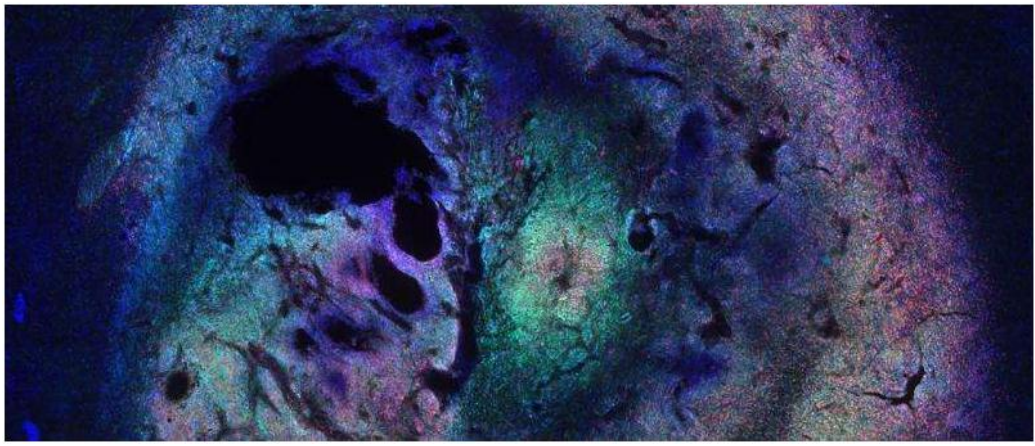
Cancer Biology, SWITZERLAND

Signaling Pathway Suppresses Brain Tumors

Researchers at the University of Basel took a close look at a signaling pathway present in most organisms and found that it suppresses the formation of specific types of brain tumor. Gliomas are the most common brain tumors in adults and the prognosis for patients is, in many cases, very bad. Therefore, novel and effective therapies for glioma treatment are needed. In order to develop these, it is crucial to understand the biology of this type of tumor. So far it has been highly debated which brain cells can form gliomas when they acquire gene mutations. However, researchers believe that brain stem cells might be a potential source of this type of cancer. Stem cells in the human brain can generate new nerve cells and, if something goes wrong in this process and uncontrolled proliferation or impaired differentiation occurs, this may lead to the formation of a brain tumor. A research team led by Professor Verdon Taylor from the Department of Biomedicine at the University of Basel has now studied whether one molecular mechanism that controls normal stem cell maintenance in the brain is hijacked and used by cancer cells during tumor formation. The researchers studied the so-called Notch pathway. This signaling pathway is central to brain stem cell activity and it has been proposed to – once aberrantly activated – contribute to the growth of gliomas. "In contrast to our expectations, we found that the opposite is the case: when activated, this pathway actually suppresses the formation of some types of glioma", says Claudio Giachino, first author of the study. Conversely, in some forms of glioma the inactivation of the pathway results in accelerated growth and makes the tumor more aggressive. Due to these properties, the Notch pathway could, in the future, not only serve as a new therapeutic target but could also be used as a new diagnostic tool in order to get more reliable prognoses for disease progression and patient survival. "Our results demonstrate major differences in the molecular requirements between seemingly similar types of brain tumor and indicate that gliomas must be carefully examined before selecting potentially specific therapeutic interventions in the future", says Taylor.



