

News Release

Functional analysis of adrenocorticotrophic-hormone-producing pituitary cells derived from human pluripotent stem cells in murine and primate models of hypopituitarism

Key Points

- **A Promising Stem Cell Strategy for a Lifelong Disease**

Hypopituitarism is a severe condition that currently requires patients to take hormone replacement therapy for their entire lives. We have developed a new potential treatment by using human pluripotent stem cell (PSC) -derived pituitary-hypothalamic tissue structures (organoids) that produce adrenocorticotrophic hormone (ACTH), a vital hormone. Our findings suggest that transplanting these lab-grown tissues just under the skin could offer a new therapeutic approach for this disease.

- **Proven to Extend Life in Mouse Models**

We tested this regenerative therapy on mice suffering from pituitary failure. After transplanting the PSC-derived pituitary-hypothalamic organoids under the skin, the organoids successfully survived and released ACTH into the body. This treatment significantly extended the lifespans of the mice.

- **The World's First Success in a Primate Model**

We successfully performed this organoid transplantation in a monkey. Using the same immune-suppression methods clinically used in pancreas transplantation, we transplanted the pituitary-hypothalamic organoids into a monkey lacking a pituitary gland. The organoids successfully produced ACTH for at least six weeks, preventing severe weight loss and proving the treatment's potential for future clinical use. This is the first report showing the therapeutic potential of pluripotent stem cell-derived pituitary-hypothalamic organoids in a monkey model.

Summary

A research team from the Nagoya University Graduate School of Medicine—including Guest Researcher Tatsuma Kondo, Associate Professor Hidetaka Suga, Professor Hiroshi Arima, and Professor Ryuta Saito—has made a significant advancement in regenerative medicine. In collaboration with RACTHERA Co., Ltd., Shiga University of Medical Science, and Kyoto University, we successfully restored hormone production in animal models (mice and a monkey) suffering from pituitary gland failure. They achieved this by growing "pituitary-hypothalamic tissues created from human pluripotent stem cells (hPSCs) (pituitary-hypothalamic organoids) and transplanting them just

under the skin. This marks the world's first successful report of pituitary regenerative medicine in a primate model.

Hypopituitarism is a rare and serious disease affecting about 45.5 out of every 100,000 people. A lack of ACTH, a crucial hormone, can lead to fatal adrenal failure. The current standard treatment requires patients to take hormone replacement drugs for the rest of their lives. However, these daily medications cannot perfectly match the body's constantly changing needs in response to stress and natural daily rhythms, which can ultimately affect a patient's lifespan and quality of life.

In this study, we transplanted these lab-grown pituitary-hypothalamic organoids under the skin (into fat or muscle) of immune-deficient mice that lacked pituitary function. The transplanted tissues successfully survived, continuously produced the ACTH for over six months, and significantly extended the mice's lifespans.

Next, we conducted tests on a monkey whose pituitary gland had been removed. Using the same immune-suppressing methods clinically used in pancreas transplantation, they transplanted the human PSC-derived pituitary-hypothalamic organoids under the monkey's skin. Because the transplant was derived from a different species (human to monkey), long-term survival of the transplant is usually very difficult to achieve. However, the transplanted tissues successfully raised ACTH levels in the blood for at least six weeks, stopping the severe weight loss caused by the disease. This is the first time in the world that a pituitary-hypothalamic organoid transplantation has been proven effective in a primate.

This research proves that these lab-grown pituitary-hypothalamic organoid can function well even when transplanted "subcutaneously" (just under the skin)—a location that is safe, simple, and very easy for doctors to monitor. Moving forward, we aims to establish mass-production methods using clinical-grade stem cells (iPS cells) and verify long-term safety, for the realization of regenerative medicine for patients suffering from hypopituitarism.

This research was supported by the Japan Agency for Medical Research and Development, grants JP24ek0109702, Japan; the Japan Science and Technology Agency (JST) FOREST Program, grant JPMJFR200N, Japan; the Ministry of Education, Culture, Sports, Science and Technology of Japan Grant-in-Aid for Scientific Research (C), grant JP23K08005, Japan; and Nagoya University Hospital Funding for Clinical Research, grant 71004191 and by

RACTHERA Co., Ltd., Sumitomo Chemical Company Limited, and Sumitomo Pharma Co., Ltd.. The findings will be published online in the BMC / Springer Nature journal Stem Cell Research & Therapy on October 2, 2026 at 10:00 JST.

