Companies compete over mutation-specific melanoma drugs

When a doctor spots a cancerous skin growth, simple surgery is often sufficient to rid the patient of cancer. Once melanoma has spread throughout the body, however, few treatment options exist. Neither chemotherapy nor the immune protein interleukin-2—the two therapies currently approved for treating metastatic melanoma—offer much hope. But a new generation of melanoma drugs nearing approval that target a common mutation implicated in driving tumor growth could revolutionize the way physicians treat skin cancer.

These new drugs target a mutated form of the B-RAF oncoprotein, and cancer specialists say they represent a major improvement over existing therapies, which suffer from low response rates and fail to significantly extend survival. "We've never seen anything like this," says Lynn Schuchter, an oncologist at the University of Pennsylvania School of Medicine in Philadelphia who is involved in trials to test the new compounds and has been treating patients with metastatic melanoma, the deadliest form of the disease, for almost 25 years. "We really have tears of joy."

In January, the Swiss drug maker Roche announced preliminary phase 3 trial results showing that its experimental targeted B-RAF therapy significantly extended lifespan in people with metastatic melanoma. In fact, the study was so successful, with some participants emerging nearly cancer free, that the trial was halted prematurely, and many of the 340 subjects in the study's control arm, who previously received only standard chemotherapy, are now being given the drug. Keith Flaherty, an oncologist at Massachusetts General Hospital in Boston and principle investigator on the trial, expects federal regulators to approve the small-molecule drug, developed in partnership with Berkeley, California–based Plexxikon, later this year. "It's sort of a slam dunk," he says. Full results from the trial will be presented in June at the American Society of Clinical Oncology's annual meeting in Chicago.

Phanie / Photo Researchers, Inc.

Breaking the mole: New melanoma treatments.

The ubiquity of B-RAF mutations—first identified in 2002 and since found in many types of tumors, including lung and colon cancer cells, albeit at lower frequencies than in melanoma, where more than half of all cases of the disease express the aberrant protein—has made it an attractive target for many pharmaceutical companies. Thus, Roche is in the midst of a heated race to develop the first-in-class, mutation-specific therapy for melanoma. Also in January, GlaxoSmithKline (GSK), the British pharma giant, launched a phase 3 trial to test its own B-RAF inhibitor, and the Swiss drugmaker Novartis has another compound currently in phase 1 trials.

Despite the buzz surrounding these drugs, they aren't without side effects. Notably, some of the study subjects developed small, cancerous skin growths that had to be surgically removed, possibly as a result of nonspecific drug targeting. But, according to Keiran Smalley, a melanoma expert at the Moffitt Cancer Center in Tampa, Florida who was not involved in any of the trials, that's a small price to pay for longer survival, as people with metastatic melanoma typically survive for less than a year.

More worryingly, B-RAF inhibitors suffer from the limitation that patients nearly always develop resistance to the drugs after around six to nine months of treatment, and the tumors return or begin growing again. Researchers have just begun to sort out how this resistance occurs. Three papers published in December suggest that tumor cells can circumvent the drugs by reactivating the B-RAF pathway through other mutations or by turning on an entirely different survival pathway (*Nature* **468**, 968–972 & 973–977, 2010; *Cancer Cell* **18**, 683–695, 2010). Knowing how cancer cells evade the medications may help researchers devise drug cocktails that can prevent resistance from occurring, says Roger Lo, a dermatologist at the University of California–Los Angeles who led one of the studies and served as a subinvestigator on both the GSK and the Roche trials.

Researchers are now testing whether combining a B-RAF inhibitor with another experimental compound that blocks a separate enzyme in the same pathway will stave off resistance (see page 270). According to Richard Kefford, an oncologist at the University of Sydney in Australia and the primary investigator on a GSK combination trial, a therapy that targets two proteins at once should be "a much more durable inhibitor of cellular growth."

Cassandra Willyard

Recent deal highlights hopes for cancer-killing viruses

Can viruses be engineered to successfully tackle cancer? The biotechnology giant Amgen certainly hopes so. At the end of January, the California-based company announced that it was buying BioVex, a pioneer in developing so-called oncolytic viruses, for an impressive $1 billion.

"Without a doubt, the Amgen deal is a validation of this field, which has often been thought of as a little bit of a backwater," says Robert Coffin, founder and chief technology officer of BioVex.

Originally spun off from University College London but now headquartered in Woburn, Massachusetts, BioVex is currently conducting phase 3 trials of OncoVEX GM-CSF, a genetically modified herpes simplex virus, for treating various cancers. It hopes to submit this vaccine for US approval at the start of 2012.

Other companies are advancing similar products. The Canadian company Oncolytics Biotech is conducting a phase 3 trial of Reolysin, a reovirus, for treating head and neck cancer. And Jennerex, headquartered in San Francisco, is conducting phase 2 trials of JX-594, a modified vaccinia virus, for treating liver cancer. Meanwhile, an engineered adenovirus for treating head and neck cancer, developed by Shanghai Sunway Biotech, was approved in China in 2005.

Scientists have known for more than a century that viral infections occasionally lead to cancer remission. Subsequent studies revealed that not only can some viruses directly infect and kill cancer cells, but also this process releases antigens that prime the immune system to attack the tumor.

Treatment approaches that target tumor suppressors mutate

For all the differences documented between cancers, they share some striking similarities. Around 80% of detected cancer-related mutations are errors in so-called 'tumor suppressor genes', and more than half of all cancers have below-normal amounts of the tumor suppressor protein p53. This makes tumor suppressors—and p53 in particular—enticing targets for drug developers. Despite failed attempts in the past, researchers have hope for new variations on this cancer treatment approach.

