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New intervention in the fight against bowel cancer

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It is widely known that bowel cancer is often driven by increased tumour cell survival and proliferation mediated by the deregulation of a key mechanism within gut cells controlled by the protein Wnt.

Despite a clear link between deregulated Wnt signalling and disease, therapies which target the Wnt pathway remain limited. There is, therefore, a substantial demand for novel approaches to inhibit the Wnt pathway.

New research at the European Cancer Stem Cell Research Institute is asking the question of whether there are any other changes within the Wnt pathway that could prevent cancer developing and thus could be targeted as a cancer treatment. This question has driven research and the subsequent publication of a new paper in *PLOS Genetics* spearheaded by Director of the Institute Professor Alan Clarke, along with Institute colleagues Dr Boris Shorning and Dr Madeleine Young, and Dr Aliaksei Holik, a former PhD and post-doctoral student of Professor Clarke's, who is now at the Walter and Eliza Hall Institute of Medical Research in Melbourne, Australia.

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This new research identifies a role in colorectal cancer for the protein Brg1, whose normal function is to switch the Wnt pathway on. Brg1 has been implicated in a variety of biological processes, in both normal and tumourous tissues. The majority of studies, both in vitro and in vivo, suggest that Brg1 acts as a tumour suppressor – that is, when inactivated it promotes tumour progression.

Professor Clarke's team addressed whether this was the case for colorectal cancer. "Tumourigenesis, or the formation of tumours, within the intestine is potently driven by deregulation of the Wnt pathway, a process epigenetically regulated by the protein Brg1," said Professor Clarke.

"In this study, we aimed to investigate the functional interaction between Brg1 and the Wnt pathway in an in vivo setting by generating mice that had Brg-1 inactivated.

"Using a range of transgenic approaches, we made the surprising discovery that inactivating Brg1 resulted in the prevention of tumour formation and an extended survival rate in mice," added Professor Clarke. "The effects of Brg-1 deletion appeared to directly influence the fate of stem-like cells within the gut. These findings highlight Brg1 as a potential therapeutic target and illustrate the viability of targeting the somatic stem cell as the 'cell of origin' of cancer, which might be particularly valuable in patients with known predisposition to cancer."

"Our findings could result in new therapies being developed that stops the initiation of a tumour at a much earlier stage of treatment of a patient. The question still remains, though, as to whether this process

could work in a fully developed tumour and this presents a set of new and relatively unexplored opportunities for such therapeutic intervention," concluded Professor Clarke.

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