Press Release

Breakthrough in Langerhans Cell Histiocytosis Research: Stem Cell Model Paves the Way for New Therapies

(Vienna, 16 December 2024) **Scientists at St. Anna Children's Cancer Research Institute (St. Anna CCRI) have achieved a milestone in the study of the rare and complex disease Langerhans Cell Histiocytosis (LCH). Using an innovative model based on induced pluripotent stem cells (iPSCs), they were able to comprehensively study the mechanisms of the disease for the first time. The groundbreaking results, published in the journal *Blood*, offer hope for new treatment strategies for those affected.**

Langerhans Cell Histiocytosis (LCH) is a rare and complex disorder of the hematopoietic system, characterized by a wide range of symptoms, from self-limiting lesions to tumor-like damage in multiple organs, systemic inflammation, and progressive neurodegeneration. Until now, the lack of suitable models has severely limited research into the disease's mechanisms.

A pioneering new study, published in the journal *Blood*, provides critical insights into the mechanisms of LCH and potential treatment strategies. A team led by Caroline Hutter—Group Leader at St. Anna CCRI, Medical Director of St. Anna Children's Hospital, and Professor of Pediatric Oncology at MedUni Vienna—has successfully developed an in vitro model of LCH. By leveraging an innovative laboratory-developed model based on iPSCs, the need for animal testing has been eliminated.

Innovative Stem Cell Model: A Breakthrough in Research

To develop the model, the researchers introduced the BRAFV600E mutation into human stem cells in the laboratory. This mutation, which is the most common genetic alteration in LCH, triggers changes in cell development, causing the cells to behave similarly to those found in LCH-associated tissue damage.

“Our research highlights how the BRAFV600E mutation drives key characteristics of LCH, including inflammatory responses and neurodegenerative damage,” says Caroline Hutter. "The iPSC model fills a critical gap in LCH research, allowing us to analyze the molecular mechanisms of disease progression in different cell types." Co-senior author Sebastian Eder, clinical scientist and pediatric oncologist at St. Anna Children's Hospital, adds, "This model provides an invaluable tool for studying disease mechanisms and testing new treatments."

From Precursor Cells to Pathological Tissue Damage

Using their model, the researchers demonstrated that the BRAFV600E mutation causes profound changes during hematopoiesis (blood formation). It alters the way certain genes are read and utilized—a process known as transcriptional regulation. These changes cause specific precursor cells in the blood to develop into cells resembling those found in the diseased tissues of LCH patients.

Reversing Molecular Damage

A particularly significant breakthrough was showing that these disease-related changes are reversible. Using specialized drugs called MAPK pathway inhibitors (MAPKi), the molecular disturbances in the cells were reversed. This finding suggests that these drugs could potentially benefit LCH patients.

Mutant Microglia Drive Neurodegeneration: New Insights into LCH Complications

The team also investigated the interplay between mutant microglia (a type of immune cell in the brain) and neurons, revealing how the BRAFV600E mutation drives neurodegeneration. They found that these mutant microglia cause significant damage to neurons and release substances that serve as markers for neurodegeneration. “Neurodegeneration is currently the most severe complication in the treatment of LCH,” explains Raphaela Schwentner, co-first author of the study. “With this system, we can study interactions between various cell types, such as neurons that are otherwise difficult to investigate, and hopefully develop new therapeutic approaches.”

This study represents a significant advance in understanding LCH and offers new hope for patients with severe and treatment-resistant forms of the disease. Through cutting-edge stem cell technology, the researchers have created a versatile tool for mechanistic studies and drug development. “Our model demonstrates the versatility of iPSCs in translational research,” says Giulio Abagnale, co-first author of the study. “We hope our work will improve the lives of LCH patients and their families.”

Publication:

Abagnale G*, Schwentner R*, Ben Soussia-Weiss P, van Midden W, Sturtzel C, Pötschger U, Rados M, Taschner-Mandl S, Simonitsch-Klupp I, Hafemeister C, Halbritter F, Distel M, Eder SK#, Hutter C#. BRAFV600E induces key features of LCH in iPSCs with cell type-specific phenotypes and drug responses. Blood. 2024 Dec 4:blood.2024026066.

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About St. Anna Children's Cancer Research Institute

The St. Anna Children's Cancer Research Institute (CCRI) is an international and interdisciplinary research institution dedicated to advancing diagnostic, prognostic, and therapeutic strategies for the treatment of children and adolescents with cancer through innovative research. Incorporating the specific characteristics of childhood tumor diseases, dedicated research groups collaborate in the fields of tumor genomics and epigenomics, immunology, molecular biology, cell biology, bioinformatics, and clinical research. Their aim is to bridge the latest scientific and experimental knowledge with the clinical needs of physicians in order to significantly improve the well-being of young patients. For more information, visit www.ccri.at or www.kinderkrebsforschung.at.

About St. Anna Children's Hospital

Since its establishment in 1837, St. Anna Children's Hospital has evolved into a leading institution in pediatric and adolescent medicine, providing state-of-the-art medical care. In addition to its role as a general children's hospital, St. Anna Children's Hospital has gained an excellent reputation nationwide and internationally as a center for the treatment of pediatric blood and tumor diseases (cancer). St. Anna Children's Hospital GmbH is a subsidiary of the Austrian Red Cross, Vienna Regional Association. It is an independent hospital affiliated with the Vienna General Hospital (AKH Wien) and serves as the Clinical Department for General Pediatrics and Pediatric Hemato-Oncology at the University Clinic of Pediatrics and Adolescent Medicine. www.stanna.at

About the Medical University of Vienna

The Medical University of Vienna (MedUni Vienna) is one of the most prestigious institutions for medical education and research in Europe. With approximately 8,000 students, it is the largest medical training institution in the German-speaking region. With 6,000 employees, 30 university clinics, two clinical institutes, 13 medical-theoretical centers, and numerous highly specialized laboratories, it is considered one of the most significant biomedical research institutions in Europe. The MedUni Vienna also houses the Josephinum, a museum of medical history. For more information, visit www.meduniwien.ac.at.

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