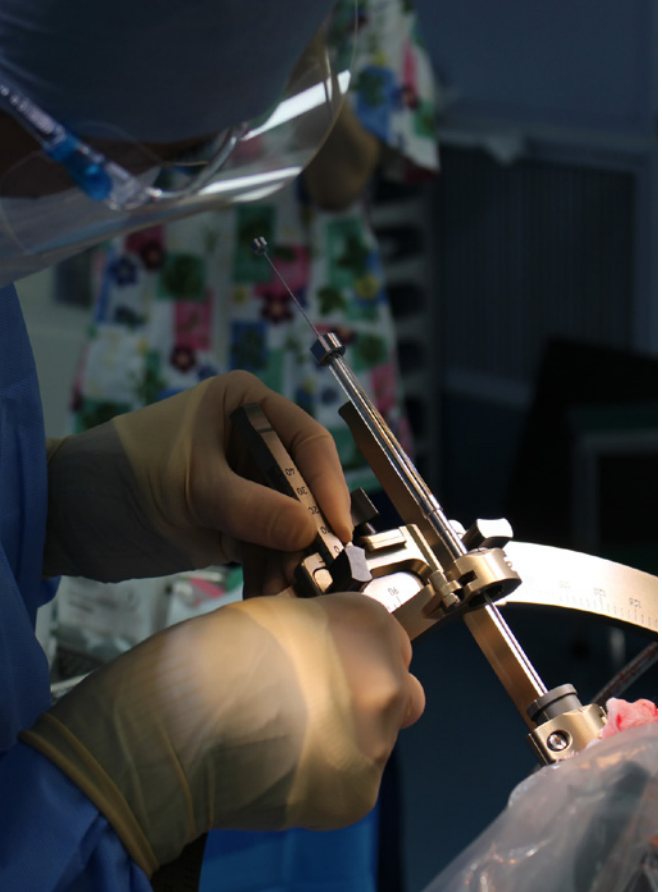

# Parkinson's disease treatment at Kyoto University Hospital

Hybrid OR procedure helps to transplant stem cells precisely

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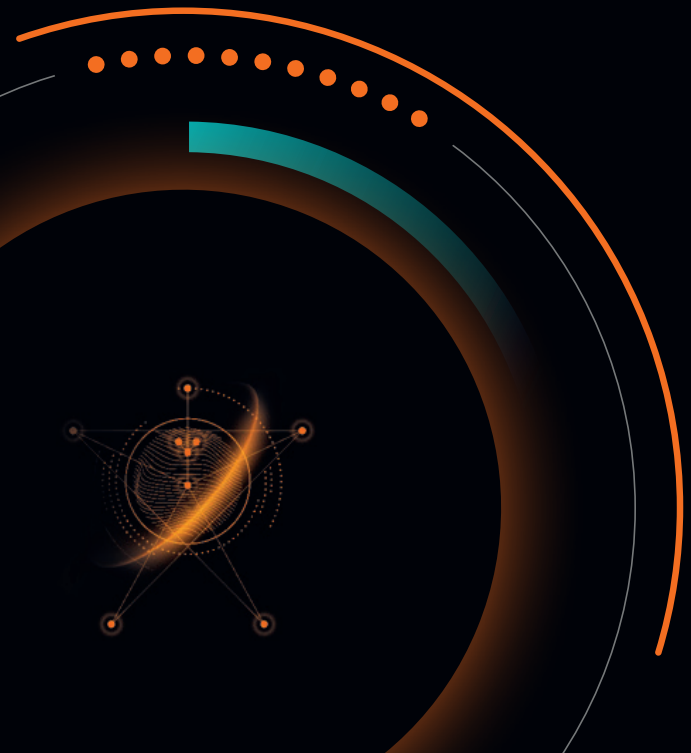


A clinical trial of cell therapy for Parkinson's disease (PD) using induced pluripotent stem cells (iPSCs) began in 2018 in Japan. In PD, many dopamine neurons in the brain are lost. To compensate for the lost neurons, iPSC-derived dopamine neurons are transplanted via cell therapy in a hybrid OR setup. To derive the dopamine neurons from iPSCs, the cells are cultured with many inducing factors.

