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A curiosity-driven genetic discovery that should impact cancer treatments

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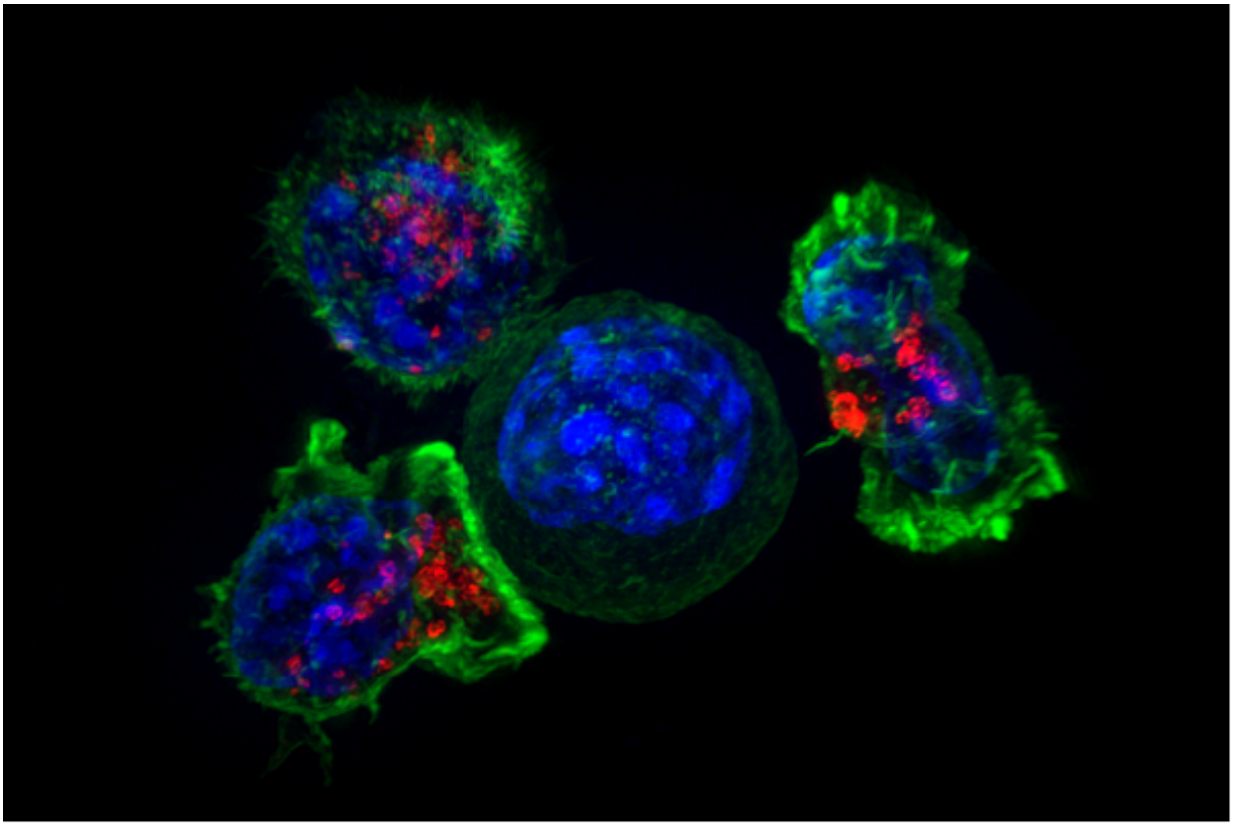

Killer T cells surround a cancer cell. Credit: NIH

A team of geneticists with a desire to understand the inner workings of genes implicated in cellular identity has discovered new biological targets that may help devise alternative therapies for cancers that are

becoming resistant to existing drugs.

First discovered in fruit flies, Polycomb genes were initially studied due to their essential roles in development and their role in regulating cellular identity. They are central to the field of epigenetics, which strives to explain how many cells in our bodies—with identical sets of genes—look and behave so differently.

In 2011 scientists discovered that a particular Polycomb gene, called EZH2, is mutated in lymphomas, a cancer of immune cells. Benefiting from knowledge derived from many years of curiosity-driven scientific research, several companies soon developed drugs to inhibit the activity of EZH2. These targeted treatments are now showing real promise in clinical trials.

However, as with many cancer therapies, resistance has begun to arise, which means scientists will need to develop alternative strategies to fight the cancerous cells. The new discovery provides some new clues as to how this might be achieved and offers another real-life example of how curiosity-driven research can provide vital insights.

Associate Professor in Genetics at Trinity College Dublin, Adrian Bracken, led the team that has just published its findings in the leading international scientific journal, *Molecular Cell*. Irish Research Council Ph.D. Fellow in Professor Bracken's lab, Dr. Evan Healy, is lead author on the paper, which was published in parallel with another study conducted by researchers at the Memorial Sloan Kettering Cancer Centre.

Both research teams discovered that EZH2 requires additional "accessory components" to target its activity to key regions in the genome and execute its critical cellular functions. Importantly, the new results suggest these "accessory components" represent very promising

alternative targets, which will be needed for oncologists to treat patients who develop resistance to existing EZH2 inhibitor drugs.

Commenting on the findings, Professor Bracken said: "This new discovery was driven purely by our curiosity to understand how Polycombs regulate cellular identity, but we also anticipate that it will lead to new opportunities to develop alternative treatments for patients with cancers driven by mutations in EZH2 and its related genes."

"We are extremely grateful for funding support from the Irish Research Council Advanced Laureate programme and Science Foundation Ireland, without which this research would not have been possible."

Commenting on the achievements of Professor Bracken's team, Director of the Irish Research Council, Peter Brown, said: "Earlier this year, the Irish Research Council announced a game-changing investment of €11.8 million in open frontier research to fund 12 researchers under our Advanced Laureate Awards programme. Adrian Bracken was one of those researchers, while members of his team are also availing of supports through other Irish Research Council programmes. We are delighted to support Adrian and his team to conduct ground-breaking research which is pushing out the boundaries of our understanding. The article in *Molecular Cell*, a leading journal in the field, reflects the calibre and significance of the research being done."

More information: *Molecular Cell* (2019). DOI: 10.1016/j.molcel.2019.08.012

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