Press Release

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Press Release

Keio University
University of Illinois
Chiba University

Development of a Novel Neuroregenerative Drug Candidate for Improved Paralysis Outcomes in Multiple Sclerosis: A Notch Inhibitor with a Novel Mechanism of Action

A Notch inhibitor with a novel mechanism of action was developed by a research team comprising Professor Midori Arai, third-year doctoral student Yuki Narushima (at the time of the study), and Senior Lecturer Shun Saito from the Department of Biosciences and Informatics in the Faculty of Science and Technology at Keio University; Associate Professor Makoto Inoue from the University of Illinois Urbana-Champaign; and Professor Takayoshi Arai from the Graduate School of Science at Chiba University. The researchers demonstrated improvements in paralysis outcomes and neural regeneration in a mouse model of multiple sclerosis (MS). The findings were published online in the international journal *Advanced Science* (Wiley) on October 30, 2026.

1. Key Findings

- The researchers elucidated a novel mechanism of action by which the natural product-like compound furapyrrodole (FP) activates the mitochondrial enzyme CYB5R3 (*Note 1*), leading to inhibited Notch signaling (*Note 2*) through mitochondrial membrane potential hyperpolarization and decreased intracellular calcium ion levels.
- FP promoted the differentiation of neural stem cells (*Note 3*) into neurons and oligodendrocytes. Furthermore, intrathecal and intraperitoneal FP administration improved paralysis outcomes in a mouse model of multiple sclerosis (*Note 4*); these improvements were accompanied by increased numbers of motor neurons and remyelination in the spinal cord. These findings suggest FP's potential as a novel therapeutic candidate for restoring neurological function.

2. Background

Multiple sclerosis (MS) is a disease in which the myelin sheaths (*Note 5*) of the central nervous system are damaged as a result of immune system dysfunction. Although existing treatments can suppress disease relapse and progression, no established therapy can adequately restore neurological functions that have already been lost. One novel treatment strategy for achieving fundamental functional recovery in adults is to replenish neurons and myelin-forming cells by promoting the differentiation of neural stem cells in the brain and spinal cord.

In recent years, the inhibition of Notch signaling, which suppresses neural stem cell differentiation in the body, has attracted considerable attention. However, conventional γ-secretase inhibitors are associated with gastrointestinal adverse effects, highlighting the need for Notch inhibitors with alternative mechanisms of action.

3. Research Findings

Development of Furapyrrodole (FP)

Using reporter cells (*Note 6*) developed by Professor Midori Arai's group to measure Notch activity, the researchers screened the Chiba Chemical Library and identified Notch-inhibitory activity in natural product-like spirooxindole compounds synthesized by Professor Takayoshi Arai's group. By further synthesizing and evaluating derivatives, they identified furapyrrodole (FP) as a variant with potent Notch-inhibitory activity.

Elucidation of FP's Mechanism of Action

The researchers further identified CYB5R3, a mitochondrial membrane–associated oxidoreductase, to be a target protein of FP and demonstrated that FP enhances its enzymatic activity. This activation resulted in hyperpolarization of the mitochondrial membrane potential and decreased levels of cytosolic calcium ions. Consequently, the activity of the calcium-dependent enzyme calcineurin decreased, suppressing the nuclear translocation of NICD (*Note 7*), a key mediator of Notch signaling. These findings reveal a novel mechanism of Notch inhibition distinct from that of conventional γ-secretase inhibitors.

Neuroregenerative Effects of FP and Improved Paralysis Outcomes in a Mouse Model of Multiple Sclerosis

The research team led by Associate Professor Inoue observed improvements in paralysis outcomes when FP was administered intrathecally or intraperitoneally in a mouse model of multiple sclerosis—namely, in mice with experimental autoimmune encephalomyelitis (EAE). In the spinal cord, Notch signaling suppression was accompanied by increased numbers of motor neurons and evidence of remyelination. These findings suggest that functional recovery can be improved by promoting the differentiation of neural stem cells into neurons and oligodendrocytes, which produce myelin.

