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Singapore researchers discover novel therapeutic pathway

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Singapore- Researchers at the Cancer Science Institute of Singapore (CSI Singapore) at the National University of Singapore (NUS) have identified a novel molecular pathway by which a circadian clock gene, SHARP1, causes the growth of acute myeloid leukemia (AML). The finding paves the way for the development of new therapeutic strategies that could impede the development of the cancer of the blood and bone marrow.

The six-year long study led by CSI director Professor Daniel Tenen, Associate Professor Reshma Taneja at the NUS Yong Loo Lin School of Medicine's Department of Physiology, Dr. Akihiko Numata, Adjunct Research Scientist at CSI Singapore, Dr Kwok Hui Si, a postdoctoral Associate at Yale University's Department of Molecular Biophysics and Biochemistry, as well as scientists from the University of Oxford, UK; Sanford Burnham Medical Discovery Institute, University of Alabama at Birmingham; Medical Erasmus University Medical Center, The Netherlands as well as the Harvard Stem Cell Institute. Their findings were published in the prestigious journal, Nature Communications in April 2018.

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The study focused on the role of SHARP1, in a particular subset of AML cells which contain alterations to the Mixed-Lineage Leukemia (MLL) gene. Alteration to the MLL gene is the most common genetic occurrence leading to AML. The alteration causes the MLL gene to fuse with other genes, thus affecting its function. When the MLL gene combines with the AF6 gene, a "fusion" gene is created, which produces a new fusion protein called MLL-AF6. Patients with this fusion gene tend to respond poorly to almost all types of treatment, including stem cell transplantation, and have very poor clinical outcomes.

"We found that MLL-AF6 binds with SHARP1, leading to an increase in the level of SHARP1. The increase of SHARP1 levels has the two-fold effect of initiating leukemia development, as well as maintaining the growth of leukemic cells. Interestingly, in addition to its own cancer-causing functions, our study also revealed that SHARP1 could act upon other target genes of MLL-AF6 to aggravate the progression of AML. But by removing or reducing the level of SHARP1, the growth of leukemic cells

could be stopped," Professor Dan Tenen explained.

The team employed an array of genetic screening techniques and cutting edge molecular biology tools to identify this new pathway in the development of this severe type of AML.