## Kyoto hospital, the leader in stem cell transplantation

In 2012, Shinya Yamanaka won the Nobel Prize in Medicine for his discovery of how to transform ordinary adult skin cells into cells capable of developing into any cell in the human body. To develop advanced cell therapies for regenerative medicine, it is essential to isolate human cells that have a specific function or to produce a target cell from stem cells. The Center for iPS Cell Research and Application (CiRA) at Kyoto University was established to process such human cells and works toward the development of new therapies for treating intractable diseases by producing safe and high-quality therapeutic cells.

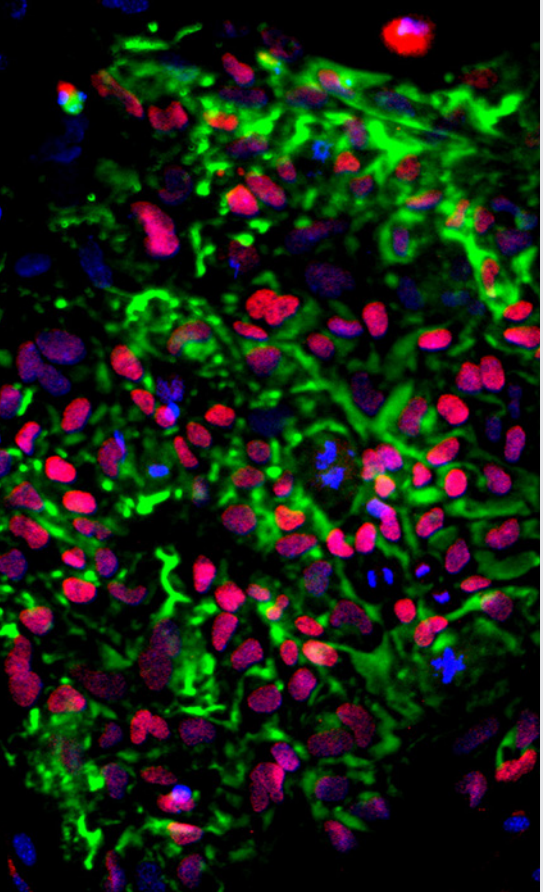
## The dopamine deficiency disease

A hallmark sign of Parkinson's disease (PD) is the breakdown and death of dopaminergic neurons in the substantia nigra, one of several structures in the midbrain. Patients with PD experience gradual worsening of tremor, bradykinesia – a slowness of movement – rigidity, and postural instability. The activities of daily life become more and more limited as the disease progresses, and the shortage of neurons producing dopamine can lead to tremors and difficulty walking.

Until now, the first line of treatment for patients with PD was medication like levodopa, a class of medications called central nervous system agents. Levodopa works by being converted to dopamine in the brain. But its effectiveness frequently dwindles over time and causes wearing-off and dyskinesia, a disturbance in the physiological movements in various body regions.

## Reprogrammed stem cells implanted into the brain of a patient with Parkinson's disease

In a global first, Kyoto University Hospital doctors injected neural progenitor cells created from induced pluripotent stem (iPS) cells into the brain of a patient to ease the symptoms of the devastating nervous system disorder using the advanced imaging capabilities provided by a neurosurgical hybrid operating room (hybrid OR). The goal of cell therapy for PD is to increase treatment options and to beneficially combine it with other treatments like medical therapy and rehabilitation.



## What are induced pluripotent stem cells?

Induced pluripotent stem cells, or iPS cells, have the ability to become many different types of body cells, and they also demonstrate high proliferative activity. They are distinct from embryonic stem cells because they are derived from adult tissue. They are also distinct from the adult stem cells that occur naturally in the human body.

