Scientists break new ground in potential treatment of common form of leukaemia

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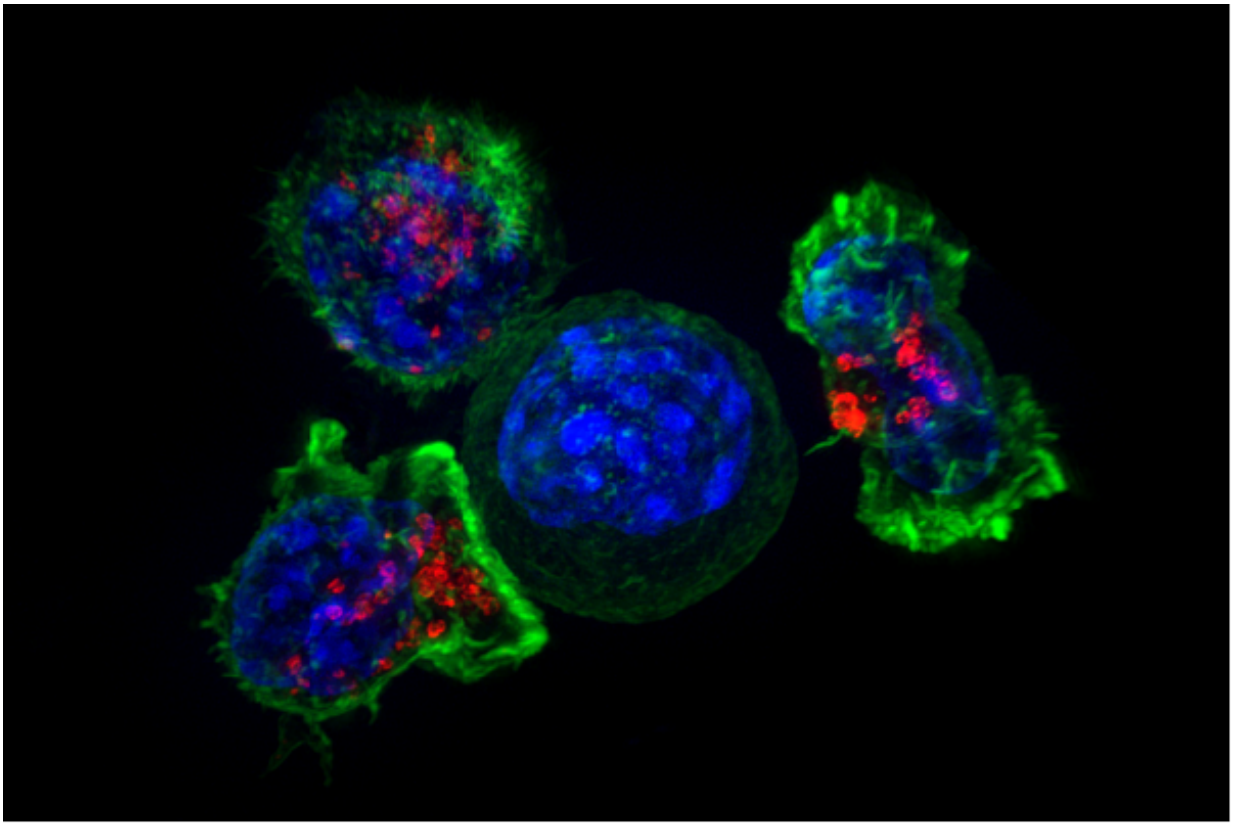

Killer T cells surround a cancer cell. Credit: NIH

Scientists at the University of Glasgow have discovered a potential combination therapy for the treatment of chronic lymphocytic leukaemia (CLL), the most common form of leukaemia in the Western world,

diagnosed in more than 3,500 people in the UK each year.

The research, carried out in collaboration with NHS Greater Glasgow and Clyde (NHSGGC) and published in *Clinical Cancer Research*, found that the combination of ibrutinib, a targeted treatment already in clinical use, with a new inhibitor called AZD8055, helped promote CLL cell death in a preclinical study.

This study, which used CLL patient samples and a CLL mouse model, found that combination of these two inhibitors activated a protein called FOXO1, which can function as a 'molecular brake," stopping the cells from multiplying and inducing CLL cell death.

Chronic lymphocytic leukaemia (CLL) is a blood cell cancer affecting white blood cells. The disease more commonly affects people over the age of 60. The disease course can vary from patient to patient, with some patients experiencing a stable low-grade disease that does not require treatment, while others develop resistance to chemotherapy treatments given and are considered "high-risk" patients.

The introduction of ibrutinib into the clinic as a treatment of high-risk CLL patients has enhanced the survival of this difficult to treat subset of CLL patients. However the CLL cells can adapt to the drugs, developing mutations and therefore becoming resistant to ibrutinib leaving few therapeutic options for patients. Novel combination of treatments offer the potential to reduce the ability of the CLL cell to adapt to the treatment which attacks the cell in two places as opposed to one.

Dr. Alison Michie, who led the study, said: "Reducing the ability of CLL cells to survive is key to interrupting disease progression. In our study, we established that by targeting and inhibiting the function of a protein called mTOR which is often deregulated in cancer, we improved the killing of CLL cells."

Dr. Michie added: "Combining mTOR inhibition with a drug called ibrutinib, which is currently being used in the clinic to treat high-risk CLL patients, enhances the activation of FOXO1, a protein that can promote cell death, in a preclinical model. Our findings are important because they could demonstrate a potential new therapeutic approach for treating patients with high-risk CLL."

The paper, "AKT/mTORC2 inhibition activates FOXO1 function in CLL cells reducing B cell receptor-mediated survival," is published in *Clinical Cancer Research*.

More information: Emilio Cosimo et al. AKT/mTORC2 inhibition activates FOXO1 function in CLL cells reducing B cell receptor-mediated survival, *Clinical Cancer Research* (2018). DOI: 10.1158/1078-0432.CCR-18-2036

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