# Signalling research waves red flag for commercial drug target candidate

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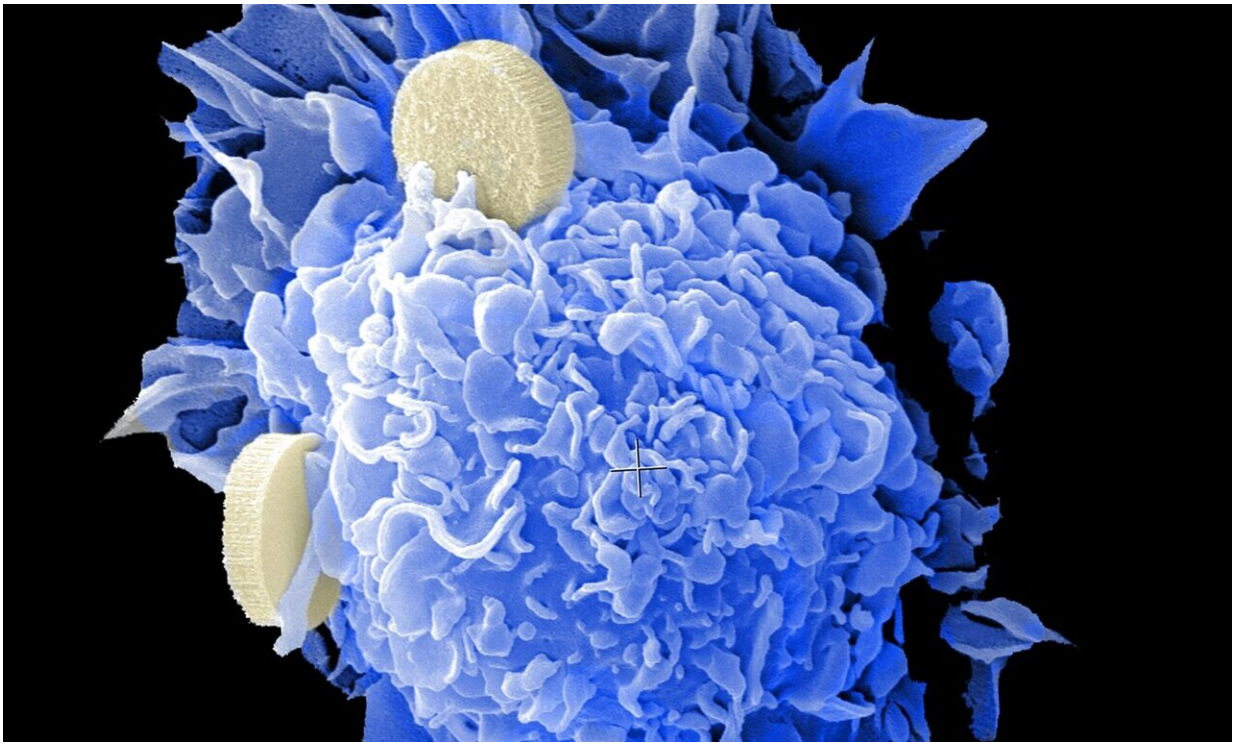

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Researchers at the Babraham Institute have used their understanding of cellular signaling to highlight a pitfall in an emerging treatment for cancer and inflammation. A new review just published in Biochemical Society Transactions summarizes the researchers' current knowledge, which includes details of their research published in *Nature*

*Communications* earlier this year. Developing awareness around these findings will prevent wasted effort and resource being spent on further drug discovery research relating to this drug target by commercial pharmaceutical companies.

The research study focused on an emerging drug target in cancer and inflammation, and the use of small-molecule inhibitors to develop a new precision medicine—one that is matched to patients based on a genetic understanding of their disease. In this case, the compounds being investigated targeted a protein involved in cell signaling called ERK5. ERK5 is known to play an important role in some diseases, most notably in inflammation and cancer, and is thought to promote cell proliferation. Inhibiting this protein is an attractive strategy to develop novel anti-inflammatory or anti-cancer therapeutics and various large pharma have commercial research programs to explore this for therapeutic purposes (for example, Bayer AG, Boehringer Ingelheim and AstraZeneca).

While conducting research using some potential ERK5 inhibitors, the research team of Drs Pamela Lochhead and Simon Cook at the Babraham Institute along with collaborators at Newcastle University, University of York in the UK, and Harvard Medical School in the U.S., noticed an unusual effect; the inhibitors acted in the opposite way what to was expected and activated ERK5 instead of blocking it. The team applied their knowledge of the ERK5 signaling pathway to dissect the molecular basis of this.

As summarized in their latest review, the team found that the unintended activation of ERK5 was due to the binding location of the inhibitors. ERK5 inhibitors that bound to the kinase domain of the protein led to the protein being shuttled to the cell nucleus and activated.

Blocking ERK5 has therapeutic potential, but activating it could have undesirable consequences in terms of stimulated unwanted cell growth.

Similar observations have been seen before with a precision medicine developed to treat melanoma (a form of skin cancer) where it unintentionally caused another type of skin cancer, cutaneous squamous-cell carcinoma.

These research findings and improved understanding will prevent this situation being repeated. Dr. Pamela Lochhead, a senior postdoctoral researcher in the Cook lab and first author on the research paper and the review, said "It was surprising that the inhibitors we tested caused activation of ERK5, but we knew that by working out how this happened, we would be able to inform drug discovery efforts in developing new, safer medicines".

**More information:** Pamela A. Lochhead et al. Paradoxical activation of the protein kinase-transcription factor ERK5 by ERK5 kinase inhibitors, *Nature Communications* (2020). DOI: 10.1038/s41467-020-15031-3

Simon J. Cook et al. Small molecule ERK5 kinase inhibitors paradoxically activate ERK5 signalling: be careful what you wish for…, *Biochemical Society Transactions* (2020). DOI: 10.1042/BST20190338

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