Treatment, Diagnosis, and Detection of Diabetes and Its Complications**

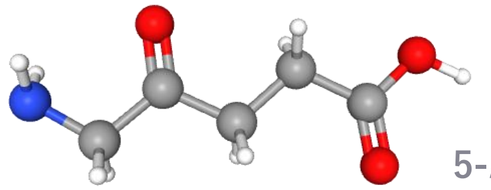
04 **Method or Agent with HDAC Regulator, for Treatment of Diabetes and Complications**

We Hold the Key to Curing Diabetes

These patented technologies enable fundamental diabetes treatment, greatly improving patients' lives.

We hold **international patents** for treatments from the causes to the cure of diabetes.

In addition, **patents related to 5-ALA and diabetic stem cells are also being filed as potential cures for diabetes**.



5-ALA

Patents pending (national phase entry in progress): PCT/JP2020/039044, PCT/JP2020/039045, PCT/JP2022/008036, PCT/JP2022/008036

WE CAN

Cure Diabetes

- ✓ Diabetes **Test Kit**
- ✓ Diabetes **Cure Medication**
- ✓ Diabetes **Complications Cure**

02

Utilization of “Biozipcode™”

Biozipcode™ (Cell Targeting Technology)

Technology Overview

Development of Targeted Drug Delivery System

Current Challenges:
Current oral and injectable drugs affect not only the target cells but also other cells in the body.

Solution

- ✓ Develop a delivery method that **transports drugs exclusively to target cells**. **-> Cell-Targeted Drugs**

Concept of Biozipcode™

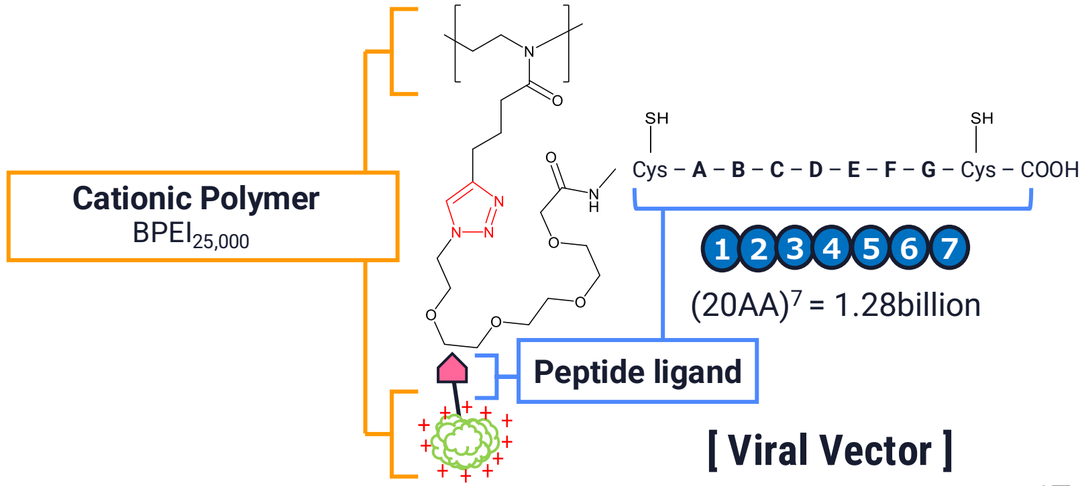
- ✓ Similar to using addresses or GPS for delivering packages, assign specific address codes to cells.
- ✓ **Use a 7-digit amino acid sequence instead of postal codes.**

Use of Amino Acid Sequences

- ✓ Create **7-digit codes** from **20 types of amino acids** (20^7 = **1.3 billion combinations**).
- ✓ Select codes that only target cells can recognize and attach them to the drug carriers.

