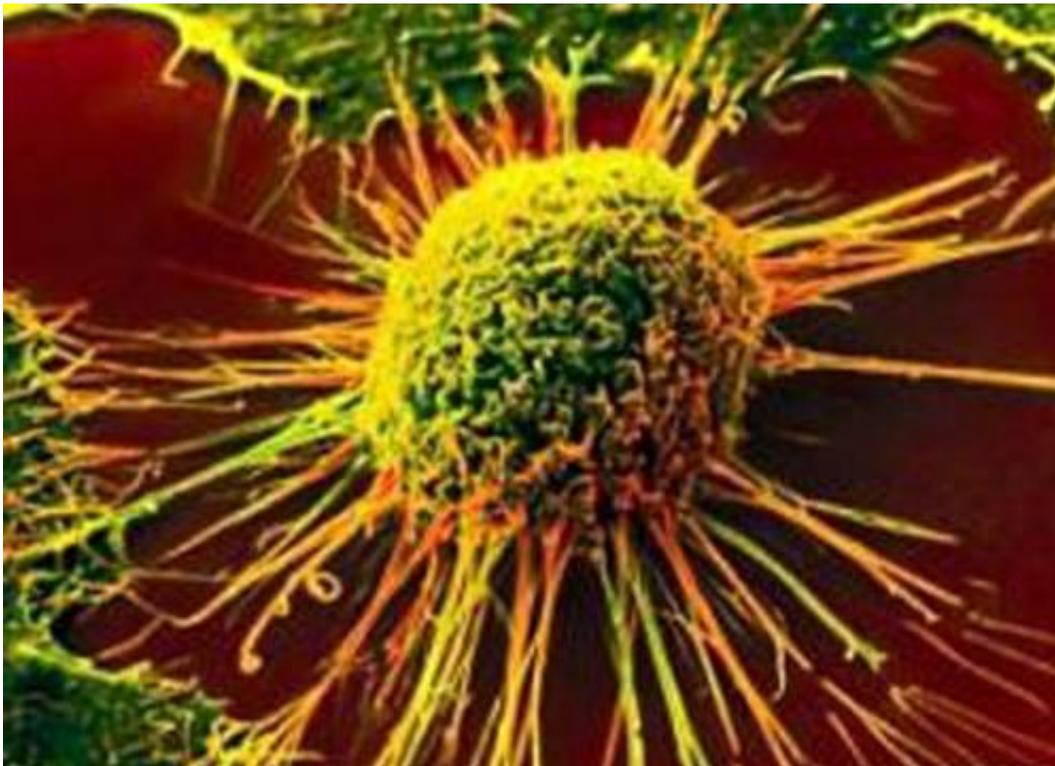


Direct drug screening of patient biopsies could overcome resistance to targeted therapy

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A new screening platform using cells grown directly from tumor biopsy samples may lead to truly individualized treatment strategies that would get around the problem of treatment resistance, which limits the effectiveness of current targeted therapy drugs. In a paper that will appear in *Science* and is receiving advance release on the *Science Express*

website, researchers from the Massachusetts General Hospital (MGH) Cancer Center describe how screening samples grown from treatment-resistant tumors against a panel of current and potential targeted therapy drugs identified previously unknown resistance mechanisms, several of which could not be found by gene sequencing.

"Genetics has been extremely useful to guiding treatment, but in many cases tumor genetics are ambiguous or do not reveal a mutation that informs a therapeutic strategy," says Jeffrey Engelman, MD, PhD, co-senior author of the report. "These functional pharmacologic studies can identify effective therapeutic choices even when the genetics fail to do so."

While the use of drugs that target genetic changes driving tumor growth induces remissions and gives many patients significant symptom relief, in almost all cases the effects are temporary because [resistance](#) appears in a year or two. Resistance develops either through secondary mutations that block the original drug's action on the target molecule or through activation of a secondary pathway to carry molecular signals that sustain tumor growth. Previous efforts to study resistance mechanisms - either by inducing resistance in the laboratory using established [cell lines](#) or by looking for new mutations in resistant tumor cells - have significant limitations.

The approach developed by the MGH Cancer Center team combines genetic analysis of resistant tumors with pharmacologic screening - testing cell lines grown directly from the patients' tumor samples against a panel of drugs that target molecules or reactions involved with cell growth and survival. Using recently developed technology that facilitates the development of cell lines from patient samples, the researchers were able to establish 24 viable lines from patients' resistant lung tumors. Each cell line was tested against a panel of 76 targeted drugs - 17 that are FDA approved and 59 in various stages of development - both alone and

in combination with the first-line drug to which the tumor had become resistant.

The pharmacological platform was applied to both the 24 patient-derived lines and to another 36 established lines in which resistance had been cultivated in the laboratory. In the five established lines with known mechanisms of resistance, the pharmacologic screen accurately identified drugs targeting the known bypass track, which confirmed the usefulness of the strategy. When the approach was then used to assess a large panel of resistant cell lines, including those established from patient biopsies, at least one effective combination - a secondary drug that restored the effectiveness of the first-line therapy - was identified in 45 of the 55 lines in which the resistance mechanism had been unknown.

Several of these "hits" identified [resistance mechanisms](#) that would not have been detected by [genetic analysis](#). For example, the effectiveness of a drug inhibiting fibroblast growth factor receptor 3 (FGFR3) in restoring sensitivity to EGFR inhibition was the first reported evidence of that molecule's involvement in [treatment resistance](#). In another patient-derived cell line, addition of a MEK inhibitor restored the treatment sensitivity of tumor cells driven by ALK mutations. Genetic analysis of that cell line revealed both a mutation known to activate the MEK pathway and another mutation affecting an enzyme called JAK3. But only the pharmacologic screen was able to determine that resistance was conferred by the MEK mutation, since JAK inhibitors did not re-sensitize that cell line to ALK inhibition.

Although combining MEK and ALK inhibitors was only effective in that one patient sample, several other ALK-positive tumors were re-sensitized by drugs that inhibit SRC enzymes, even though no SRC-related mutations were present. Further evidence indicated that inhibiting ALK led to activation of SRC-controlled pathways that promoted resistance and that combining ALK and SRC inhibitors as first-

line therapy might delay the emergence of resistance. The efficacy of this combination was demonstrated in multiple mouse models.

"We expected effective combinations to be specific against particular cell lines rather than broadly active, and this is largely what we found," says Cyril Benes, PhD, of the MGH Cancer Center, co-senior author of the report. "The broad activity of the combination of ALK and SRC inhibitors across ALK-driven models suggests this may be a common, previously unsuspected resistance mechanism. We were able to validate four of these combinations in animal models, but many more were indicated across the cell lines that we tested."

The team is now working to develop technologies - including biopsy and culturing procedures that will yield enough cells to screen within a few weeks of the patient biopsy - that could make it practical to incorporate pharmacologic screening into clinical practice. "This screen was so effective that we think it warrants a serious effort to develop the technology for personalized treatment decision making," says Engelman. He is the Laurel Schwartz Associate Professor of Medicine, and Benes is an assistant professor of Medicine at Harvard Medical School.

More information: "18 Patient-derived Models of Acquired Resistance Can Identify Effective Drug Combinations for Cancer," by A.S. Crystal et al. *Science*, www.sciencemag.org/lookup/doi/10.1126/science.1254721

Provided by Massachusetts General Hospital

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