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Scanning for oncogene addiction

By Lauren Martz, Staff Writer

A method developed at the **Stanford University School of Medicine** for computationally analyzing CT scan images based on an improved model of oncogene addiction could help predict patient response to targeted cancer therapies better than biopsies.[1] The researchers now plan to validate the underlying model in a large clinical trial.

Oncogene addiction refers to a phenomenon whereby certain tumors are highly sensitive to therapies targeting just one oncogene out of all the deregulated genes that could serve as potential targets.[2] Although the mechanisms underlying oncogene addiction are not yet fully understood, this phenomenon is at the root of the success of existing targeted cancer therapies.

In principle, knowing that a patient's tumor is addicted to a particular oncogene should enable a clinician to choose the therapy with the highest odds of producing the best response. The challenge is identifying the relevant oncogene in the first place.

The task could be accomplished via tumor biopsies, although the process is invasive and the genetic information obtained only suggests an oncogene's presence and not whether it is a driving force for the particular cancer.

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> ***—Sebastian Nijman, Research Center for Molecular Medicine of the Austrian Academy of Sciences***

Given the difficulties associated with taking tumor samples, a Stanford team led by Dean Felsher and David Paik hypothesized it might be better to noninvasively image and monitor tumor growth dynamics before and during therapy to deduce the presence of a particular oncogene addiction. Felsher is associate professor of oncology at the Stanford University School of Medicine; Paik is assistant professor in **Stanford University**'s Department of Radiology.

The researchers reasoned that oncogene addiction would likely depend on disruptions in multiple signaling pathways involved in cell proliferation, survival and apoptosis. Those disruptions, in turn, might cause alterations in tumor growth that are detectable with imaging. Computational analysis of all these events could provide a model that might help determine the specific oncogene a tumor is addicted to solely from imaging the tumor, thus opening the way for more effective therapeutic intervention.

To test the idea, the team looked at a transgenic mouse model of lung cancer driven by a *K-ras* oncogene addiction. CT scans of the mice showing tumor progression or tumor regression correlated with activation or inactivation of *K-ras* in the lung tumors, respectively. Immunohistochemistry studies showed that the variations in tumor growth also coincided with alterations in prosurvival signaling pathways at the cellular level.

The researchers incorporated these mouse data into a computational model that linked oncogene addiction in lung tumors to variations in prosurvival and prodeath cell signaling.

Finally, they tested how well the model could predict whether a tumor was oncogene addicted based on imaging analysis alone.

In mice given K-Ras-targeted therapy, CT imaging before and during treatment distinguished oncogene-addicted cancers that responded to treatment from those that failed to respond. The technique's sensitivity was 100%, and its specificity was 87.5%.

The strategy was next applied to human lung cancer patients receiving Tarceva erlotinib, which targets the *epidermal growth factor receptor* (*EGFR*) oncogene. Using images taken before and during the first 4 weeks of treatment, the researchers determined with 100% positive and 91% negative predictive power which patients' tumors were addicted to *EGFR* and would thus respond best to Tarceva.

The findings were published in *Science Translational Medicine*. The team included researchers from **Memorial Sloan-Kettering Cancer Center** and **The University of Tokyo**.

Tarceva is marketed by OSI Pharmaceuticals Inc., now a part of **Astellas Pharma Inc.**, and **Roche**'s **Genentech Inc.** unit to treat non–small cell lung cancer (NSCLC) and pancreatic cancer.

Improving outcomes

Paik told *SciBX* a next step toward a clinically useful tool will be to perform a large prospective trial to further increase the accuracy of the approach. The researchers have funds for such a trial through the Molecular Imaging Program at Stanford. Paik declined to disclose details about the planned study.

One question will be whether the strategy can offer more information than a standard biopsy.

Adam Margolin, director of computational biology and coleader of strategy at **Sage Bionetworks**, told *SciBX* the Stanford team's model potentially reflects a more accurate description of the mechanisms of oncogene addiction than looking at a tumor's genetic profile obtained from a biopsy.

In addition, and because obtaining and analyzing biopsies is a complex process, Paik added, "patients must wait much longer to determine whether or not a treatment is working for them, wasting time when they could be put on other potentially more effective treatments."

Sebastian Nijman, principal investigator at the **Research Center for Molecular Medicine of the Austrian Academy of Sciences**, concurred. "It remains difficult to predict a priori who will respond

to the treatment, and there is no single diagnostic test that does this perfectly. As a consequence, patients that do not benefit from a treatment often receive the therapy nonetheless." Nijman told *SciBX* that this causes the patients to suffer the side effects regardless of whether the treatment is effective and wastes time and money.

Nijman cautioned, though, that "it is not entirely clear whether the developed model is better than current methods to stratify the patients, such as measuring *EGFR* and *K-Ras* mutations. I don't think they compare these methods in the paper in terms of performance. Therefore, even though the method is noninvasive, it may not be an actual improvement."

He added that "the model requires high-quality imaging at multiple time points, something that may not always be available in the clinic."

Stanford's Felsher said his group plans to "further refine the model by including more refined imaging methods and by incorporating other variables including the role of host immune mechanisms, angiogenesis and the program of self-renewal."

He said Stanford is considering whether to patent the findings and that the technique is available for licensing.

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