

Discovery brings hope of new tailor-made anti-cancer agents

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Dr Guillaume Lessene and his collaborators have tailor-made a new chemical compound that blocks a protein that has been linked to poor responses to treatment in cancer patients. Credit: Walter and Eliza Hall Institute, Australia

Scientists at the Walter and Eliza Hall Institute and their collaborators have tailor-made a new chemical compound that blocks a protein that has been linked to poor responses to treatment in cancer patients.

The development of the compound, called WEHI-539, is an important



step towards the design of a potential new anti-cancer agent. WEHI-539 has been designed to bind and block the function of a protein called BCL-XL that normally prevents cells from dying. The death and elimination of <u>abnormal cells</u> in the body is an important safeguard against <u>cancer</u> <u>development</u>. But <u>cancer cells</u> often acquire genetic changes that allow them to bypass cell death, which also reduces the effectiveness of anti-cancer treatments such as chemotherapy.

Cancer cells can become long-lived by producing high levels of BCL-XL protein, and high levels of BCL-XL are also associated with poorer outcomes for patients with lung, stomach, colon and pancreatic cancer.

Dr Guillaume Lessene, Professor Keith Watson and Professor David Huang from the institute's ACRF <u>Chemical Biology</u> division, and Dr Peter Czabotar and Professor Peter Colman from the institute's <u>Structural Biology</u> division led the development of WEHI-539 in collaboration with colleagues at <u>Genentech</u>, a member of the Roche group. The research is published online today in the journal *Nature Chemical Biology*.

Dr Lessene said the development of WEHI-539 was an important milestone on the way to creating potential anti-<u>cancer agents</u> that act to restore cell death by inhibiting BCL-XL. "Although WEHI-539 is not optimised for use in patients, it will be a very valuable tool for researchers to use to dissect how BCL-XL controls cancer cell survival," he said.

WEHI-539 belongs to a class of chemicals called 'BH3-mimetics', which all bind to the same region of BCL-XL or related proteins. Two BH3-mimetics, called navitoclax (ABT-263) and ABT-199/GDC-0199 are currently in clinical trials for the treatment of cancer, particularly those of the blood and lymph glands (leukaemia and lymphoma).



Dr Lessene said WEHI-539 was the product of a sustained research program. "We were very excited to see the team's work culminate in a compound that specifically inhibits BCL-XL," he said. "WEHI-539 is the first compound that our chemists have developed from scratch, using the three-dimensional structure of BCL-XL to build and refine its design."

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Provided by Walter and Eliza Hall Institute

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