Chemical probe to dissect role of potential cancer-causing proteins

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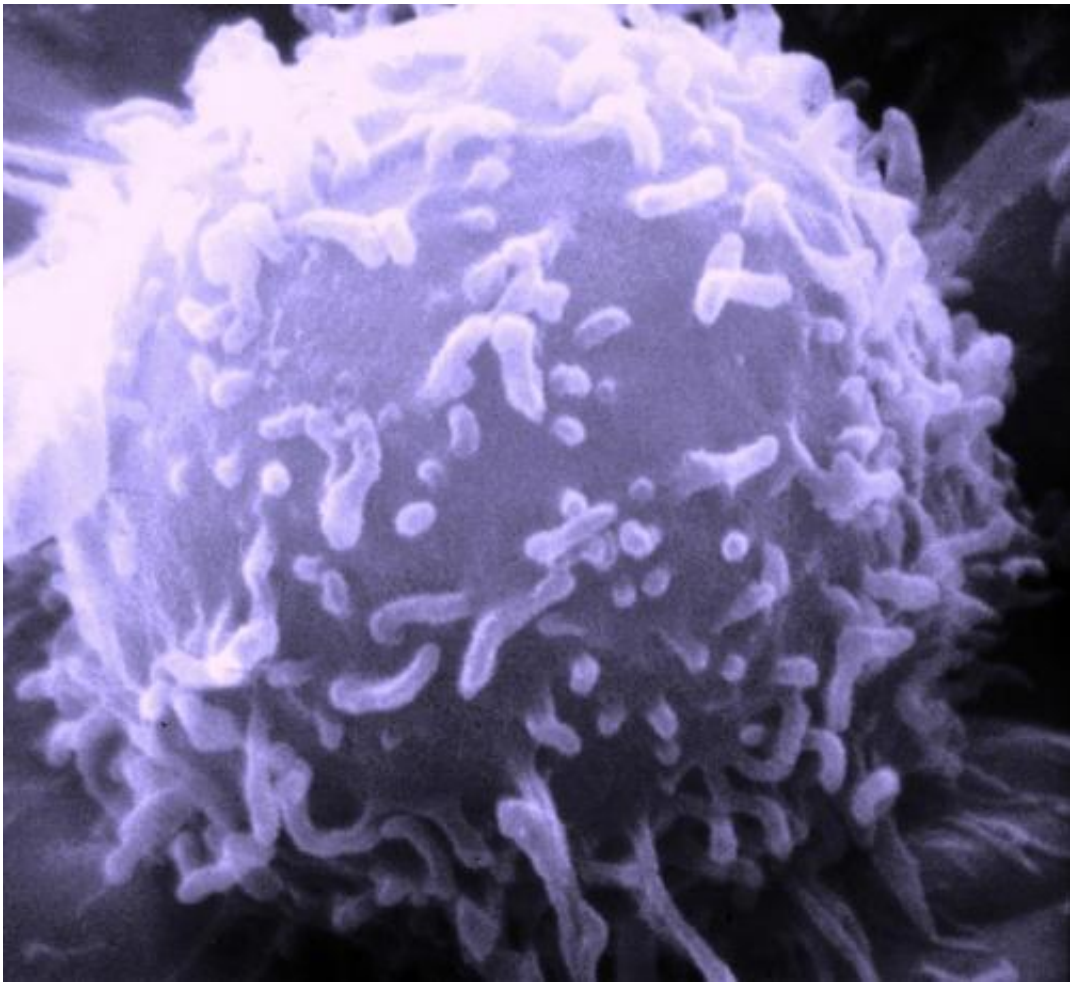

Electron microscopic image of a single human lymphocyte. Credit: Dr. Triche National Cancer Institute

Scientists have created a highly specific and well-characterised chemical probe which can switch off two important proteins implicated in cancer—shedding new light on the role these proteins play in driving cancer cell proliferation.

A major new study, published in *Nature Chemical Biology* today (Monday), announces the discovery of the first highly selective modulator of two proteins called CDK8 and CDK19—members of an important family known as kinases—whose function is to regulate gene activation.

This well-characterised chemical probe will allow more precise analysis than ever before of the biological the roles of CDK8 and CDK19 in cancer and other cells.

The study comes from a research partnership between The Institute of Cancer Research, London, the University of Cardiff, pharmaceutical company Merck Serono, and Cancer Research Technology—the commercial arm of Cancer Research UK, which was one of the study's funders.

The chemical probe (CCT251545) - published by the same team earlier this year—was discovered by screening a large collection of chemicals against the WNT signalling pathway in cancer cells.

In the new study, the team describe the discovery that CDK8 and CDK19 are the biochemical targets of CCT251545.

The researchers report their work using a range of biological and biophysical techniques to show that CCT251545 potently and selectively binds to CDK8 and CDK19. They go on to explain how the probe binds to CDK8 and CDK19 and how this in turn blocks the WNT signalling pathway, a known driver of many bowel cancers.

Study co-leader Professor Julian Blagg, Deputy Director of the Cancer Research UK Cancer Therapeutics Unit at The Institute of Cancer Research, London, said:

"This collaborative study describes our detailed characterisation of CCT251545 as a highly specific chemical probe for the kinases CDK8 and CDK19 that control gene activation. Publishing our work will enable the scientific community to use our probes to further explore the role of these closely related proteins in cancer and other diseases."

Study co-leader Professor Trevor Dale, Deputy Head of Molecular Biosciences at Cardiff University, said:

"This study is a superb example of how an inter-disciplinary team of scientists from academia and industry can cooperate to produce work of the highest quality. It is great to look back and see how much was achieved."

Fellow study author Professor Paul Workman, Chief Executive of The Institute of Cancer Research, London, said:

"The discovery of this new, highly specific chemical probe could help us to shed new light on an important pathway in cancer—and in biology generally—and help researchers to understand how to influence and exploit it.

"Chemical probes are very important tools in the development of new drugs, because they allow us to explore the effect of blocking cancer-causing proteins in cells. Our discovery through collaborative team science of highly potent, selective inhibitors for cancer proteins addresses an important need to find such probes for the huge area of the cancer signalling network that is still largely unexplored."

More information: A selective chemical probe for exploring the role of CDK8 and CDK19 in human disease, *Nature Chemical Biology*, DOI: 10.1038/nchembio.1952