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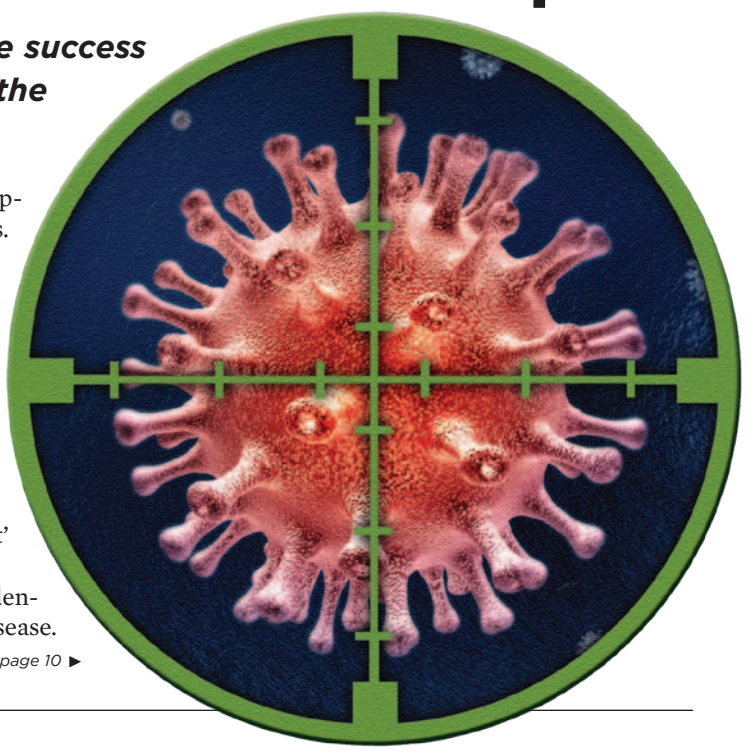
INSIDE

Targeted Therapy:

Not All Mutations Are Created Equal

Uncovering the abnormalities that dictate the success or failure of existing drugs and determining the aberrations that drive tumor progression



LIVERPOOL, ENGLAND—A long-running goal in oncology drug development is to create more targeted, personalized treatments for patients. However, developing these treatments requires understanding which genetic and epigenetic aberrations drive individual cancers, which ones respond to a particular drug, and whether it's necessary to hit a pathway at different points.

"The key point in this is that not all mutations are created equal," said Gordon Mills, MD, PhD, the chair of Systems Biology at the University of Texas MD Anderson Cancer Center in Houston, speaking at the session "Oncology Drug Development in 2012" at the 2012 National Cancer Research Institute (NCRI) conference in Liverpool, England. "Less than half in breast and 10% in ovarian have 'hot spot' mutations with known effects in known tumor suppressor genes."

That is why the approach to drug discovery has moved toward identifying and treating subsets of mutations that occur in a single disease.

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ASH 2012

Ibrutinib Changing CLL Treatment Landscape

ATLANTA—Ibrutinib (Pharmacyclics), a first-in-class, oral Bruton tyrosine kinase inhibitor, has shown promise in two Phase II studies of patients with chronic lymphocytic leukemia (CLL). Both studies were presented at the recent American Society of Hematology annual meeting (abstracts 187 and 189).

"Ibrutinib offers great potential to significantly change the treatment landscape in CLL," said John Byrd, MD, the director of hematology at the Wexner Medical Center at Ohio State

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Vogl, NY...

Faulty Rhetoric: 'Save a Life'

Faulty End Point: 'Cancer-Specific Survival'

Steven Vogl, MD

The rhetorical argument of "saving a life" recently has been resurrected in public controversy about mammogram screening (frequency, age of onset, age of cessation) and prostate-specific antigen (PSA) screening (to screen or not to screen). Our goal as physicians—the well-being of our patients and the well-being of the population as a whole—is best served by avoiding this rhetoric altogether.