Research Background

We aim to realize regenerative medicine for the pituitary gland to treat hypopituitarism. Given its critical clinical significance, we have designated adrenocorticotrophic hormone (ACTH) deficiency as our primary therapeutic target. Our approach involves differentiating hPSCs into ACTH-producing pituitary-hypothalamic organoids for subsequent transplantation. We are continuously advancing this technology with the goal of realizing pituitary regenerative medicine.

Having already established a differentiation method for clinical application, our current imperative is the optimization and practical implementation of the transplantation procedure. As one of transplantation routes, we are considering a subcutaneous transplantation approach, which is easy to monitor transplanted cells. Aiming to establish a proof-of-concept for a pituitary cell-based therapeutic, we first identified and validated optimal subcutaneous sites for transplantation in a murine model. Building on these findings, we then conducted transplantation experiments using a cynomolgus macaque model to confirm therapeutic efficacy.

Research Results

We generated pituitary-hypothalamic organoids containing ACTH-producing cells differentiated from human embryonic stem (ES) cells. Using hypophysectomized, immunodeficient mice as a model of pituitary dysfunction, we evaluated optimal engraftment sites by transplanting the cells into subcutaneous white adipose tissue and skeletal muscle. In this murine evaluation, the transplanted organoids successfully engrafted in both the subcutaneous adipose and intramuscular sites for over six months. They significantly elevated plasma ACTH levels (Figure 1a–d) and demonstrated a higher overall survival rate compared to the sham-operated group (Figure 1e).

Next, using an immunocompetent, hypophysectomized cynomolgus macaque as a non-human primate model of pituitary dysfunction, we subcutaneously transplanted the pituitary-hypothalamic organoids into the dorsal region. This was performed under a clinically validated immunosuppressive regimen analogous to that used in human pancreas islet transplantation. In the macaque, the transplanted organoids remained functional and elevated plasma ACTH levels for six weeks post-transplantation (Figure 2a). While xenotransplantation typically provokes robust immune rejection—which was indeed observed in this

macaque study—histological examination at three months post-transplantation revealed the persistence of the graft. Coupled with the aforementioned plasma ACTH data, this indicates that the transplanted organoids successfully achieved short-term engraftment.

No unexpected cellular proliferation or tumorigenesis was observed in either the murine or macaque models. Furthermore, while hypophysectomized macaques typically exhibit gradual weight loss even when receiving corticosterone replacement therapy (mimicking current standard-of-care), their body weight was successfully maintained without corticosterone supplementation during the six-week period when the graft was presumed functional. This strongly suggests a physiological therapeutic effect driven by the organoid transplantation (Figure 2b).

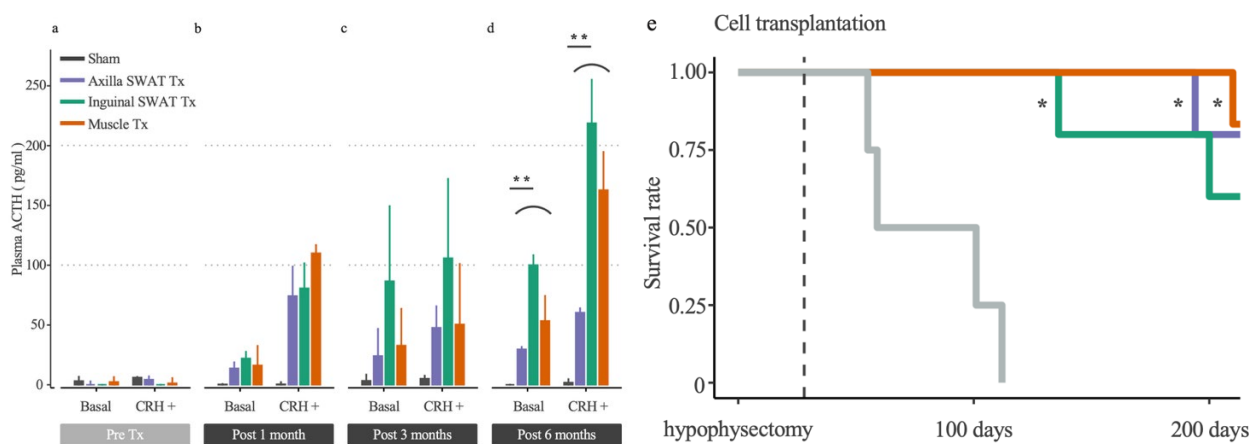


Figure 1: Subcutaneous transplantation of hESC-derived pituitary-hypothalamus organoids in mice.