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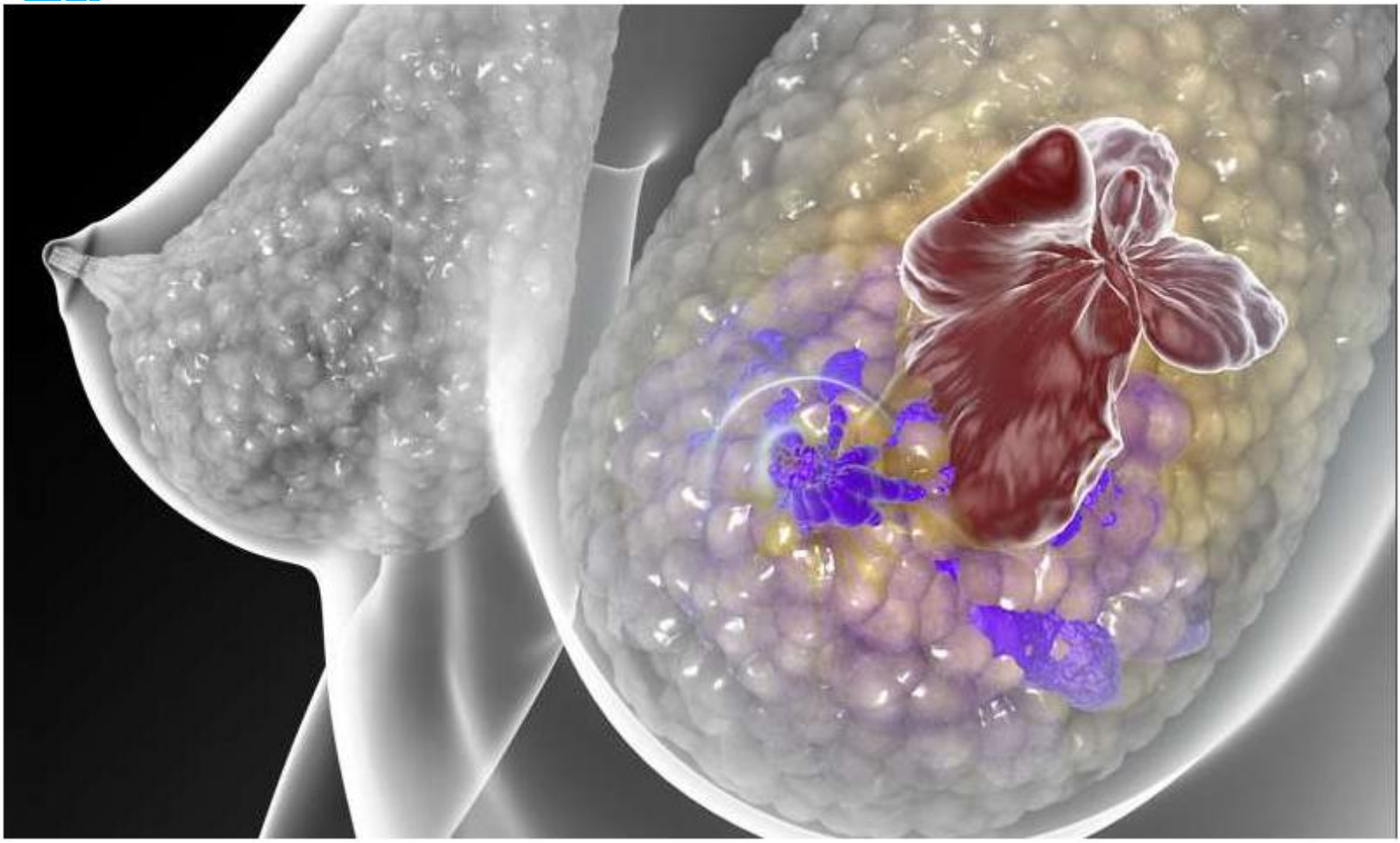
Pharmacy, USA

New compound successfully targets hard-to-treat breast cancer

Findings from a new study led by scientists from the Florida campus of The Scripps Research Institute (TSRI) suggest a potent new therapeutic approach for a number of hard-to-treat breast cancers. The study points to an enzyme called casein kinase 1δ (CK1δ), a critical regulator of growth, as a novel and highly vulnerable therapeutic target. Increased CK1δ expression is common to breast cancer, including the difficult-to-treat subtype called "triple negative breast cancer" (those cancers not driven by estrogen, progesterone, or the HER-2/neu gene), affecting 10 to 20 percent of breast cancer patients. The study, which was published today in the journal *Science Translational Medicine*, was a collaboration among the Florida labs of Derek Duckett and William R. Roush, both of TSRI, and John Cleveland, formerly of TSRI and currently at the Moffitt Cancer Center. "Our findings confirm that aberrant CK1δ regulation promotes tumor growth in breast cancers by activating the protein β-catenin," said Duckett, an associate professor at Scripps Florida. "The best news, however, is that we have been able to treat CK1δ-expressing breast cancers with a highly selective and potent CK1δ inhibitor developed by Bill Roush's lab that triggers rapid tumor cell death." At the beginning of the study, the team knew that the β-catenin protein was an oncogene in many cancers, but it was unclear why it was activated in these breast cancer types since they lacked typical mutations in those pathways. The researchers suspected the link



could be overexpression of CK1δ. Their experiments showed that, indeed to be the case. To confirm the new target, the study used the Roush lab compound, called SR-3029. SR-3029 was remarkably successful at blocking the growth of tumors in both animal models and in studies with tumor tissue from breast cancer patients. "SR-3029 removes β-catenin from cancer cells, killing the tumors," explained Duckett. "This is an extraordinarily promising strategy for targeted treatment with SR-3029, especially in breast cancers that lack targeted treatment options." "These results are just the tip of the iceberg," added Roush, who is professor, associate dean and executive director of medicinal chemistry at TSRI. "Inhibitors such as SR-3029 are being studied in a host of different cancers, and we are hopeful this platform can be translated into clinical applications."

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