The drug that can put some cancer cells to sleep

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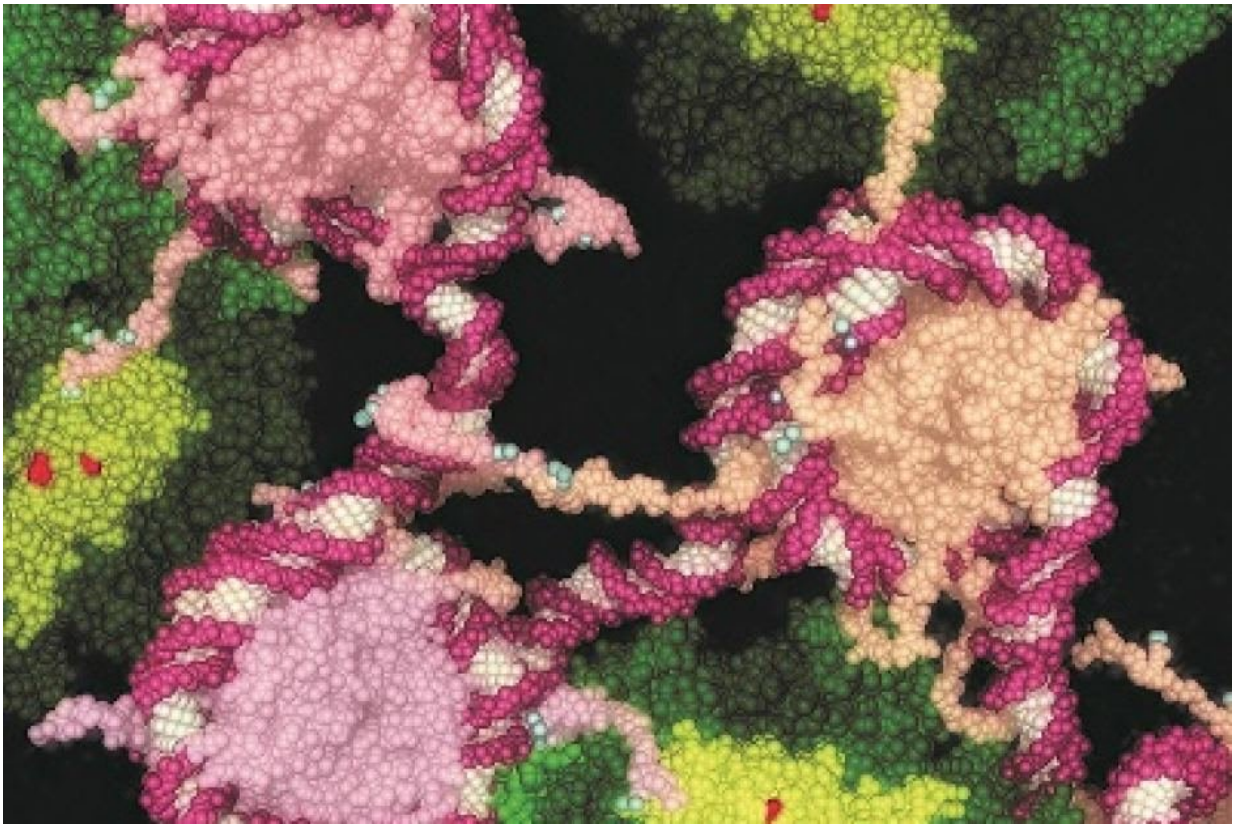

Credit: Monash University

As soon as *Nature* published findings on cancer research by a team including Monash University's Professor Jonathan Baell, his phone started ringing and his email pinging.

Such is the huge measure of hope in the community that cancer can one day be cured. The research he helped with went a small way towards that, but of course it's all incremental, experimental and, in the end, only the beginning.

As with all cancer research, it's baby-steps towards a monumental final goal.

The research, in pre-clinical settings, showed that a new class of anti-cancer drug can put some cancer cells into a permanent sleep – or 'senescence' – with no side effects. It showed promise in stopping cancer growth in pre-clinical models of blood and liver cancer, as well as delaying or stopping relapse.

"I got heart-wrenching messages from people," Professor Baell said. "These people wanted help for their loved ones. All I could say was, 'I'm so sorry – this is just experimental and we're not allowed to give it to people yet'."

He's a professor and Larkins Fellow in the Department of Medicinal Chemistry at Monash's Faculty of Pharmacy and Pharmaceutical Sciences.

The researchers with Professor Baell were from the Walter and Eliza Hall Institute and the Cancer Therapeutics CRC – a collaboration between medicinal chemists and biologists. What they looked at – over a decade – was inhibiting two proteins, KAT6A and KAT6B, known to amplify cancers. They found that genetically depleting KAT6A worked very well in pre-clinical settings with blood cancers.

Beginning with biology

It all began, says Professor Baell, with "fundamental biological

research".

"My colleagues on this are the biologists, I'm the chemist. In drug discovery the biology precedes everything; they find an interesting disease target and then start talking to the chemists. Then translation [making useful drugs] begins."

He describes the key difference between biologists and medicinal chemists – one is more fickle, they'll go where the action is. That's the chemists. The biologists spread the net wide.

"We're not married to any particular biology; we just start liaising with biologists when it looks like they've found a relevant disease target. If one disease isn't looking good, we switch. We're quite promiscuous in that way."

Professor Baell admits it's a "lateral" approach to cancer treatment. Instead of killing the disease – as chemotherapy and radiotherapy do – the disease is put to sleep.

"There's already quite a bit of discussion amongst oncologists about whether this is good or bad," he says. "But it seems that if you put it to sleep for long enough it's irreversible, so maybe it is a better approach? We don't know yet; it's too soon. But we do know that if we administer our compounds to cells for more than eight days then take the compound away, the cells never wake up.

"Maybe combination therapy (with chemotherapy and radiotherapy) right from the beginning will be effective? This is all ahead of us to find out. We cannot think too far ahead just yet."

Chemotherapy and radiotherapy work by damaging DNA. Cancer cells can't repair the damage, so they die. The problem is these therapies can't

be targeted, so healthy cells are also affected.

Professor Baell said part of the project's significance was that the scientific community thought the enzymes the researchers targeted were undruggable.

"There were many hurdles to overcome with this project," he said.

"This compound certainly didn't fall into our laps, requiring dedicated Ph.D. students and National Health and Medical Research Council [NHMRC]-supported postdoctoral medicinal chemists to drive the chemistry forward. But with perseverance and commitment, we're excited to have developed a potent, precise and clean compound that appears to be safe and effective in our pre-clinical models.

"Our team is now working on developing this compound into a drug that's appropriate for human trials.

"We showed," he says, "that the enzymes in question are not undruggable. We think our work will be the catalyst for a whole new area of scientific interest internationally."

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

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