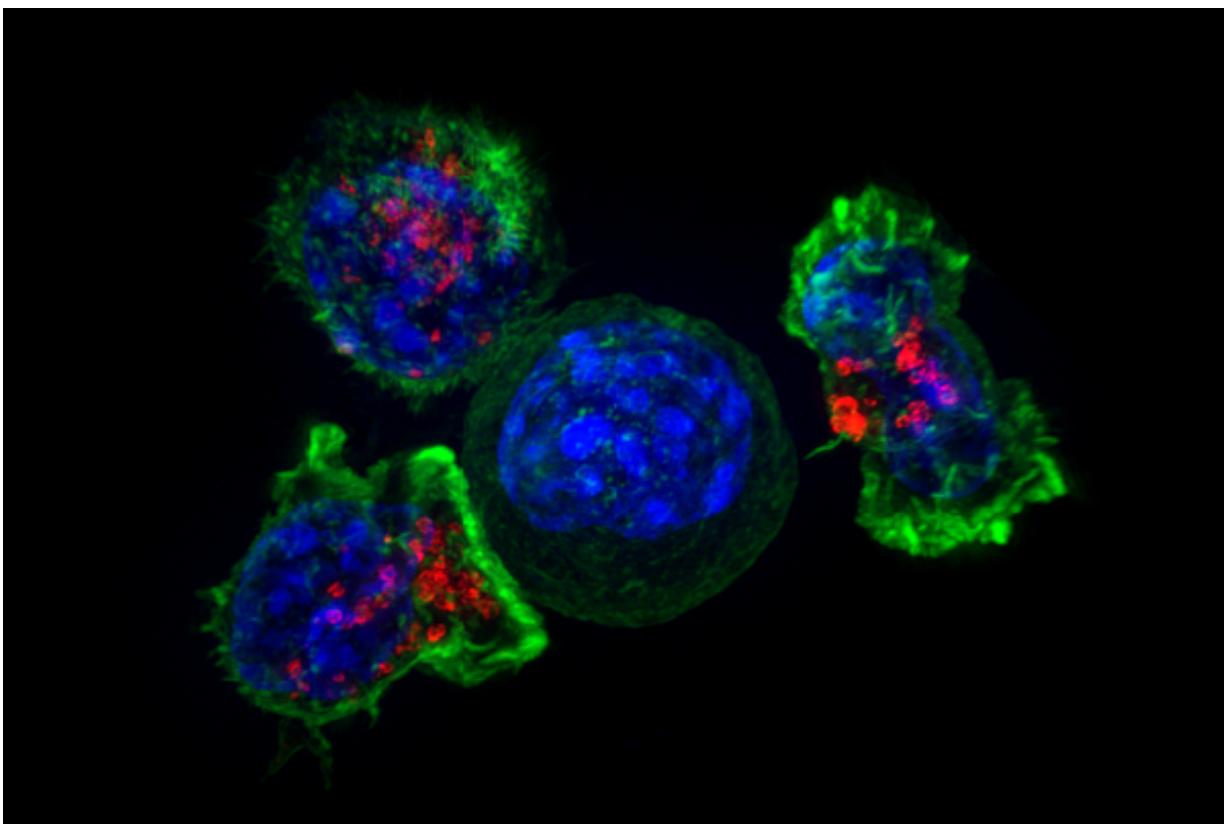


New anti-cancer drugs put cancers to sleep—permanently

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Killer T cells surround a cancer cell. Credit: NIH

In a world first, Melbourne scientists have discovered a new type of anti-cancer drug that can put cancer cells into a permanent sleep, without the harmful side-effects caused by conventional cancer therapies.

Published today in the journal *Nature*, the research reveals the first class of [anti-cancer drugs](#) that work by putting the [cancer](#) cell to sleep – arresting tumour growth and spread without damaging the cells' DNA.

The new class of drugs could provide an exciting alternative for people with cancer, and has already shown great promise in halting cancer progression in models of blood and liver cancers, as well as in delaying cancer relapse.