## Transplanted cells were functionally active in model animals

In research on PD cell therapy, it is common to use disease model animals like mice or cynomolgus monkeys that have been depleted of dopamine neurons by injecting a neurotoxin. The iPSC-derived dopamine neural progenitor cells are transplanted into the PD model animals, and their behavioral improvements and cell survival are examined. Observation using a neurological score system and video analysis showed improvements in spontaneous movement after transplantation.

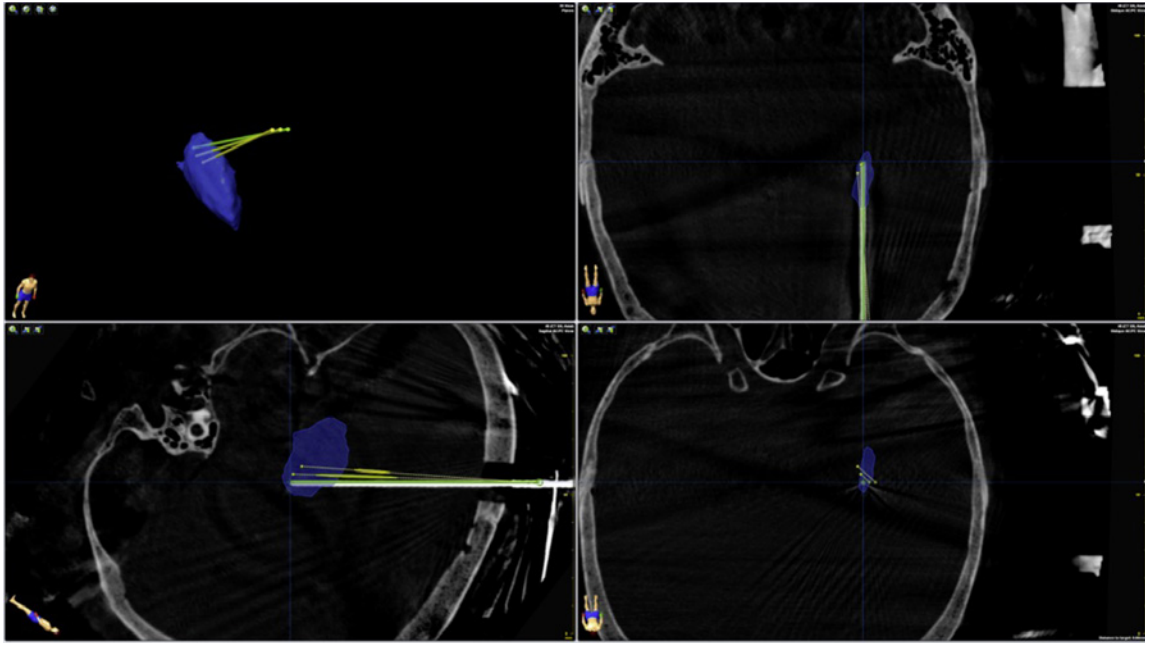
It was also shown that the transplanted cells were functionally active using positron emission tomography.

## Five million dopamine precursor cells implanted into brain of a PD patient

Because the cells were shown to improve symptoms of PD in monkeys, neurosurgeon Takayuki Kikuchi at Kyoto University Hospital decided to implant five million dopamine precursor cells into the brain of a 50-year-old patient. During a three-hour procedure, the team deposited the cells at 12 sites known to be centers of dopamine activity.

Stem cell scientist Jun Takahashi and colleagues derived the dopamine precursor cells from a stock of iPS cells stored at the university.

They were developed by reprogramming blood cells taken from an anonymous donor so that they reverted to an embryonic-like state from which they could develop into other cell types. To prepare for the transplantation, the scientists used the technique to differentiate iPS cells into precursors to the neurons that produce the neurotransmitter dopamine.



Intraoperative trajectory planning to transplant stem cells precisely in the putamen.

## Workflow: Transplantation procedure in a hybrid OR

To determine the transplantation location precisely, a stereotactic procedure was used to deliver the cells. The transplantation target was the bilateral putamen. Three trajectories were chosen for each side of the putamen. The injection needle specifically designed for this procedure was carefully inserted in the target along each trajectory according to the preoperative stereotactic plan.