The tacit assumption in this rhetoric is that only one "cause of death" counts. If that is prevented, the subject "lives happily ever after." Framing the issue in all-or-nothing terms, with this sort of solution (salvation vs. perdition), is more properly the place of religion, which deals with fundamental moral questions like "why do we die?" and "why do bad things happen to good people?"

In medicine and public health, grounded in the practical and the empirical, the

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REVIEWS & COMMENTARIES

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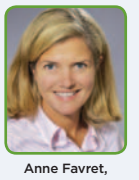

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MUTATIONS

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Early efforts to target specific mutations in tumors have shown preliminary success. For instance, in an open-label, randomized multicenter trial, researchers showed that the KIT kinase inhibitor imatinib (Gleevec, Novartis) prompted a partial response in just over 50% of patients with a KIT mutation-positive gastrointestinal stromal tumor (*N Engl J Med* 2002;347:472-480, PMID: 12181401). More recently, a Phase I, dose-escalation trial found that the majority of patients with *BRAF* mutation-positive melanoma who carried the *BRAF* mutation, V600E, had a partial or full response to the study drug, vemurafenib (Zelboraf, Roche), designed to target mutated *BRAF* (*N Engl J Med* 2010;363:809-819, PMID: 20818844).

However, common solid tumors such as breast, lung and colorectal cancer remain difficult to treat because they may be caused by several different pathways and molecular abnormalities, not just a single aberration (*Mol Cancer Ther* 2007;6:1175-1179, PMID: 17431100; *Sci Transl Med* 2012:4:127ps10, PMID: 22461637). In other words, the same tumor type may behave differently in different people, which explains why a drug may be effective against breast cancer in one patient but not in another.

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In the session, the panelists discussed efforts to uncover the abnormalities that dictate the success or failure of existing drugs, allowing clinicians to personalize treatment, as well as efforts to determine what aberrations drive tumor progression in cancers with no available drugs, allowing investigators to develop highly targeted therapies.

"We're shifting our focus to a patient-based approach, which means we want a molecular definition of an individual patient's disease," said Susan Galbraith, PhD, vice president and head of Oncology Innovative Medicines at AstraZeneca in Macclesfield, England, who introduced the session. Dr. Galbraith noted that having a better molecular understanding of patients will make it possible to identify new targets for drugs, develop better preclinical disease models and personalize treatments to patients based on who is most likely to respond.

"We're seeing that cancer is not one disease, 10 diseases or even 100 diseases; it's thousands of diseases, and that is going to take a long time to sort out," said Maurie Markman, MD, senior vice president of clinical affairs and the national director for medical oncology at Cancer Treatment Centers of America in Philadelphia, who was not on the panel. "However, there's been tremendous progress so far. The advances we've seen in the past five years are greater than those we've seen in the past 200."

