

Unraveling of genetic mechanism behind tumor formation may improve targeted treatment for cancer patients

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Genetic alterations in the *FGFR2* gene occur in various cancer types and represent a promising target for therapies. However, clinical responses to

available therapies remained variable and unpredictable, making it difficult to select patients who would benefit from these types of treatments. An international team of researchers, including Shridar Ganesan, MD, Ph.D., chief of molecular oncology and associate director for translational research at Rutgers Cancer Institute of New Jersey, the state's leading cancer center and only NCI-designated Comprehensive Cancer Center, together with RWJBarnabas Health, have found new opportunities to improve diagnostics and targeted therapy for many cancer patients. The research, published in the online version of *Nature*, highlights the importance of studying the functional consequences of genetic changes in tumors.

In various types of cancers including bile duct cancer, stomach cancer and breast cancer, copy number alterations and fusions in the Fibroblast Growth Factor Receptor 2 (FGFR2) gene are relatively common; however, how these genetic variations contribute to the formation of tumors was unclear, and targeting FGFR2 with therapies brought variable and unpredictable results. In this project, the team—led by Jos Jonkers, Ph.D., and Lodewyk Wessels Ph.D., both investigators at Onco and group leaders the Netherlands Cancer Institute, along with Dr. Ganesan—took a data-driven approach to solve this puzzle presented by FGFR2.

"These findings, which go from mouse models into cancer genomics and human clinical trial data, will lay the groundwork for development of clinical trials aimed at rationally increasing the number of patients who will benefit from FGFR inhibitor therapy," says the work's co-senior author Dr. Ganesan, who is also the Omar Boraie Chair in Genomic Science at Rutgers Cancer Institute and professor of medicine and pharmacology at Rutgers Robert Wood Johnson Medical School. "This work also demonstrates the growing power of using clinical [tumor](#) sequencing data and sophisticated pre-clinical models to tackle basic questions in tumorigenesis and guide development of targeted

therapeutics."

"The story of our new findings began over a decade ago," says Jonkers. "By using a mouse model in which we could induce genetic alterations in a controlled manner, we observed a specific variation in the last part of the FGFR2 gene leading to the presence of an incomplete FGFR2 protein. Follow-up mouse experiments then showed that this truncated form of FGFR2 leads to the formation of tumors."

In parallel, the team started looking for evidence of the presence of this truncated form of FGFR2 in human cancer samples. With the datasets available at the Hartwig Medical Foundation and Foundation Medicine, they uncovered that many of the known alterations in the FGFR2 gene lead to the expression of the truncated protein. "We found data confirming our model at the genetic level, but also at the gene expression level," notes first author Daniel Zingg, Ph.D. "Existing diagnostic approaches usually focus on the increased amounts of the protein in tumor samples. What we uncovered now is that it is not the amount of FGFR2 what is causing cells to become cancerous, but the expression of the truncated form. Tumor formation is not caused by more of the normal protein, but by a little bit of the truncated protein."

The results showcase the importance of collaboration and a data-driven approach, say the authors. Rutgers Cancer Institute investigators actively collaborated with Jonkers and colleagues at the Netherlands Cancer Institute, other Oncode investigators, and with Amsterdam Academic University and biopharmaceutical companies Incyte and Debiopharm.

"It's great that through our Oncode base funding and a broad collaborative effort, we could bring this basic and data driven project towards the point where we can have a clinical impact. From a scientific perspective, our work highlights the importance of the functional analysis of mutations we find in cancer. This will allow us to better

interpret the ever-growing set of genetic data from tumors, and advance our understanding of [cancer](#) biology," Jonkers concludes.

More information: Daniel Zingg et al, Truncated FGFR2 is a clinically actionable oncogene in multiple cancers, *Nature* (2022). [DOI: 10.1038/s41586-022-05066-5](#)

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