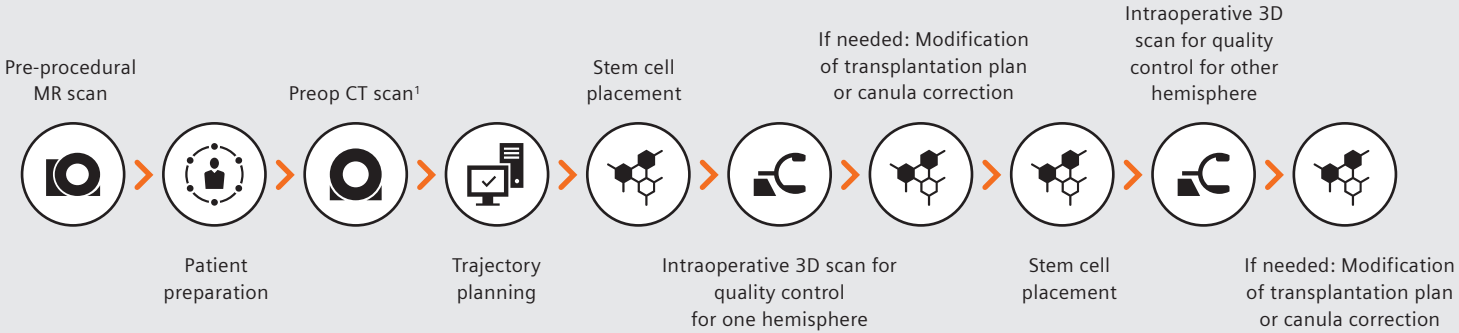
To get an actual view the tip of the cannula in relation to the target anatomy, a cone beam CT (CBCT) was then acquired intraoperatively using Artis zeego while the cannula and stereotactic arc were in place. If the gap between the target and the tip of the cannula is large but the trajectory penetrates the target structure, the transplantation site can be adjusted without changing the trajectory. A thin-slice DICOM image was created and sent to the RIS server. The CBCT data was transferred from Artis zeego to the stereotactic planning system and integrated in the planning data.

The cells were transplanted at one to two-millimeter intervals along each trajectory (at seven to eight points in each trajectory).

To confirm the accuracy of the stereotactic procedure, an intraoperative evaluation using Artis zeego CBCT scanning was performed after the first puncture of each hemisphere. The CBCT image was displayed alongside the preoperative planning so that the location of the cannula tip and the presumed target could be compared.

# Overview about the intraoperative workflow

Intra-op CBCT was acquired when puncturing the first trajectory of each side. There was no case of canula correction. The decision of cell numbers for the 2nd and 3rd trajectory was defined by the amount of implanted cell number according to the result of CBCT of 1st trajectory.



## A new chapter begins

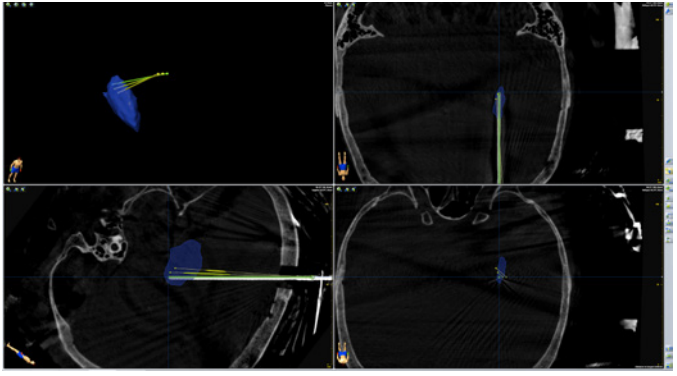
Cell replacement therapy shows a lot of potential for the treatment of PD and is a promising approach for various other diseases. It may not be effective for all PD patients because there are different disease types and stages that are not suited for cell therapy. Yet with the first iPS cell-based clinical trial in Japan, a new and exciting chapter has begun. Researchers from different countries around the world have been working on the development of stem cell-based treatments for Parkinson's for years and have founded a consortium called "GForce-PD" that works together to develop approaches for clinical use. The mainstay of treatment for PD will remain medical therapy for the foreseeable future. However, clinical trials will continue to contribute to the development of new cell-based treatments for Parkinson's disease.
It is a major step on the path to designing patient-specific cell-based therapy, even if it will still be a few years before this treatment for Parkinson's is ready for the market.