Expected Benefits

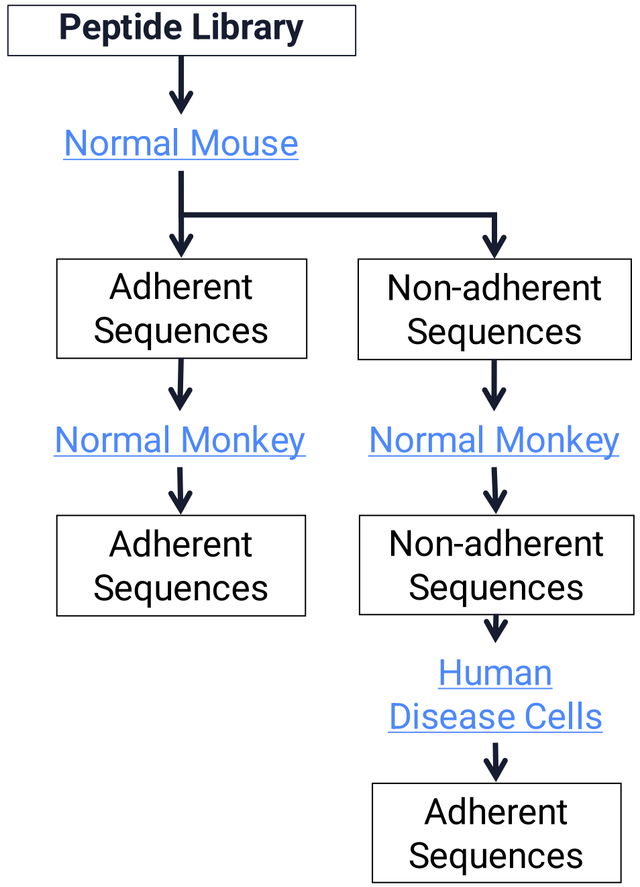
- ✓ **Drugs reach only the target cells** through blood vessels or cerebrospinal fluid.
- ✓ **Minimize effects on non-target cells.**
- ✓ **Development of drugs without side effects is possible** (Including the reuse of drugs previously abandoned due to strong side effects)



Japanese postal codes are composed of 7 digits. 〒□□□-□□□□

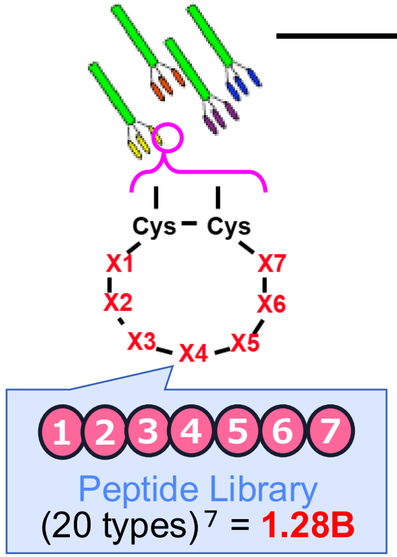
Method of Collecting Cell-Targeting Peptides

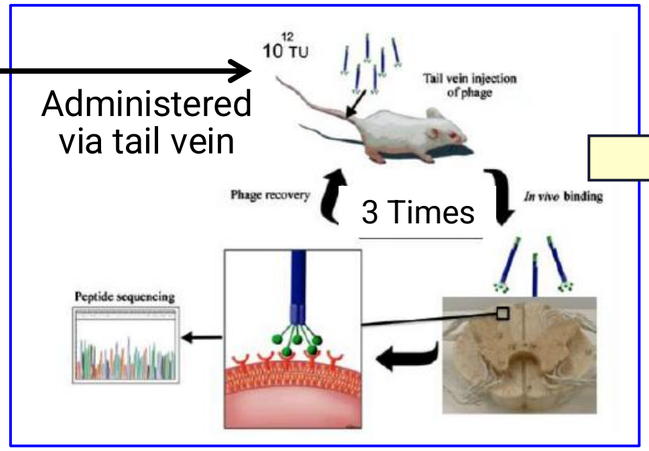
Overall Process



In Vivo Biopanning

M13 Phage





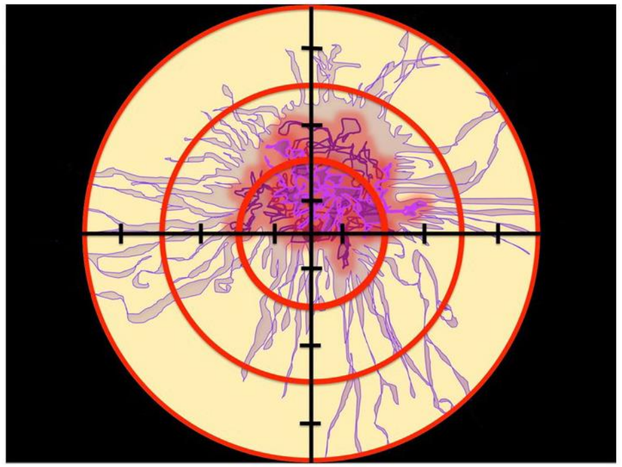
Cell Targeting Peptide

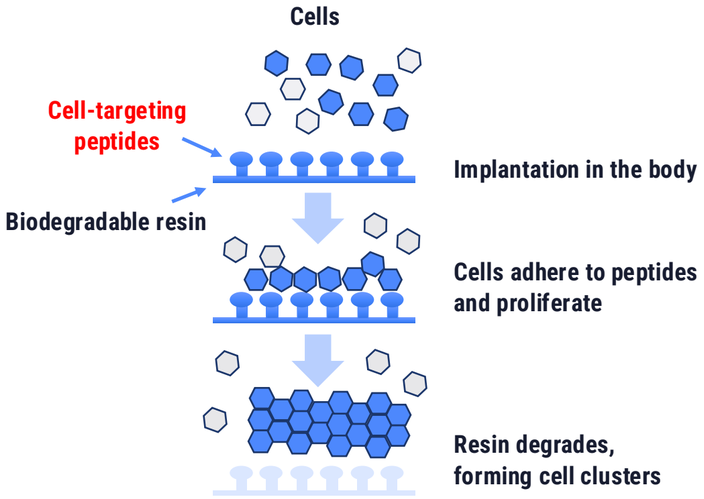
"Biozipcode™"

