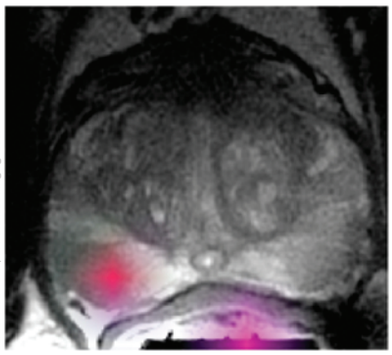


Surbeck Laboratory of Advanced Imaging, UCSF

In this hyperpolarized MRI image of early-stage human prostate cancer, the bright color on the left side shows an area of elevated lactate, indicating cancerous tissue, which corresponds to a region of biopsy-proven cancer. The color to the right is not from prostate tissue but from blood vessels surrounding the rectum.

to inject into the human body—and must be warmed and injected quickly because its half-life is only about 60 seconds.

Nelson's group at UCSF developed a way to rapidly filter and warm the hyperpolarized pyruvate so that it can be injected in an arm within 66 seconds, with observable uptake following within 20 seconds. The group also designed special pulse sequences for the MRI scanner, and coils to create the pulses.

The researchers and their colleagues tested the safety of the agent in a clinical trial of 31 men with biopsy-proven early-stage prostate cancer. They found no dose-limiting toxicity. Areas known to be cancerous had higher levels of lactate relative to pyruvate than normal tissues, and in some cases cancer was identified in regions where it had not been seen by other imaging methods.

With the current widespread use of prostate-specific antigen blood tests, "a lot of men are getting a diagnosis of cancer, and we don't know if it's going to be aggressive or benign," says Nelson. She hopes that metabolic imaging will help doctors make better treatment decisions and monitor therapeutic responses.

Robert Gillies, PhD, vice-chair of radiology and director of imaging research at the Moffitt Cancer Center in Tampa, FL, is excited to see hyperpolarized MRI in human studies. "We can follow not only where these substrates go but what they get turned into, and measure the flux of metabolic reactions in real time," he says. Gillies adds that the technology allows more extended tracing of metabolites over time than does positron emission tomography (a common tool for imaging tumors) and is likely to be less expensive. ■

FDA Gives Drug Codevelopment Guidance

As drug combinations play a steadily increasing role in cancer treatment, the U.S. Food and Drug Administration (FDA) is encouraging the development of investigational agents that will be used only as part of a novel combination, even if the agents show minimal efficacy on their own.

In one example of the promise of such combinations, researchers from Massachusetts General Hospital in Boston and Wellcome Trust Sanger Institute in Hinxton, UK, reported in March that the BH3 mimetic ABT-737 and the deacetylase inhibitor vorinostat (Zolinza; Merck), when combined, synergized to kill squamous cell carcinoma (SCC) cells *in vitro* and dramatically shrank established SCCs *in vivo* (Cancer Discov 2013;3:324–37). The findings support the idea of testing the combination in patients with head and neck SSC (HNSCC), a disease with poor overall survival.

Although vorinostat is approved for cutaneous T-cell lymphoma, a related commentary noted that both drugs "are likely to fail (or have already failed) in single-agent trials in HNSCC. Only the combination therapy is expected to show benefit. However, it is very difficult to initiate a clinical trial using two failed therapeutics" (Cancer Discov 2013;3:258–9).

In June, the FDA issued a guidance document, "Codevelopment of Two or More New Investigational Drugs for Use in Combination," that should help create a smoother clinical-trials process for such novel therapies.

Codevelopment is the concurrent development of multiple drug products intended only to be used together and not as monotherapies. It might be an appropriate option if, for example, therapy with one of the agents rapidly leads to drug resistance, or if the agents are likely to have limited efficacy when used alone, making their individual approval unlikely, the document notes.

One goal of the guidance document is to "address general uncertainty in industry about how the existing regulatory paradigm for single-agent development would apply to development of a novel combination," says Stephen King, an FDA spokesperson. He adds that there are also concerns that current FDA regulations "would be an impediment to development of combinations of novel agents where it may not be possible to extensively study and characterize the activity of individual components of the combination in clinical trials. The guidance is intended to signal that there is flexibility in the amount and types of data that could be relied on to demonstrate the contributions of the components."

According to the guidance document, codevelopment may be appropriate if these criteria are met:

- The combination is intended to treat a serious disease or condition.
- There is a strong biologic rationale for the use of the combination.
- A full nonclinical characterization of the activity of the combination and the individual drugs suggests that the combination may provide a significant advance over available therapies and is superior to the individual agents.
- There is a compelling reason why the new drugs cannot be developed independently.

Although industry has shown some interest in the codevelopment of drugs for use in oncology, infectious diseases, and other specialties, no codeveloped drug combinations have been approved yet, says King.

Given the financial risk of developing drugs for use in a combination when they show minimal efficacy as single agents, codevelopment is "virtually unnavigated" by industry, says Fadlo R. Khuri, MD, deputy director of the Winship Cancer Institute of Emory University in Atlanta, GA, and codirector of its Cancer Discovery and Developmental Therapeutics Program.