## Jun Takahashi

Jun Takahashi, MD, is a professor and Director of the Center for iPS Cell Research and Application at Kyoto University. He graduated from Kyoto University's School of Medicine in 1986 and is a neurosurgery specialist. In 2018, Takahashi initiated a clinical trial of dopaminergic neural progenitor cell transplantation for Parkinson's disease.


## Department of Neurology, Kyoto University Hospital

With the rapidly growing number of older individuals in Japan, the number of patients with age-related neurological diseases like stroke, dementia, and neurodegenerative diseases is increasing dramatically. The treatment of these patients requires precise diagnosis based on clinical evidence. Several faculties at Kyoto University Hospital are involved in establishing the guidelines for treating Parkinson's disease and epilepsy. Their goal is not simply to treat current patients but also to contribute to the welfare of future patients through medical research.



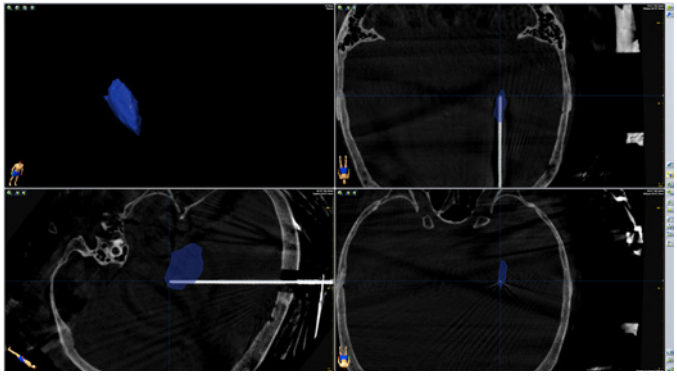


**Figure 1, 2**
Trajectory view of intraoperative CBCT with (Fig. 1) and without (Fig. 2) corresponding trajectories. The CBCT image was fused with the preoperative magnetic resonance image and displayed with the planning data. The cannula was inserted accurately in the planned target. Blue areas indicate putamen. Blue cross-bars indicate the target point based on the preoperative planning. Trajectories were displayed as green, yellowish green, and yellow (green solid lines indicate the trajectory corresponding to the path of the inserted cannula). Solid line segments indicate trajectories on the image plane. Dotted line segments indicate trajectories outside of the plane.

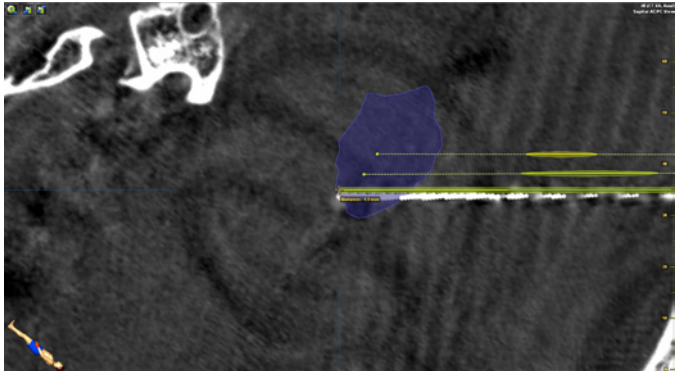


**Figure 3**
CBCT image overlaid on the planning image demonstrates a 1.3-mm gap between the planned trajectory and the actual cannula location (trajectory view and two other orthogonal views). As a result, the total trajectory length in the putamen (blue area) was shorter compared to the planning image. In this situation, adjusting the transplantation site was considered.

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