Finding New Uses for Existing Medications

Several strategies bring agents approved for other conditions into the oncology clinic

First developed as an osteoporosis drug, raloxifene (Evista; Eli Lilly) was approved in 2007 by the U.S. Food and Drug Administration (FDA) for breast cancer prevention in high-risk women. That’s just one example of an agent that has been approved for one condition and later also shown to help beat back cancer. Many research groups are now attempting to “repurpose” or “reposition” other existing drugs, using various strategies.

In many cases, discovering that an existing drug may counter cancer is pure serendipity. Experimenting with a cell line of nasopharyngeal carcinoma cells that they developed, Ohio State University Comprehensive Cancer Center (OSUCCC) researchers Ronald Glaser, PhD, Eric Yang, PhD, and their colleagues found that norepinephrine upregulated the production of matrix metalloproteinases (MMP) and the pro-angiogenic cytokine VEGF, which could be inhibited by the β blocker propranolol. That initial finding was “totally accidental,” says Glaser, director of the Institute for Behavioral Medicine Research.

The researchers went on to reveal that norepinephrine could regulate VEGF expression in multiple myeloma, as well as interleukin (IL)-6, IL-8, and VEGF in cultured melanoma cells. The presence of β-adrenergic receptors in these tumor cells suggests that β blockers might offer therapeutic potential in these cancers, too.

For more evidence of β blockers’ effectiveness, the team turned to OSUCCC’s Stanley Lemeshow, PhD, a biostatistician and dean of OSU’s College of Public Health. Lemeshow collaborated with Danish researchers who dug into Denmark’s vast national registry, as well as pharmacy records. Disease-specific mortality was 13% lower in melanoma patients who had been taking β blockers compared with those who had never taken the blood pressure medication (Cancer Epidemiol Biomarkers Prev 2011;20:2273–9).

With reproducible data in 3 different malignancies, Glaser convinced the OSU Medical Center to finance an initial clinical trial of propranolol in melanoma patients.

The “aha” moment for Reuben Kapur, PhD, came after experiments targeting RAC GTPase signaling in acute myeloid leukemia (AML) yielded mediocre results. The Indiana University School of Medicine pediatrics professor and his colleagues thought they might have more luck targeting a related protein, Rho kinase (ROCK), which was hyperactive. Indeed, the ROCK inhibitor fasudil, a vasodilator prescribed in Japan, slowed the growth of leukemia cells in the lab and later prolonged the survival of mice with the disease (Cancer Cell 2011;20:357–69).

SYSTEMATIC SCREENING

Other groups have adopted more systematic search strategies. Canadian researchers compiled a library of 312 FDA-approved drugs and then used a high-speed, pipette-handling robot to test the drugs against 2 human AML cell lines. The most potent was tigecycline (Tygacil; Pfizer), an intravenous antibiotic used to treat serious skin and abdominal infections. Experiments in mice showed that the drug destroyed leukemia cells by cutting off energy production in the cells’ mitochondria (Cancer Cell 2011;20:674–88). They have now launched a multicenter phase I trial in patients with relapsed, refractory AML.

“Technology made this discovery possible,” says study leader Aaron Schimmer, MD, PhD, a clinician-scientist in Toronto’s Princess Margaret Cancer Program. “In 3 days, we found potential leukemia drugs hiding in plain sight. Sifting through every combination by hand would’ve taken months.”

Johns Hopkins researchers took a similar tack. They screened more than 3,000 compounds in their drug library against 2 prostate cancer cell lines, uncovering 38 that inhibited cell proliferation by more than 50%. These drugs were then tested in 6 prostate cancer cell lines. One of the most effective drugs turned out to be digoxin (digitalis), often prescribed for arrhythmias and heart failure.

Using data from Harvard’s Health Professionals Follow-up Study, an ongoing prospective study of nearly 48,000 men, they found that men who regularly took digoxin had a 25% lower risk of prostate cancer (Cancer Discovery 2011;1:68–77).

The study’s co-first author, Johns Hopkins epidemiologist Elizabeth A. Platz ScD, MPH, says that digoxin isn’t likely to become a cancer drug. Because of safety concerns, people who don’t need digoxin for a heart condition shouldn’t take it. However, other researchers can study how the drug might exert its anticancer effects. “Then someone could develop something similar that would work directly on the prostate and that can be used in a broader population,” explains Platz.

ATTRACTION OPPORTINES

Stanford University researchers led by Atul J. Butte, MD, PhD, took another approach. They hypothesized that effective drugs might induce gene expression profiles that are opposite of the profiles caused by the condition they treat. In other words, if a disease causes activity in certain genes, drugs that decrease the genes’ activity might treat the disease.

Using public databases containing thousands of genomic studies, Butte’s team created a computer program to compare the expression profiles induced by about 164 compounds and 100 diseases. The program pointed to potential drugs for 53 of the diseases. They selected 2 drug–disease pairs for further testing, including the ulcer drug cimetidine, which the computer matched with lung cancer. Subsequent laboratory studies confirmed cimetidine’s effectiveness both in vitro and in vivo using mouse xenograft models (Sci Transl Med 2011;3:96ra77).

Admittedly, says Butte, “Mice are not humans, so it’s still not a perfect model. But with so much unmet medical need in cancer, we can’t stop trying new approaches to find new therapies.” —Suzanne Rose

Cancer Discovery, published OnlineFirst February 9, 2012, doi: 10.1158/2159-8290.CD-ND2012-008

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