Target Adherent Sequences
– Non-adherent Sequences
= Sequences that only adheres to the target

- ✓ Collect organs/cells and **isolate adherent phages**.
- ✓ Infect and proliferate phages in E. coli.
- ✓ Collect phages from plaques and sequence DNA using NGS.
- ✓ **Identify cell-adherent peptides from DNA sequences.**

The ultimate new technology beyond molecular targeting





Development of a Side-Effect-Free Cure for Diabetes

- ✓ **Directly targets "diabetes stem cells**," the root cause of diabetes.

Development of a Side-Effect-Free Cancer Treatment

- ✓ Pain relief treatment for nerve cells.
- ✓ **Cancer treatment targeting only cancer cells**
- ✓ Obtains a **Biozipcode™ common to all cancers**.

Cell Targeting for Tissue Regeneration

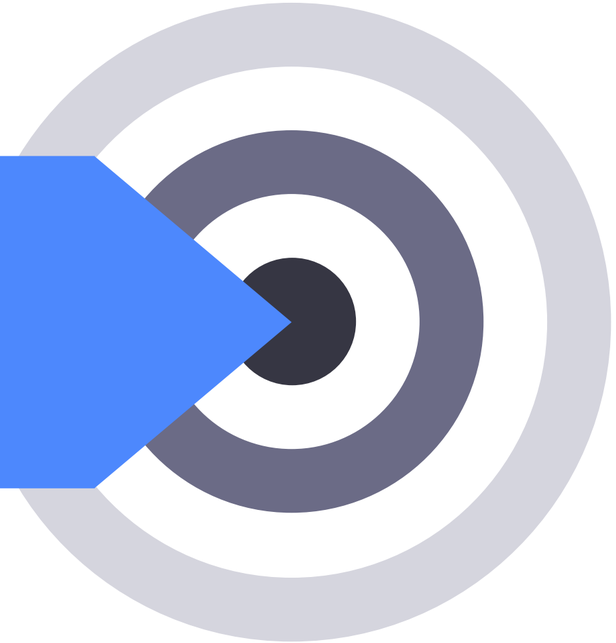
- ✓ **Promotes tissue integration without the need for transplantation or sutures.**
- ✓ Natural stratified tissue regeneration progresses, ensuring wound healing without hypertrophic scars or keloids.

"Biozipcode™" for Developing a Specific Cure

The Biozipcode™ for **each organ**, **diabetes stem cells**, and **various types of cancer tumors bindings** have already been largely obtained. In the future, experiments will be conducted using actual human cells, and the results will be analyzed using supercomputers and AI. **This will enable the development of specific cures that target only the "cells" of interest.**

Cell-Targeting Technology

Utilizing "Biozipcode™," the ultimate new technology surpassing molecular targeting.



"Utilization of sequence information that adheres only to the target."

Why Drugs Without Side Effects Can Be Developed

By applying cell-targeting technology using a new delivery system called **"Biozipcode™," which delivers drugs only to specific target cells, it is possible to develop drugs that act directly.**

Molecular Targeted Drugs

- ✓ **Targets specific molecules or proteins**
- ✓ Can cause side effects if the target molecule is present elsewhere
- ✓ Resistance can develop with continuous use

Cell-Targeted Drugs

- ✓ **Targets only specific target "cells"**
- ✓ Does not bind to non-target cells, so no side effects occur
- ✓ Unlikely to cause resistance as it does not act elsewhere

Solution Using “Biozipcode”

Addressing using “Biozipcode™”

A method to tag all cell groups/types with a unique address "Biozipcode™” for Cell-Targeted Drugs

DDS with “Biozipcode™”

A way to reach those addresses through proprietary mechanism

Vectors for “Biozipcode™”

Practical application of DDS vectors using "Biozipcode™"

ABILITY TO CREATE

Cell-Targeted Drugs

Development of a Side-Effect-Free

- ✓ Cure for **Diabeteses**
- ✓ Drugs for **Cancer Treatment**

Cell Targeting for

- ✓ Tissue **Regeneration**

APPENDIX

About the Department of Biocommunication Development at Kyoto University Graduate School of Medicine and Faculty of Medicine

