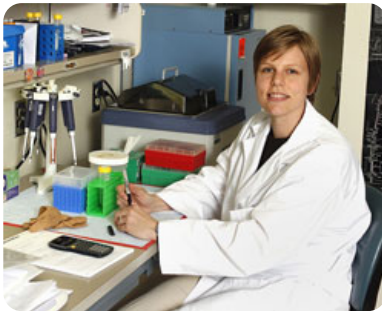


Laboratory study confirms target of potent chronic leukaemia drug

A new study led by researchers at The Ohio State University Comprehensive Cancer Centre - Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC - James) helps confirm that a molecule targeted by the experimental drug ibrutinib is critical for the development of chronic lymphocytic leukaemia, the most common form of adult leukaemia.



Amy Johnson, PhD.

- The experimental drug ibrutinib can be exceptionally effective in treating chronic leukaemia, but it is unclear whether its primary target, a molecule called BTK, is important for controlling leukaemia.
- This study blocked BTK function both genetically and by using the drug ibrutinib to investigate the importance of BTK in chronic leukaemia.
- BTK loss greatly slowed CLL-cell growth and CLL development in animal models, confirming that BTK is an important target for ibrutinib and future CLL drugs.

In clinical trials, ibrutinib has often shown exceptional activity in people with [chronic lymphocytic leukaemia \(CLL\)](#). The agent targets a molecule called Bruton's tyrosine kinase (BTK). It permanently incapacitates the molecule, and this stops the transmission of an important signal that promotes cell growth and proliferation.

But ibrutinib also inhibits other molecules in CLL cells. Like BTK, these molecules are proteins called [kinases](#), and they may be important for CLL-cell survival, the researchers say.

"Ibrutinib's lack of selectivity might mean that BTK is not the critical target in CLL, and that future drugs developed for CLL should focus on other molecules," says principal investigator Amy Johnson, PhD, associate professor of medicine in the division of haematology, and an OSUCCC - James researcher.

However, the findings, published in the journal *Blood*, validated BTK inhibition.

"This study shows that BTK is an important therapeutic target in CLL," says first author Jennifer Woyach, MD, assistant professor in the division of haematology and an OSUCCC - James researcher. "Inactivating BTK alone delayed CLL development in a mouse model, confirming that BTK is a clinically important target in CLL. This suggests that development of selective BTK inhibitors - in addition to multi-kinase inhibitors like ibrutinib - is reasonable in CLL."

To investigate the role of BTK in CLL, Johnson, Woyach and their colleagues used CLL cells from patients and two CLL mouse models, one of which spontaneously develops a malignancy very similar to human CLL. The researchers blocked BTK activity two ways: genetically and pharmacologically, using ibrutinib.

Key findings included:

- Inhibiting BTK expression in human CLL cells significantly decreased survival in tumour cells from 31 patients;
- A mouse model with inactive BTK due to a point mutation survived significantly longer than mice with active BTK (18.3

versus 13.2 months, respectively);

- In a mouse model of spontaneous CLL, animals treated with ibrutinib survived significantly longer than controls from the time of leukaemia diagnosis (46 versus 24 days, respectively);
- In the same mouse model, treatment with ibrutinib significantly delayed leukaemia onset compared with controls (10.7 versus 7.0 months) and extended overall survival (14.5 versus 12.3 months, respectively).

"Overall," Johnson says, "our findings validate BTK as a target for CLL therapy and strongly suggest that selective kinase-inhibitors might work in CLL like the drug imatinib does in [chronic myeloid leukaemia](#)."

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The Ohio State University Comprehensive Cancer Centre - Arthur G. James Cancer Hospital and Richard J. Solove Research Institute strives to create a cancer-free world by integrating scientific research with excellence in education and patient-centred care, a strategy that leads to better methods of prevention, detection, and treatment. Ohio State is one of 41 National Cancer Institute (NCI)-designated Comprehensive Cancer Centres and one of only four centres funded by the NCI to conduct both phase I and phase II clinical trials. The NCI recently rated Ohio State's cancer program as "exceptional," the highest rating given by NCI survey teams. As the cancer program's 228-bed adult patient-care component, The James is a "Top Hospital" as named by the Leapfrog Group and one of the top cancer hospitals in the nation as ranked by U.S. News & World Report.

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