



Press release
30 October 2023

Publication of Preclinical Results from Joint Research with Keio University on Severe Spinal Cord Injury

Kringle Pharma, Inc. (Head office located in Osaka, Japan; President & CEO, Kiichi Adachi; “KRINGLE”), a late clinical-stage biopharmaceutical company, today announced the publication of a peer-reviewed article in the international scientific journal *Inflammation and Regeneration* online edition issued on October 16, 2023, presenting preclinical results generated from the collaborative research between KRINGLE and Keio University (Located in Tokyo, Japan; President, Kohei Itoh) regarding the dual therapeutic intervention for the treatment of acute to subacute severe spinal cord injury.

KRINGLE is currently conducting a Phase III clinical trial of recombinant human hepatocyte growth factor (“HGF”) in subjects with acute spinal cord injury. In parallel, KRINGLE launched a collaborative research program with Professors Hideyuki Okano and Masaya Nakamura at Keio University School of Medicine in 2021, aiming to create next-generation therapies for spinal cord injury.

In this research, administering HGF developed by KRINGLE in the acute phase, followed by transplantation of human induced pluripotent stem cell-derived neural stem/progenitor cell (“hiPSC-NS/PC”) owned by Keio University in the sub-acute phase, substantially enhanced motor functional recovery in the rat model of severe spinal cord injury compared to each single treatment group. The finding led to the patent application claiming a priority, jointly filed by KRINGLE and Keio University as announced in the KRINGLE news release dated September 8, 2023.

The research results published in the journal demonstrated that pretreatment with HGF in the acute phase of spinal cord injury improved the spinal cord microenvironment by promoting tissue regeneration including angiogenesis, neuronal regeneration and myelination, as well as suppressing inflammation. In addition, the survival rate of hiPSC-NS/PC transplanted in the sub-acute phase was improved in this favorable environment, leading to further acceleration of neuronal regeneration. Consequently, locomotor function was substantially restored in rats with severe spinal cord injury that had not shown sufficient recovery with cell transplantation alone. This research opens the door to the promising combination therapy of HGF and hiPSC-NS/PC transplantation to treat the acute and subacute phases of spinal cord injury. Clinical development and practical application of the combined therapeutic approach is expected in the future.

【Publication】

- Title: Hepatocyte growth factor pretreatment boosts functional recovery after spinal cord injury through human iPSC-derived neural stem/progenitor cell transplantation
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About Hepatocyte Growth Factor (HGF)

HGF was originally discovered as an endogenous mitogen for mature hepatocytes. Subsequent studies demonstrated that HGF exerts multiple biological functions based on its mitogenic, motogenic, anti-apoptotic, morphogenic, anti-fibrotic, and angiogenic activities, and facilitates regeneration and protection of a wide



variety of organs. HGF exerts neurotrophic effects and enhances neurite outgrowth, and the therapeutic effect of HGF on spinal cord injury has been demonstrated in animal models by Professors Hideyuki Okano and Masaya Nakamura at Keio University School of Medicine. Expectations for HGF as a novel therapeutic agent are increasing for spinal cord injury.

A group led by Professor Shigeru Hirano of the Department of Otolaryngology and Head and Neck Surgery, Kyoto Prefectural University of Medicine, focused on the anti-fibrotic effects of HGF and demonstrated its pharmacological effects on vocal cord scar. HGF is also expected to have the potential to be an effective therapeutic agent for various fibrotic diseases including vocal fold scar.

About Human Induced Pluripotent Stem Cell-derived Neural Stem/Progenitor Cell (hiPSC-NS/PC)

hiPSC-NS/PC is derived from human induced pluripotent stem cells and has the self-renewal capability, enabling proliferation maintaining undifferentiated state, as well as pluripotency, enabling differentiation into cells constituting the central nervous system such as neurons, astrocytes, and oligodendrocytes. The first-in-human clinical trial of transplantation: regenerative medicine using hiPSC-NS/PC to treat complete subacute spinal cord injury is currently underway at Keio University Hospital. For more information, please see the press release dated January 14, 2022, by Keio University.

<https://www.keio.ac.jp/en/press-releases/files/2022/1/14/220114-1.pdf>

About Spinal Cord Injury

Spinal cord injury is caused by trauma, leading to a variety of paralytic or painful symptoms. In descending order of incidence, tripping over, traffic accidents and falls from height are the main causes of spinal damage. Recently, due to the rise in the elderly population, tripping over is becoming an increasingly common cause. In Japan, there are approximately 100,000 to 200,000 chronic spinal cord injury subjects with an incidence of about 6,000 new cases per year*. By appropriate early treatment after the injury and specialized rehabilitation, some degree of functional recovery can be expected, but complex severe symptom, including motor paralysis, muscular spasticity, sensory paralysis, dysfunction of internal organs (rectal and bladder disorder, thermoregulatory dysfunction, decreased visceral function, decreased respiratory function) may often remain. For these reasons, therefore, there is a strong need for the development of a novel drug.

*Source:

Miyakoshi N et al. Spinal Cord 2021 Jun;59(6):626-634.

Sakai H et al. J Spine Res. 2010 1(1):41-51.

About Kringle Pharma, Inc. <https://www.kringle-pharma.com/en/>

Kringle Pharma is a late clinical-stage biopharmaceutical company established in December 2001 to develop novel biologics based on HGF. Currently, Kringle conducts two Phase III clinical studies, which is the final stage of the drug development, in spinal cord injury and vocal fold scar among other target indications. Kringle's mission is to contribute to societal and global healthcare through the continued research, development, and commercialization of HGF drug for patients suffering from incurable diseases.

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