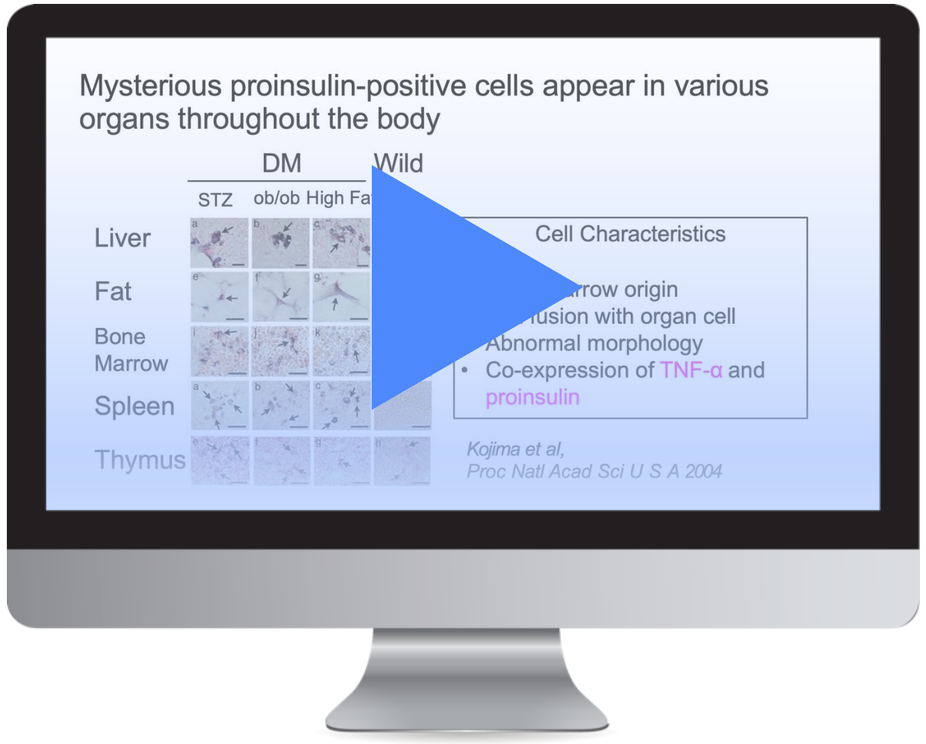
"Aiming to Cure Diseases Rather Than Just Treat Symptoms"

Applying the unique technology developed by Special Professor Kojima, we aim to redevelop existing drugs and develop new drugs and medical materials for tissue regeneration. This is targeted at intractable chronic diseases such as diabetes, cancer, autoimmune diseases, multi-organ failure, and conditions resistant to conventional surgical and pharmacological treatments.

- **Establishment**
  April 1, 2026 (Year of Reiwa 8th)
- **Web Site**
  https://biozipcode.org

Professor Hideto Kojima

Complete remission of STZ diabetes by removing "Diabetes Stem Cells”



YouTube:
https://youtu.be/Aff8h_x8_KQ

We discovered that abnormal hematopoietic stem cells, named "Diabetes Stem Cells (DSC)," inhibit islet regeneration and impede diabetes remission in STZ mice. By combining insulin and an HDAC inhibitor and treating for a certain period, these "Diabetes Stem Cells" were eliminated, leading to complete remission of diabetes.

*Presentation Content at ENDO2024 (Endocrine Society 2024), 4th Edition of World Congress on Endocrinology, Diabetes and Metabolism, and Communications Biology 2003

*Approximately 15-minute Presentation in English (with Japanese and English Subtitles)

A New Path to Wellness with 5-ALA

"Transform Your Body from the Mitochondria Up!"

YouTube:

https://youtu.be/Aff8h_x8_KQ

The key to a healthier body starts with your cells! 5-ALA enhances mitochondrial energy, supporting metabolism, skin hydration, and collagen production. It has also been reported to help with diabetes, improve sleep quality, and reduce fatigue and negative moods—making it a powerful ally in daily life.

What is 5-ALA (5-Aminolevulinic Acid)?

Specific Actions of 5-ALA and its Medical Applications

5-Aminolevulinic Acid (5-ALA) plays an important role in our bodies. It serves as a precursor to heme, a component necessary for energy production within mitochondria. Heme is involved in generating ATP, the energy source, and in breaking down reactive oxygen species.

When eight molecules of 5-ALA come together, they transform into a substance called PPIX (Protoporphyrin IX) in the body. PPIX tends to accumulate in cancer cells and has the property of emitting light when exposed to specific wavelengths. This property is utilized in medical applications, such as identifying cancerous areas during surgery.

Additionally, adding iron to PPIX produces heme, which is essential for energy production in mitochondria and forms hemoglobin that carries oxygen in the blood. When magnesium binds to PPIX, chlorophyll is produced, contributing to photosynthesis in plants.