Docket #: S20-137

Efficient Microglia Replacement without Genetic Modification via Bone-Marrow Derived Cells

Recent studies have linked microglia damage to various neurodegenerative and aging brain diseases. Relatedly, bone marrow transplantation has been shown to result in incorporation of macrophages into the brain, but the incorporation is variable, slow and inefficient. While the replacement of microglia with bone marrow-derived cells holds great therapeutic promise, there is currently a low brain incorporation efficiency due to the difficulty of delivering therapeutic agents across the blood brain barrier.

The Wernig Lab developed a method enabling highly efficient and highly reproducible replacement (>90%) of endogenous microglia with circulation-derived cells derived from the bone marrow. The method does not require any genetic modification of either donor cells or recipient animals: it leverages two small molecule drugs, a cytostatic drug for bone marrow transplantation, and a colony stimulating factor 1 receptor (CSF1R) inhibitor. In addition to delivering biologic agents to the brain, the invention also eliminates the risk of graft versus host diseases through the re-transplanting of hemopoietic stem cells. This novel delivery technique will be a valuable research and therapeutic tool for neurodegenerative and age-related diseases

Applications

- -Therapeutics for neurodegenerative and other CNS diseases
- -Stem-cell therapeutics
- -Delivery tool for neurological research

Advantages

- -Achieve high levels of chimerism in the brain
- -Deliver transgenic cells that are only active in the brain
- -Eliminates risk of graft-vs-host disease by enabling re-transplanting of HSCs
- -No genetic modifications needed
- -Bypass the blood brain barrier

Publications

- Treatment of a genetic brain disease by CNS-wide microglia replacement. Science translational medicine
- Shibuya, Y., Kumar, K. K., Mader, M. M., Yoo, Y., Ayala, L. A., Zhou, M., Mohr, M. A., Neumayer, G., Kumar, I., Yamamoto, R., Marcoux, P., Liou, B., Bennett, F. C., Nakauchi, H., Sun, Y., Chen, X., Heppner, F. L., Wyss-Coray, T., Südhof, T. C., Wernig, M. 2022; 14 (636): eabl9945

Patents

- Published Application: WO2022067105
- Published Application: 20230398153

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