"I can't overstate how important it is that the FDA put out this document and supports this approach," Khuri

NOTED

- **The U.S. Food and Drug Administration (FDA) approved Celgene's Abraxane (paclitaxel protein-bound particles for injectable suspension) to treat patients with metastatic pancreatic cancer,** in combination with Eli Lilly's gemcitabine.
- **Amgen announced plans to buy Onyx Pharmaceuticals of South San Francisco, CA, for $10.4 billion.** Onyx's Kyprolis (carfilzomib) is approved by the FDA for treating multiple myeloma. The company's other assets include partnerships with Bayer HealthCare Pharmaceuticals on Nexavar (sorafenib), approved for treating liver cancer and kidney cancer, and Stivarga (regorafenib), approved for treating colorectal cancer and gastrointestinal stromal tumors.
- **Roche decided to relinquish patent rights to its breast cancer drug Herceptin (trastuzumab) in India, opening the market to generic versions**. The move, which follows months of debate about the cost of Herceptin, precludes the Indian government from issuing a compulsory license to another manufacturer. Herceptin currently faces no competition in India.
- **The median cost to bring a drug to market was $350 million for companies that launched one drug in the past decade, but rose to $5.5 billion per drug for companies that brought more than eight drugs to market** in that time, according to an analysis in *Forbes*.
- **With every daily drink of alcohol a girl or woman consumes before her first full-term pregnancy, she increases her lifetime risk of breast cancer by 13%** (JNCI 2013 Aug 29. [Epub ahead of print]). The analysis is based on a review of the health histories of 91,005 mothers enrolled in the Nurses' Health Study II from 1989 to 2009.
- **The X Prize Foundation cancelled its Genomics X Prize competition, explaining that genomic sequencing technologies have advanced so quickly that the prize no longer offered a suitable goal**. Announced in 2006, the competition offered a $10 million reward for accurately and rapidly sequencing 100 whole human genomes at a cost of $10,000 or less per genome.

continues, noting that codeveloped drugs "present an unrealized opportunity" for pharmaceutical companies. "Hopefully, it will encourage companies to move such work forward." ■

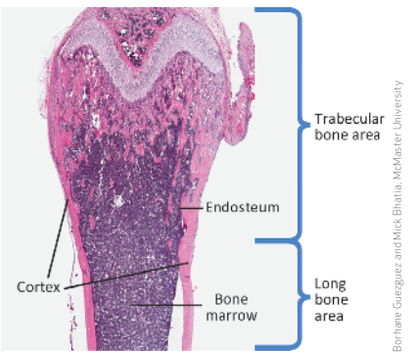
For HSC, Location Matters

Harvesting hematopoietic stem cells (HSC) from the ends of bone—the trabecular area—yields a wealth of cells with superior regenerative and self-renewing abilities, according to research published in August (Cell Stem Cell 2013;13:175–89).

"It's similar to a bottle of milk—if you want the cream, you skim it off the top," says study lead author Mickie Bhatia, PhD, professor and scientific director of the McMaster Stem Cell and Cancer Research Institute in Hamilton, Ontario, Canada.

Bhatia's team harvested cells from distinct areas of bone from humans and immunodeficient mice engrafted with human HSCs. Compared with the long bone area, trabecular bone contained higher numbers of HSCs, but the HSCs from both the human and the mouse samples had different molecular and functional characteristics. Among the functional differences between cells from the two locations, transplants done in mice showed that stem cells from trabecular bone had a greater ability to engraft in the marrow of the recipient. One likely reason: Bone-forming osteoblasts in the trabecular area exhibit higher expression of Notch, a protein thought to be important for stem cell renewal. (Osteoblasts play a key role in regulating HSCs in bone marrow.)

"This paper shows that the best stem cells like to live near trabecular bone surfaces, close to the bone cortex, instead of in endosteal regions in the long bones or deep within the bone marrow space, near blood vessels," says Edmund Waller, MD, PhD, associate director of the Bone Marrow and Stem Cell Transplantation Center at Emory University's Winship Cancer Institute in Atlanta, GA, who was not involved in the research. "If you think of stem cells as the seeds and the bone as the soil, the trabecular bone provides the most fertile soil," he says.



Borhane Guezguez and Mick Bhatia, McMaster University

Hematopoietic stem cells harvested from locations near the bone cortex in the trabecular bone area seem to have superior regenerative and self-renewing abilities, according to a study published in *Cell Stem Cell*.

Pending further validation, Bhatia's findings might affect how surgeons harvest HSCs for transplants, says Waller. "If you put a needle into someone's hip to draw out stem cells, you may want to collect cells just after you go through the bone's hard cortical surface, rather than extracting them from deep within the bone," he says.

When considered with a 2012 *New England Journal of Medicine* paper, these findings might further encourage transplants of HSCs from bone rather than from peripheral blood, which is currently the most common source for U.S. procedures. Last year, a multicenter, randomized trial comparing HSCs from peripheral blood with those from bone marrow from unrelated donors to treat leukemia and related diseases found similar survival rates after 2 years (N Engl J Med 2012;367:1487–96). Although peripheral-blood HSCs had a lower risk of graft failure, they conferred a significantly higher risk of chronic graft-versus-host disease, which can be extremely debilitating, notes Waller, possibly causing the recent slight shift in preference among some doctors for HSCs taken from bone marrow. ■

For more news on cancer research, visit *Cancer Discovery* online at http://CDnews.aacrjournals.org.