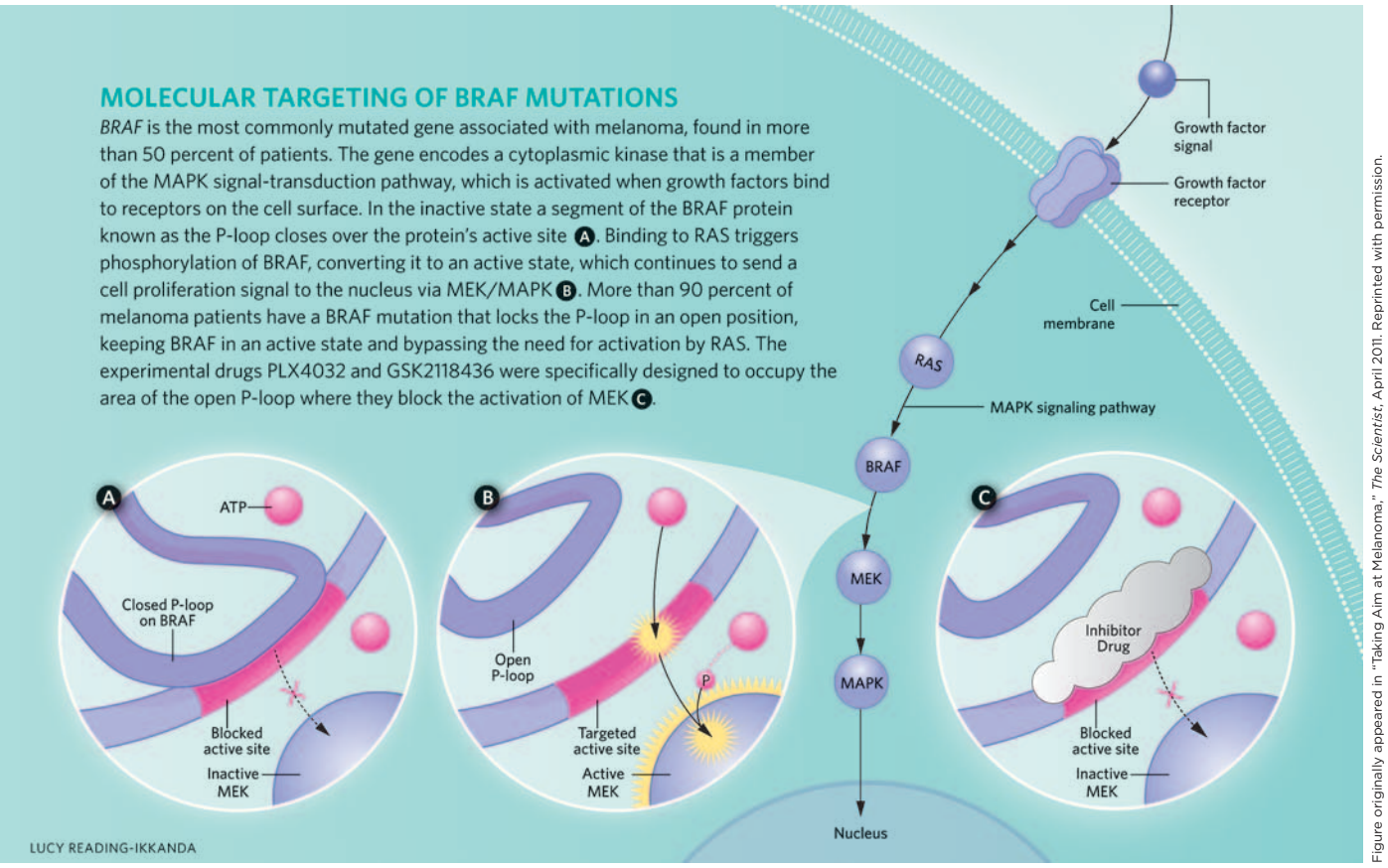


Figure originally appeared in "Taking Aim at Melanoma," *The Scientist*, April 2011. Reprinted with permission.

Mutations Predict Response to Therapy

Understanding the mutations that sensitize patients to a particular drug is critical to improving patient care. Panelist Nigel Brooks, PhD, a senior project director of Cancer and Infection Research at AstraZeneca in Cheshire, England, discussed challenges in translating preclinical hypotheses to the clinic by comparing and contrasting efforts to target epidermal growth factor receptor (EGFR), a kinase that is mutated or overexpressed in various cancers, including non-small cell lung cancer (NSCLC), and fibroblast growth factor (FGFR), which is genetically dysregulated in tumor types, including squamous NSCLC and breast cancer.

Several decades ago, researchers hypothesized that targeting solid tumors that express or overexpress EGFR would make an effective therapy, and in 1995, the first selective inhibitor of EGFR, called gefitinib (Iressa, AstraZeneca and Teva), was developed to treat advanced NSCLC.

However, in two Phase II IDEAL (Iressa Dose Evaluation in Advanced Lung Cancer) trials, only 19% of patients with recurrent NSCLC showed a dramatic clinical response to the drug in IDEAL 1 and 10% in IDEAL 2 (*J Clin Oncol* 2003;21:2237-2246, PMID: 12748244; *JAMA* 2003;290:2149-2158, PMID: 14570950). However, it was striking that some specific patient subgroups responded to the drug, including women, Asians, nonsmokers and patients with adenocarcinomas (*J Clin Oncol* 2004;22:1103-1109, PMID: 15020612).