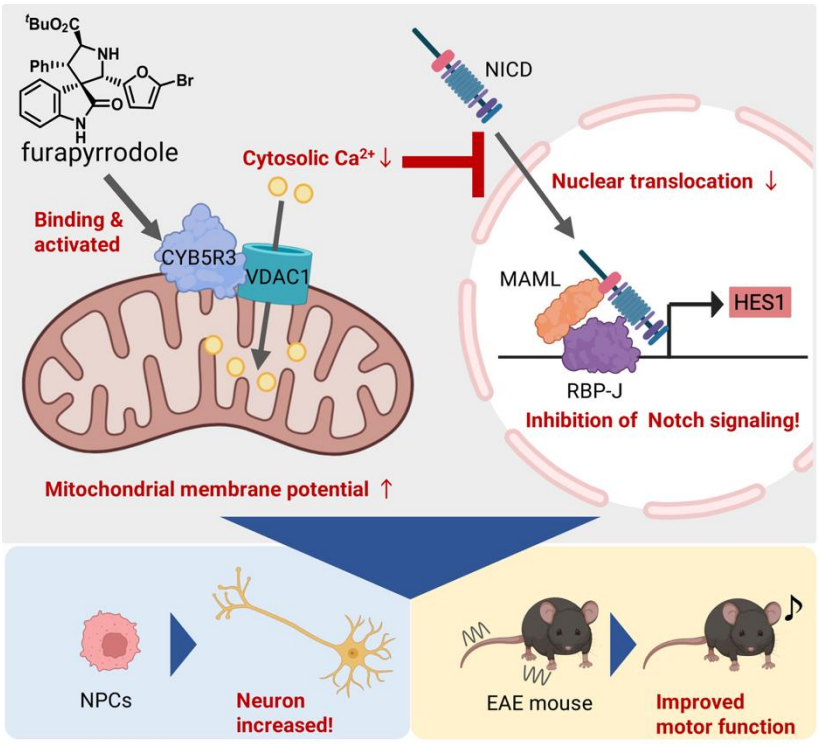


Figure 1. Summary of findings
This figure was created using BioRender.

FP Has Minimal Effect on the Intestine in Contrast to Conventional Notch Inhibitors

Conventional γ-secretase inhibitors can induce an excessive differentiation of intestinal cells into mucus-secreting goblet cells, resulting in gastrointestinal adverse effects. By contrast, in the experiments, FP showed little to no signs of promoting goblet cell differentiation. This difference may be related to CYB5R3, the target of FP, having relatively low expression in the intestine. Nevertheless, the safety profile of FP requires further investigation.

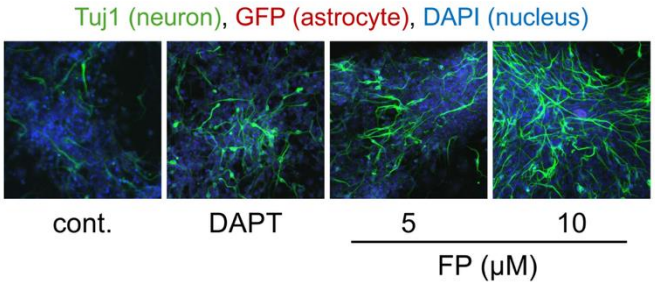


Figure 2. FP-induced neurogenesis.

4. Future Prospects

FP administration was associated with improved paralysis outcomes and substantial neuroregenerative effects in a mouse model of multiple sclerosis. Future studies will investigate the efficacy, safety, and pharmacokinetic properties of FP to explore its potential therapeutic applications in MS and other neurological disorders.

＜Manuscript＞

Narushima, Y.; Saylor, J.; Saito, S.; Zhou, J.; Kawano, H.; Anwar, S.; Oba, H.; Huezo, R.; Okano, M.; Matsuda, H.; Kawatani, M.; Honda, K.; Osada, H.; Kikuchi, Y.; Ohue, M.; Ishibashi, M.; Arai, T.*; Inoue, M.*; Arai, M. A.* "Targeting Mitochondrial Redox Signaling Promotes Neuroregeneration and Functional Recovery in a Multiple Sclerosis Model" *Adv. Sci.* in press.
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Glossary of Terms (Notes)

**(1) CYB5R3 (Cytochrome b5 reductase 3):* An enzyme involved in intracellular oxidation–reduction (redox) reactions.

**(2) Notch signaling:* A signaling pathway that regulates cell development and differentiation. In neural stem cells, Notch signaling suppresses differentiation into neurons.

**(3) Neural stem cells:* Stem cells capable of differentiating into various cell types, including neurons, astrocytes, and oligodendrocytes, which form myelin sheaths. Neural stem cells are also present in the central nervous system of adults.

**(4) Multiple sclerosis (MS):* An autoimmune disease in which immune cells attack and destroy the myelin sheaths surrounding neuronal axons in the central nervous system, including the brain and spinal cord. MS is a debilitating disease that can cause a wide range of symptoms, including numbness, paralysis, and visual impairment. No curative treatment has yet been established.

**(5) Myelin sheath:* A multilayered membrane structure that surrounds neuronal axons. In the central nervous system, myelin sheaths are formed by oligodendrocytes. Myelin sheaths increase the speed of nerve impulse conduction and are essential for efficient neural communication.

**(6) Reporter cells:* Genetically engineered cells designed to detect the activity of specific intracellular signaling pathways through measurable signals such as luminescence or fluorescence. In this study, luminescence intensity from reporter-cell reactions was used to measure Notch signaling activity.

**(7) NICD (Notch intracellular domain):* A portion of the Notch receptor located in the cell membrane. Upon activation of Notch signaling, NICD is cleaved from the receptor and released into the cell. NICD then translocates into the nucleus, where it promotes the expression of specific genes and thereby regulates cellular processes such as differentiation and proliferation.

Media Inquiries and Contact Information

For media inquiries, please contact the relevant researchers in advance.
This press release has been distributed to the Ministry of Education, Culture, Sports, Science and Technology (MEXT) Press Club, the Science Press Club, and the science departments of various media organizations.

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