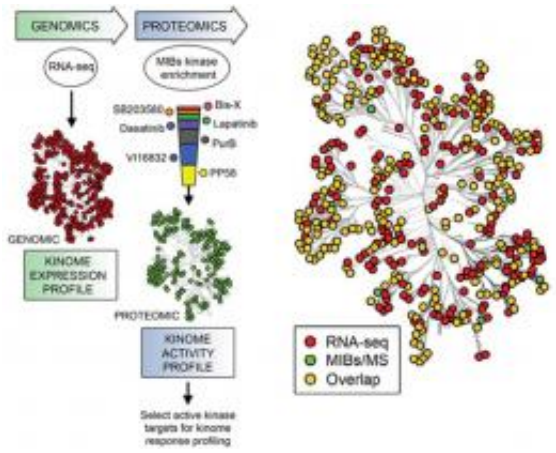
Kinase test may yield big gains for drug-resistant cancers

April 12 2012



This shows the experimental strategy for the rational design of kinase inhibitor combination therapies. Expression profiling is used to define what kinases are expressed in cancer cells. Kinase capture using technology developed by the Johnson laboratory is used to measure which of the expressed kinases are activated in cancer cells. The kinome tree on the right shows the comprehensive capture of expressed kinases (yellow dots). Defining which kinases are activated in cancer is then used to design and test combination therapies in preclinical models of triple negative breast cancer. Courtesy of Gary Johnson, Ph.D., University of North Carolina at Chapel Hill

In a paper published today in the journal *Cell*, a team from the University of North Carolina at Chapel Hill unveils the first broad-based test for activation of protein kinases "en masse", enabling measurement of the mechanism behind drug-resistant cancer and rational prediction of

successful combination therapies.

Kinases are proteins expressed in human tissues that play a key role in cell growth, particularly in cancer. Of the 518 known human kinases, about 400 are expressed in cancers, but which ones and how many are actually active in tumors has been difficult to measure. Tremendous efforts have been made to develop kinase inhibitors as cancer treatments, which have resulted in key drugs such as Herceptin, Tykerb, and Gleevec. However, in spite of the effectiveness of this class of cancer drugs, most cancers eventually become resistant. The UNC team has developed a test that can measure both the presence and activity of 60-70 percent of all kinases simultaneously, allowing investigators to see how cancers evade treatment with kinase inhibitors so that they can combine drugs to block resistance.

Gary Johnson, PhD, the project's principal investigator, says, "Single-agent kinase inhibitors are promising in principle, but often fail in practice because the network of tumor kinases learns how to get around the inhibitor, leading to rapid drug resistance. We're very excited about the test our lab has developed because it works very well in a model of breast cancer to predict the success of combination therapies."

Johnson, who is the Kenan Distinguished Professor and chair of the department of pharmacology in the UNC School of Medicine and a member of UNC Lineberger Comprehensive Cancer Center, is working with UNC Breast Center medical director Lisa Carey, MD, UNC Lineberger director Shelley Earp, MD, and surgical oncologist Keith Amos, MD, to perform clinical trials using the technology with the goal of real-time, personalized therapies for breast cancer.

"One of the most frustrating things as an oncologist is when a patient's tumor develops resistance to a treatment," says Carey, who is also a member of UNC Lineberger. "We are excited about the ability to

examine tumor samples before, during, and after kinase inhibitor treatment to see how the tumor kinase profile changes, and potentially respond to those changes using different inhibitors."

The team hopes to be able to track and define the kinase 'reprogramming' that takes place in tumors during therapy and to use the new test to identify combinations of drugs that will block the cancer's adaptive behavior that leads to drug resistance. A patent application has been filed for the testing technology.

Provided by University of North Carolina School of Medicine