To understand why the drug only helped certain patients, researchers at Massachusetts General Hospital Cancer Center and Harvard Medical School in Boston analyzed *EGFR* mutations in patients with NSCLC (*N Engl J Med* 2004;350:2129-2139, PMID: 15118073). The investigators found that specific mutations in *EGFR* (exon 19 deletions and exon 20 mutations) were associated with clinical response to gefitinib. In particular, eight of nine patients with NSCLC who responded to gefitinib had these *EGFR* mutations, compared with none of the seven patients who did not respond to the drug. The mutations were observed more frequently in adenocarcinoma, women and nonsmokers with NSCLC. The authors concluded that mutations in *EGFR* predicted sensitivity to gefitinib.

In the Phase III, open-label IPASS (Iressa Pan-Asia Study) trial, investigators demonstrated that East Asians with advanced lung adenocarcinoma who were either light or never-smokers derived a greater benefit from gefitinib than from standard chemotherapy if they had *EGFR* mutations (*N Engl J Med* 2009;361:947-957, PMID: 19692680). Patients with *EGFR* mutations who were treated with gefitinib 250 mg daily had a higher objective response rate (71.2%) than did those who received carboplatin-paclitaxel (47.3%; $P<0.001$), and better progression-free survival at 12 months (hazard ratio [HR] with gefitinib, 0.48; $P<0.001$). In patients without *EGFR* mutations, the objective response rate with gefitinib was low (1.1%), and progression-free survival favored the chemotherapy group (HR with gefitinib, 2.85; $P<0.001$).

'We need to dramatically change the paradigm for drug development. The idea that we should continue to do clinical trials to help a few [who] we don't understand is not sustainable or rational and it's got to stop. This strategy costs tens of millions of dollars per trial to give a benefit of a few weeks, maybe months.'

—Maurie Markman, MD

The study helped confirm that "*EGFR* mutations are a strong predictor of gefitinib benefit versus double chemotherapy," concluded Dr. Brooks, who was not involved in this study. "From this evidence, we were able to develop predictive biomarkers after clinical trials. In the future, however, having predictive biomarkers before clinical trials is the ultimate goal. That way we can prospectively select

patients that will benefit from therapy."

Dr. Brooks then used the development of AZD4547 (AstraZeneca), a potent and selective inhibitor of FGFR1, 2 and 3, to illustrate how a compelling preclinical hypothesis that links drug response to a predictive marker (in this case, *FGFR* gene amplification), allowed prospective selection of patients at a much earlier stage in the drug development process.

Using this logic, researchers at the University of Texas MD Anderson Cancer Center devised a hypothesis based on compelling preclinical data that suggested mutations in the *PIK3CA* gene predicted response to inhibitors of the phosphatidylinositol 3 kinase (PI3K)/AKT/mammalian target of rapamycin (mTOR) pathway, which is overactive in a range of cancers (*Nat Rev Cancer* 2009;9:550-562, PMID: 19629070). In a Phase I trial, *PIK3CA* mutations were detected in 11.5% of patients (25 of 217) with diverse solid tumors (*Mol Cancer Ther* 2011;10:558-565, PMID: 21216929). Of the 25 patients with *PIK3CA* mutations, 17 (68%) were treated with a PI3K/AKT/mTOR pathway inhibitor and six (35%) achieved a partial response compared with 15 of 241 patients (6%) without *PIK3CA* mutations treated with the same protocols (*P*=0.001).