(a-d) Evaluation of transplanted mice. Basal and CRH-stimulated plasma ACTH levels in mice subjected to pituitary-hypothalamus organoids transplantation. Groups were (b, c) sham (n=4, grey), axillary subcutaneous white adipose tissue (Axilla SWAT Tx, n=5, purple), inguinal subcutaneous white adipose tissue (Inguinal SWAT Tx, n=6, green), and intramuscular transplantation (Muscle Tx, n=6, orange); (d) sham (n=4), Axilla SWAT Tx (n=5), Inguinal SWAT Tx (n=4), and Muscle Tx (n=6); (e) sham (n=4), Axilla SWAT Tx (n=3), Inguinal SWAT Tx (n=3), and Muscle Tx (n=4). Bars indicate median (IQR). **p<0.01 for the comparison between the sham-operated group and all transplanted groups as a whole (Wilcoxon rank-sum test).

(e) Survival curves of sham and transplanted groups. Day 0 was defined as the day of hypophysectomy. Cell transplantation was performed between days 28 and 35 for each site. Survival times are shown for sham (n=4, grey), Axilla SWAT Tx (n=5, purple), Inguinal SWAT Tx (n=6, green), and Muscle Tx (n=6, orange).

Survival analyses were performed employing the Kaplan-Meier method, with group comparisons made using the log-rank test. * $p < 0.05$ indicates a significant difference from sham.

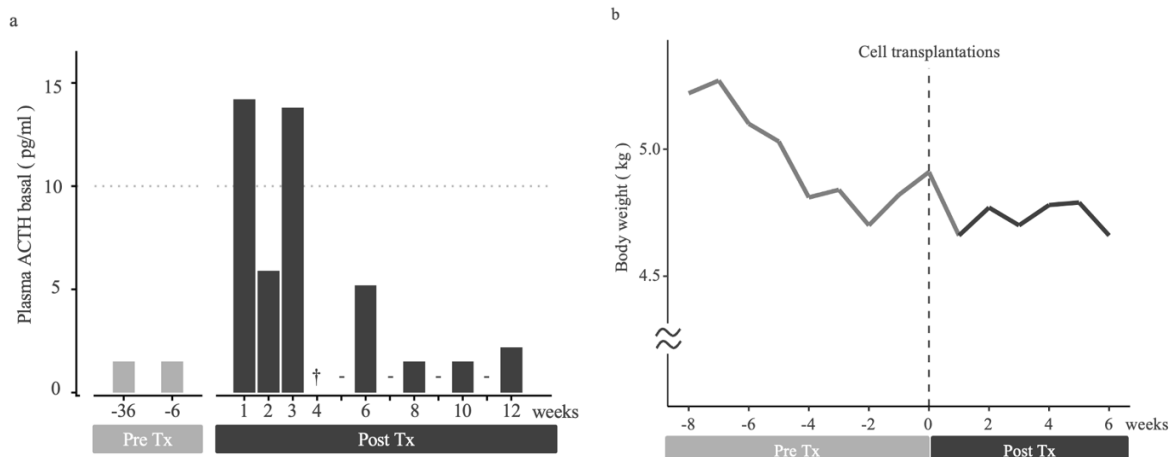


Figure 2: Evaluation of grafted monkey.

(a) Basal plasma ACTH concentrations in a cynomolgus monkey transplanted with pituitary-hypothalamus organoids. Subcutaneous transplantation group, $n=1$. Although fluctuations were observed due to blood sampling under anaesthesia, an increase in basal ACTH concentrations was confirmed up to approximately 6 w after transplantation. († Data at 4 w after transplantation were excluded because of a measurement error.)

(b) Changes in body weight before and after cell transplantation in cynomolgus monkey with hypopituitarism.

Body weight trajectory before and after transplantation of pituitary-hypothalamus organoids. In the hypopituitarism model, where pronounced weight loss occurs due to ACTH deficiency, attenuation of weight loss was suggested during the period in which the graft was presumed to be functional.

Research Summary and Future Perspective

In conclusion, this study provides definitive evidence that subcutaneously transplanted pituitary-hypothalamic organoids exert significant therapeutic efficacy in both murine models and a cynomolgus macaque model. Furthermore, it represents the world's first report confirming improved ACTH secretion and histological engraftment—albeit short-term—following the transplantation of hESC-derived ACTH-producing pituitary-hypothalamic organoids into a

non-human primate model of pituitary dysfunction.

Moving forward, we will continue to establish a robust foundation for the clinical application of pituitary cell-based regenerative medicine. Future developmental efforts will focus on optimizing surgical techniques and immunosuppressive protocols, determining the optimal therapeutic cell dose, and establishing a large-scale manufacturing methods applicable for future clinical application.

Publication

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DOI:10.1186/s13287-026-05098-y

Japanese ver.

https://www.med.nagoya-u.ac.jp/medicalJ/research/pdf/Ste_261002.pdf