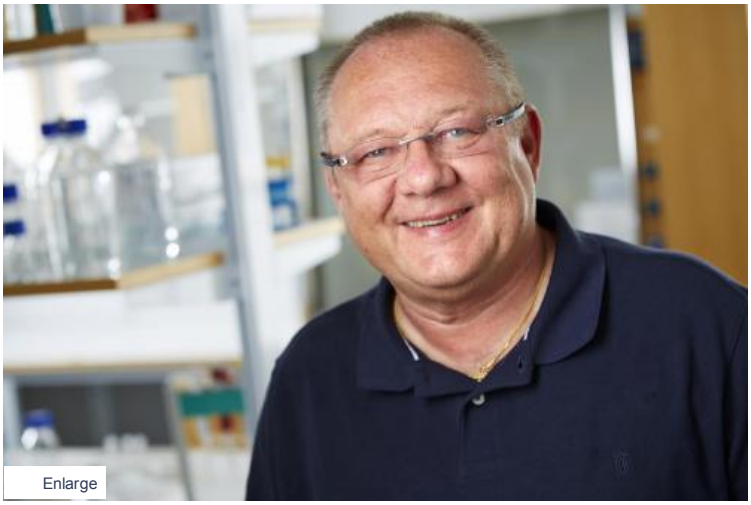
New knowledge on EphB signaling may improve treatment of intestinal cancers



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Sven Pettersson, Ph.D., is a Professor at Karolinska Institutet in Sweden and the LKC School of Medicine at NTU of Singapore. Credit: John Sennett/Karolinska Institutet

A new study led by researchers at Sweden's Karolinska Institutet and Nanyang Technological University in Singapore, provides experimental evidence that a drug that inhibits the EphB-signaling pathway in the cell effectively can suppress the development of intestinal tumors. According to the investigators, this knowledge may be important in the design of new treatments for abrogating adenoma formation and cancer progression in patients predisposed to develop colorectal cancer.

Colorectal cancer is one of the three most common cancers worldwide and almost 95 percent of colorectal cancers are adenocarcinimas. In the current study, being published in the journal *Science Translational Medicine*, the international interdisciplinary research team demonstrates that the drug Imatinib, a tyrosine kinase inhibitor widely used to treat leukemia, can inhibit adenoma initiation and growth in the intestine through a signaling pathway related to a group of cell receptors called EphB.

The investigators reached this conclusion by treating different groups of mice, genetically engineered to develop intestinal adenomas of varying severity with Imatinib and comparing them with untreated control. Imatinib was able to block adenoma initiation, at the stem cell level, by around 50 percent which significantly reduced tumor growth and proliferation. Human colonic tumor explants from patients were subsequently used to confirm this effect of Imatinib.

"Using Imatinib, we have shown that the EphB-signaling pathway is specifically inhibited which results in reduced intestinal tumor initiation and growth", said Dr. Parag Kundu at Nanyang Technological University, first author of the study. The team could also show interesting long term effects in which Imatinib increased the life span of a mouse model that mimics human colon cancer. Interestingly, the drug was also effective in increasing the survival of mice with late-stage adenomas and rectal bleeding.

According to the investigators, these findings suggest that short term intermittent chemotherapies would also be possible to consider as a treatment model. Such an approach would substantially reduce the side effects known to occur when Imantinib have been given for longer periods.

"Our findings provide experimental evidence that Imatinib treatment did not interfere

with the tumour suppressor function of EphB receptors", said Jonas Frisén, Professor of Stem Cell Research at Karolinska Institutet, who supervised the study."

"Our work may have important clinical implications, as Imatinib is a potentially novel drug for the treatment of adenoma formation and cancer progression in patients predisposed to develop colorectal cancer", commented co-author Sven Pettersson, Professor of Host-Microbe Interactions at Karolinska Institutet, and at the Lee Kong Chain School of Medicine at Nanyang Technological University.

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More information: 'An EphB Abl signaling pathway is associated with intestinal tumor initiation and growth', P. Kundu, M. Genander, K. Stråat, J. Classon, R. A. Ridgway, E. H. Tan, J. Björk, A. Martling, J. van Es, O. J. Sansom, H. Clevers, S. Pettersson, J. Frisén, *Science Translational Medicine*, online 1 April 2015, Vol. 7 Issue 281. stm.sciencemag.org/lookup/doi/… scitranslmed.3010567

Journal reference: Science Translational Medicine

Provided by Karolinska Institutet

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