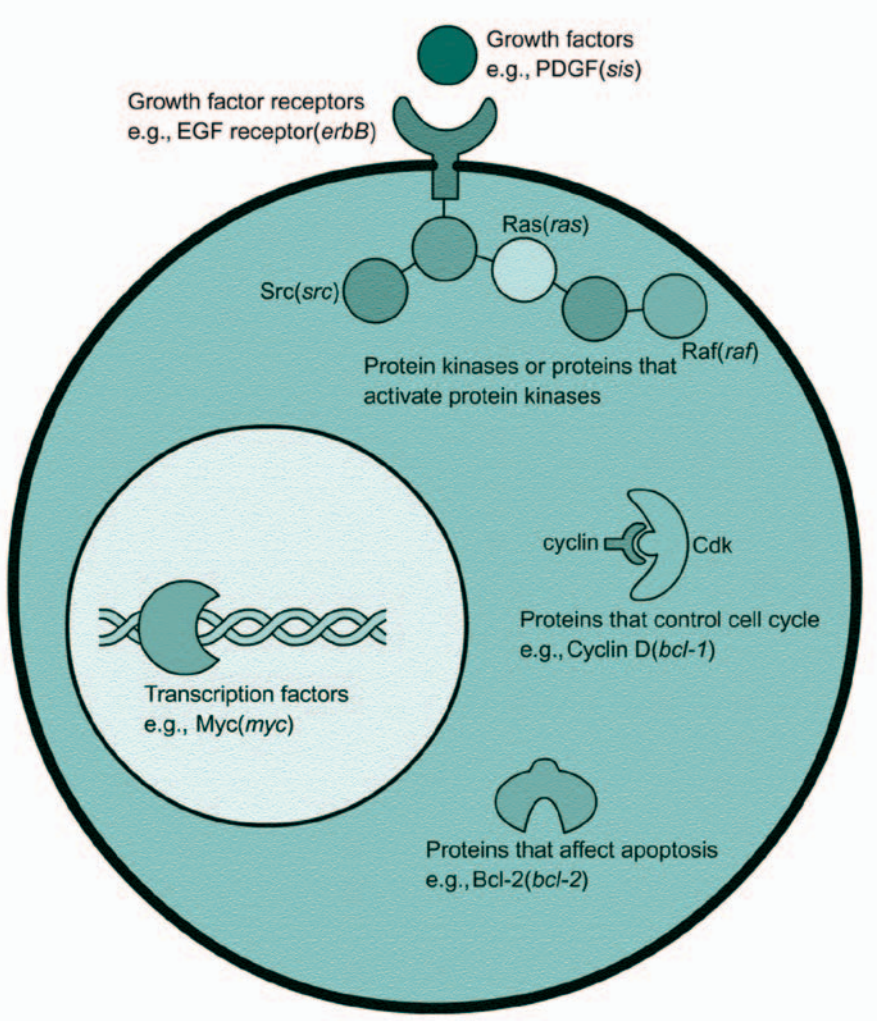
"Usually, we're begging to find one patient who will respond in a Phase I trial, but this is remarkable. More than 30% of patients demonstrated a benefit," said Dr. Mills. "The study shows that matching aberrations to drugs works. We see endometrial cancer shrinking, ovarian cancer shrinking."

Nontargetable Aberrations: Drivers and Passengers

Investigators also are working to identify aberrations that drive cancer but that don't yet have drugs to target them. In his talk at NCRI, Dr. Mills focused on abnormalities along the PI3K pathway—the most common activating aberration in cancer—to determine which ones are drivers and which are passengers. To this end, Dr. Mills' team is conducting a clearinghouse study, which encompasses nearly 30,000 new patients a year, in which all participants undergo tumor biopsies. The investigators have demonstrated that fewer than half of the patients characterized so far had actionable events, but "for the 50% of patients with no targetable aberration, we don't know what the aberrations mean," Dr. Mills said.

Dr. Mills' team is now conducting deep characterization of the tumors, using DNA/RNA sequencing proteomics, to find drivers. Many of the aberrations his group has characterized are turning on unpredicted pathways, which is why "we are going to have to look at life in a mutation-specific event, not a gene-specific event to have a better way to handle patients going forward," Dr. Mills said.