"There has been a huge amount of interest in therapeutic targeting of p53 for over 15 years," says Alex Swarbrick at the Garvan Institute in Sydney. For example, in a small subset of cancer cases, the gene producing p53 is inhibited by the protein MDM2, murine double minute 2. A class of drugs called Nutlins, made by the Swiss pharma giant Roche, have shown promise for its ability to block MDM2 and are currently in clinical trials to treat people with tumors in their fat tissue. Meanwhile, several small molecules are being studied for their ability to restore mutant p53 proteins, but results have been mixed.

So far, there are no approved anticancer agents that target p53. One reason for the absence is that cancer cells sometimes completely lack that gene, and therefore there is nothing to target. Other times, p53 is present, but mutated, and restoring the function of a protein is inherently difficult.

The latest idea for targeting tumor suppressors is through microRNAs, small pieces of single-stranded, noncoding RNA that regulate an estimated 20% to 30% of all protein-coding genes, including both tumor suppressor genes and oncogenes (*Cancer Res.* **70**, 7027–7030, 2010).

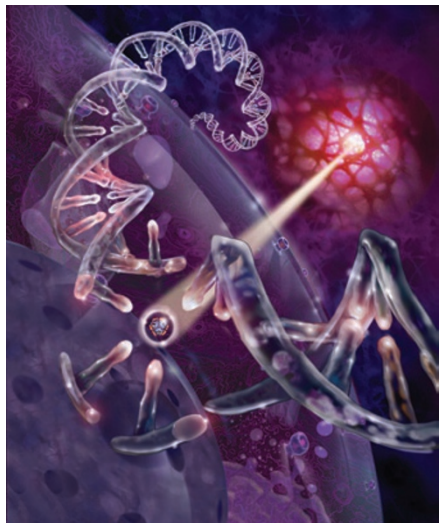
In the same way that tumor suppressor proteins are often absent or nonfunctional in cancer cells, so are certain microRNAs. A strategy known as microRNA replacement therapy aims to create the same sequence of missing RNA and restore it to the cancer cells. The approach could be more powerful than restoring the missing protein, because individual microRNAs regulate upwards of a hundred protein-coding genes at once, so "targeting microRNAs in cancer cells can have a very potent effect," says Joshua Mendell, of the Johns Hopkins University School of Medicine in Baltimore, whose group is studying these molecules in liver cancer.

Pathways to success?

Last year, for example, Mendell and his colleagues showed that introducing a microRNA called miR-26a could reduce the size of liver tumors in mice by about a third without any harmful effects on healthy tissue (*Cell* **137**, 1005–1017, 2009). More recently, scientists at Mirna Therapeutics, a biotech company in Austin, Texas, showed that another microRNA called miR-34a, which regulates the p53 pathway, blocks the growth of human lung tumors in mice (*Cancer Res.* **70**, 5923–5930, 2010) and inhibits prostate cancer stem cells and metastasis (*Nat. Med.* **17**, 211–215, 2011). According to Mirna's associate director of research Andreas Bader, the company intends to apply for human testing of their microRNA sometime next year.

Despite these recent advances, several hurdles remain. Because miRNAs regulate so many genes, researchers worry about how they will affect healthy tissue, even though no serious adverse events have been detected in any of the mice studied so far.

Even more challenging is the problem of designing an effective way to deliver microRNAs to the site of the tumor without the small strands of RNA getting degraded or filtered out of the body, notes Bader. "Delivery still remains the major hurdle to bringing this to the clinic," he says. Various strategies under development include encasing microRNAs in lipid membranes that can then be coated with tumor-specific peptides to act like homing agents, as well as using nanoparticles or viral vectors as delivery mechanisms.



Jim Dowdalls / Photo Researchers, Inc.

On target: microRNAs replace mutated genes.

Nevertheless, researchers are cautiously optimistic. "It would be circumspect to propose that microRNAs will be magically easier to work with than tumor suppressors," says Swarbrick, who is studying the role of microRNAs as both tumor suppressors and oncogenes. All the same, he adds, there's clear evidence that microRNAs will be important molecules to try and target in cancer. "The field is exploding."

Monica Heger

Historically, scientists have had a tough time finding viruses that attack cancer cells without harming healthy tissue. But researchers can now engineer oncolytic viruses that lack certain regulatory genes—such as the *E1A* or *E1B* genes—that they use to defeat the antiviral defense mechanisms possessed by normal cells, rendering the viruses harmless in healthy tissue. These defense systems are often switched off in cancer cells, making them vulnerable to the engineered infectious agents.

On top of this, genes coding for proteins that enhance the body's immune response, such as granulocyte-macrophage colony–stimulating factor, can be added to stimulate the expansion of white blood cells that enhance the immune response against tumors, as with BioVex's and Jennerex's products. So can genes coding for enzymes that turn a separately injected drug precursor into a toxic anticancer agent.

"The issue of targeting oncolytic viruses selectively to cancer cells is largely solved and not as much of a barrier anymore," says Timothy Cripe, a physician at Cincinnati Children's Hospital Medical Center who develops oncolytic viruses for treating pediatric cancers.

Other challenges still persist, though. The immune system, for example, can be a double-edged sword, prone to attacking the oncolytic viruses as well as the tumor. "The barriers now are getting the viruses to spread efficiently within a tumor microenvironment and to persist long enough to have their effect," says Cripe.

Scientists are continuing to evaluate how viruses might join chemotherapy and radiotherapy in the arsenal of cancer treatments. "What we're going to continue to see over the next couple of years is a careful assessment of safety and some glimpses of efficacy as an add-on to existing therapeutic regimens," predicts William Phelps, program director of preclinical and translational cancer research at the American Cancer Society in Atlanta.

Jon Evans