MedicalXpress

Combining stem-cell and gene-therapy techniques to tackle a deadly blood disease

October 22 2010

The National Institutes of Health has awarded a three-year, $3.9 million grant to Children's Hospital Boston researchers and their colleagues to develop a therapy to treat Fanconi anemia, a fatal genetic blood disease.

The researchers will investigate new ways to create induced pluripotent stem (iPS) cells from a patient's skin or other tissue and transform them into genetically repaired hematopoietic stem cells that can make normal blood cells.

Fanconi anemia is characterized by progressive bone marrow failure, multiple congenital anomalies and a predisposition to cancer. Somehow, a defect in DNA repair causes progressive blood stem cell loss, usually resulting in death by age 20. Although the rare syndrome could potentially be treated with gene therapy, since it usually results from a single genetic mutation, the same DNA repair defect has thwarted gene therapy efforts to date. The team will push to understand the barriers to genetic correction of Fanconi anemia in mice, hoping their findings will translate to patients.

The research project is a collaboration among three members of Dana-Farber/Children's Hospital Cancer Center: David Williams, MD, chief of Hematology/Oncology and director of Translational Research, George Daley, MD, PhD, director of Stem Cell Transplantation, and Alan D'Andrea, MD, chief of research in Radiation Oncology.

Two of the co-principal investigators will be discussing their efforts in

Boston this weekend at the Congress of the International Society of Paediatric Oncology, the world's largest pediatric oncology meeting.

- On Friday, Oct. 22, 10:30-noon (Ballroom A), Williams will give a talk titled "Somatic Cell Reprogramming to Facilitate Genetic Correction in Fanconi Anemia" in a session on gene therapy and pediatric oncology. Williams, who completed an early study in children with Fanconi anemia to try to genetically correct endogenous blood stem cells, will discuss how clinical trials have defined a new research focus. "At the end of three years, one hope would be, in the mouse system, to generate corrected iPS cells and be able to differentiate them into corrected blood stem cells," Williams says.
- On Sunday, Oct. 24, 3-3:30 pm (Auditorium), Daley will give a keynote talk titled "Modeling Bone Marrow Failure Syndromes with Induced Pluripotent Stem Cells." Daley plans to address some of the limitations of reprogramming Fanconi anemia cells. "The grant is aimed at defining precisely what mechanism is lacking in Fanconi cells that is required for efficient reprogramming," Daley says. "We believe the DNA repair defects of Fanconi cells are a problem—because the reprogramming technique may stress the DNA repair response and make them relatively resistant to reprogramming. With improved methods, we should achieve reprogramming of Fanconi cells too."

The grant combines the efforts of three leading experts in the field. Their three projects are connected by common goals: To better understand the reprogramming technology and DNA repair pathways involved in Fanconi anemia cells first in mice, and then to leverage those insights for rapid development of new therapeutic approaches for translation to patients.

Williams' group will concentrate on reprogramming patient-specific cells, using state-of-the-art methods to genetically correct these cells, and transforming them into functional hematopoietic stem cells for transplant. Daley's lab will probe how defects in DNA double-strand break repair affects reprogramming of iPS cells. D'Andrea's team will concentrate on the details of how the hematopoietic stem cell defect generates bone marrow failure and test new potentially therapeutic small molecules.

The Fanconi anemia grant marked Children's Hospital final research award from the 2009 American Recovery and Reinvestment Act, the biggest boost in federal research funding in U.S. history. The stimulus funding infused hospital labs and clinics with about $55 million in direct support of more than 100 projects.

More information: http://www.siopboston2010.com/

Provided by Children's Hospital Boston