



Kringle  
Pharma

Press release  
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## **Filing of Patent Application on Combination Therapy Using HGF and iPS Cell for the Treatment of Spinal Cord Injury**

Kringle Pharma, Inc. (Head office located in Osaka, Japan; President & CEO, Kiichi Adachi; “KRINGLE”) today announces that it has jointly filed a patent application with Keio University (Located in Tokyo, Japan; President, Kohei Itoh) on the combination use of recombinant human hepatocyte growth factor (“HGF”) with human induced pluripotent stem cell-derived neural stem/progenitor cell (“hiPSC-NS/PC”) as an effective treatment for spinal cord injury.

Title of the invention: Therapeutic agent for the acute to sub-acute phase of spinal cord injury

Application No.: JP2022-143261

Filing date: September 8, 2022

KRINGLE has continued collaborative research with Professors Hideyuki Okano and Masaya Nakamura at Keio University School of Medicine since 2021, aiming to create novel therapies for spinal cord injury. As a result of this joint research, KRINGLE and Keio University already filed a patent application in March 2022, based on the improvement of functional recovery in the animal model of chronic complete spinal cord injury by transplanting hiPSC-NS/PC with the scaffold-mediated delivery of HGF (please see KRINGLE IR News dated March 11, 2022). Further in the joint research, HGF administration in the acute phase, followed by transplantation of hiPSC-NS/PC in the sub-acute phase, significantly improved motor function in the animal model of severe spinal cord injury compared to each single treatment group, leading to the second patent application jointly filed by KRINGLE and Keio University. Currently, HGF monotherapy in acute spinal cord injury is being tested in a Phase III clinical trial by KRINGLE, and hiPSC-NS/PC transplantation in the sub-acute phase is ongoing in clinical research by Keio University, respectively. Therefore, a next-generation regenerative therapy combining the HGF and iPS cell technologies is expected to be put into clinical use before long for the treatment of acute and sub-acute spinal cord injuries. The preclinical results will be presented by Keio University School of Medicine during the 57th Annual Meeting of the Japan Medical Society of Spinal Cord Lesion (November 17 to 18, 2022 at Pacifico Yokohama, Japan).

### ***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 effects of HGF on spinal cord injury have been demonstrated in animal models by Professors Hideyuki Okano and Masaya Nakamura at Keio University School of Medicine. KRINGLE is currently conducting a Phase III clinical trial of HGF in subjects with acute spinal cord injury. Expectations for HGF as a novel therapeutic agent are increasing for spinal cord injury.



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***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.

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