For instance, in a recent study, the investigators examined 243 endometrial carcinomas—a PI3K kinase–driven disease—and found that two mutations, *PIK3R1* and *PIK3R2*, were critical drivers of endometrial cancer pathogenesis.



Oncogenes and tumor suppressor genes

> 'For patients with a particular biomarker, only subpopulations benefit and the responses are usually short. I think that's one of the things we forget to emphasize—we're seeing remarkable steps forward, but they're usually measured in months, not years and certainly not in cures.'
>
> *—Gordon Mills, MD, PhD*

PIK3R1 mutations occurred at a higher rate in endometrial cancer than in any other tumor lineage (20% of endometrial cancers), and *PIK3R2*, not previously demonstrated to be a cancer gene, was mutated in 5% of endometrial cancers (*Cancer Discov* 2011;1:170-185, PMID: 21984976).

Drug Resistance

Understanding resistance, both intrinsic and acquired, also remains a challenge. Despite the initial response to inhibitors, such as gefitinib, most NSCLC patients relapse and develop acquired resistance, with the underlying mechanism unclear. After being exposed to chronic drug treatment, cancer cells often adapt their signaling circuitry—for instance, taking advantage of pathway redundancies—and develop acquired resistance (*Cancer Biol Ther* 2011;11:793-800, PMID: 21307659).

"If we understand what's driving resistance to these pathways, we might be able to develop the right combinations of drugs to take into the clinic," Dr. Mills said.

To determine the mechanisms underlying acquired drug resistance in NSCLC, researchers from Massachusetts General Hospital Cancer Center performed systematic genetic and histologic analyses of tumor biopsies from 37 patients with drug-resistant NSCLCs who carried *EGFR* mutations (*Sci Transl Med* 2011;3:75ra26, PMID: 21430269). The investigators found that 55% of tumors developed known mechanisms of resistance. Unexpected genetic changes, such as mutations in the *PIK3CA* gene, occurred in 10% to 20% of tumors, and five resistant tumors (14%) turned into small cell lung cancer (SCLC), which was sensitive to standard SCLC treatments. Additionally, three patients overcame their acquired resistance once treatment ceased, and became sensitive to another round of treatment with *EGFR* inhibitors. The results highlighted the importance of continuing to assess cancers throughout the course of the disease.

"Much research is now focused on strategies to combat secondary resistance to targeted agents," said Timothy Yap, MBBS MRCP, a clinical research fellow at the Royal Marsden Hospital and The Institute of Cancer Research in Sutton, England. "Such approaches are likely to include the use of different combination regimens to decrease the opportunities for acquired drug resistance. The key challenge will be to establish how such novel molecular agents should be combined, and which drugs they should be given with, bearing in mind issues of toxicities and pharmacokinetic interactions."

Future Challenges

As investigators embrace a personalized medicine approach to cancer care, they can glean a fuller picture of what aberrations drive cancer and how to combat them.

"We can characterize the patient, tumor and tumor environment in a way we've never been able to do before," Dr. Mills said.

However, there are still major challenges in this area. Even after identifying relevant aberrations and useful biomarkers, the scope of this knowledge remains limited.

"For patients with a particular biomarker, only subpopulations benefit and the responses are usually short," Dr. Mills said. "I think that's one of the things we forget to emphasize—we're seeing remarkable steps forward, but they're usually measured in months, not years and certainly not in cures."

Dr. Markman stressed, "We need to dramatically change the paradigm for drug development. The idea that we should continue to do clinical trials to help a few we don't understand is not sustainable or rational and it's got to stop. This strategy costs tens of millions of dollars per trial to give a benefit of a few weeks, maybe months."

He added: "The future of research is looking at individual patients, collecting data in these patients worldwide, making info available to doctors and insurers, and figuring out how to do this quickly and less expensively. Although there's been lots of talk of change, I've seen no action yet."

—Victoria Stern

Dr. Mills reported consulting for AstraZeneca and Novartis, among others; stock ownership in Catena Pharmaceuticals and Spindle Top Ventures; and research sponsored by AstraZeneca and Roche, among others.