Permanent sleep

Research led by Associate Professor Tim Thomas and Associate Professor Anne Voss from the Walter and Eliza Hall Institute, Professor Jonathan Baell from the Monash Institute of Pharmaceutical Sciences and Dr. Brendon Monahan from Cancers Therapeutics CRC investigated whether inhibiting KAT6A and KAT6B could be a new approach to treating cancer.

Associate Professor Thomas said the new class of drugs was the first to target KAT6A and KAT6B proteins. Both are known to play an important role in driving cancer. KAT6A sits at number 12 on the list of genes most commonly amplified in cancers.

"Early on, we discovered that genetically depleting KAT6A quadrupled the life expectancy in animal models of blood cancers called lymphoma. Armed with the knowledge that KAT6A is an important driver of cancer, we began to look for ways of inhibiting the protein to treat cancer," Associate Professor Thomas said.

The compounds had already shown great promise in preclinical testing, he said.

"This new class of anti-cancer drugs was effective in preventing cancer

progression in our preclinical cancer models. We are extremely excited about the potential that they hold as an entirely new weapon for fighting cancer.

"The compound was well tolerated in our preclinical models and is very potent against tumour cells, while appearing not to adversely affect healthy cells," Associate Professor Thomas said.

No more DNA damage

The research efforts were almost a decade in the making, requiring strong collaboration between experts in cancer research, medicinal chemistry and [drug](#) discovery.

There is a critical difference between this new class of drugs and standard cancer therapies.

Chemotherapy and radiotherapy work by causing irreversible DNA damage. Cancer cells are unable to repair this damage, and die. The downside is that the therapies cannot be targeted only to [cancer cells](#), and cause significant damage to healthy cells as well. This causes well-known short-term side effects, such as nausea, fatigue, hair loss and susceptibility to infection, as well as long-term effects such as infertility and increased risk of other cancers developing.

"Rather than causing potentially dangerous DNA damage, as chemotherapy and radiotherapy do, this new class of anti-cancer drugs simply puts cancer cells into a permanent sleep," Associate Professor Voss said.

"This new class of compounds stops cancer cells dividing by switching off their ability to 'trigger' the start of the cell cycle," she said. "The technical term is cell senescence. The cells are not dead, but they can no

longer divide and proliferate. Without this ability, the cancer [cells](#) are effectively stopped in their tracks."

Associate Professor Voss said the team believed the drugs might be effective in delaying cancer recurrence.

"There is still a lot of work to be done to get to a point where this drug class could be investigated in human cancer patients," she said.

"However our discovery suggests these drugs could be particularly effective as a type of consolidation therapy that delays or prevents relapse after initial treatment."

"The possibility of giving clinicians another tool that they could use to substantially delay cancer recurrence could have a big impact for patients," Associate Professor Voss said.

'Undruggable' no more

Professor Baell said the project was particularly significant because the scientific community had coined the gene family 'undruggable'.

"There were many hurdles to overcome with this project; this compound certainly didn't fall into our laps, requiring dedicated Ph.D. students and NHMRC-supported postdoctoral medicinal chemists to drive the chemistry forward," Professor Baell said. "But with perseverance and commitment, we are excited to have developed a potent, precise and clean compound that appears to be safe and effective in our preclinical models. Our teams are now working on developing this compound into a drug that is appropriate for human trials."

Professor Baell said the project was indebted to funding from the Australian Government and proved that public research could be an effective translational vehicle.

"It can be difficult to secure funding for medicinal chemistry and higher-risk drug discovery projects," he said. "We are grateful to the Cooperative Research Centres (CRC) Program and National Health and Medical Research Council (NHMRC) for the early funding that supported this project."

Dr. Ian Street, chief scientist at Cancer Therapeutics CRC said it had been a great collaboration between the three organisations.

"This has been a very tough nut to crack," Dr. Street said. "There is no doubt that the KAT6 inhibitors have played an important role in elucidating the potential of this new and exciting strategy to treat cancers."

More information: Jonathan B. Baell et al. Inhibitors of histone acetyltransferases KAT6A/B induce senescence and arrest tumour growth, *Nature* (2018). [DOI: 10.1038/s41586-018-0387-5](https://doi.org/10.1038/s41586-018-0387-5)

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