elite group of 68 other U.S. cancer centers with world-class research programs dedicated to developing more effective approaches for preventing, diagnosing, and treating cancer.

Four other NCI-designated cancer centers—the Huntsman Cancer Institute (HCI) at the University of Utah in Salt Lake City; the University of Texas Southwestern’s Harold C. Simmons Cancer Center in Dallas; the Dan L. Duncan Cancer Center at Baylor College of Medicine in Houston, TX; and the University of New Mexico (UNM) Cancer Center in Albuquerque—gained comprehensive status, the highest federal designation, which is held by just 45 cancer centers nationwide.

To be awarded NCI designation, institutions must successfully complete a highly competitive application process for 5-year core grants from the NCI’s cancer centers program to fund research infrastructure, advance scientific investigation, foster collaborative programs, and develop shared resources. Standard core grants and NCI designation are awarded to institutions demonstrating superior organizational, scientific, and clinical strengths. The higher comprehensive level, meanwhile, demands additional depth and breadth in laboratory, clinical, and population-based research.

The Tisch Cancer Institute will receive $8.5 million, which will help them “continue building team science,” says director Steven Burakoff, MD.

This multidisciplinary approach drove the design of the Leon and Norma Hess Center for Science and Medicine, where research floors are located close to those for outpatient treatment. “Everyone is only one stairwell away from each other,” Burakoff notes. Tisch will also use their new funds to boost key research areas, he adds, including “moving forward more rapidly with individualized cancer vaccines.”

The HCI has been NCI-designated since 1987; its upgraded status recognizes expansion efforts that include doubling enrollment in clinical trials in the last 5 years, and doubling the size of the cancer hospital in 2011, says director Mary Beckerle, PhD. Their $8.2 million award comes as the HCI is doubling its research space, and will contribute considerably to vital infrastructure.

“Much of our research is focused on cancer genetics, and comprehensive genotyping—and it may potentially identify different treatment options as a patient’s disease evolves (Lancet Oncol 2015;16:937–48).

“This liquid biopsy technology is paving the way for real-time molecular monitoring of tumors to detect not only if a treatment works, but also how the tumor escapes that initially successful treatment,” says Heinz-Josef Lenz, MD, a lead author on the study and associate director of the USC Norris Comprehensive Cancer Center at the University of Southern California Keck School of Medicine in Los Angeles.

In this retrospective study, researchers used only about 2 mL of plasma to identify tumor mutations, as well as other prognostic factors, in patients with colorectal cancer already treated with drugs that target VEGF and EGFR. The work was part of the CORRECT trial, a phase III study assessing the effectiveness of regorafenib (Stivarga; Bayer), a multikinase inhibitor, versus a placebo in patients whose disease progressed during or just after standard treatment.

The researchers sequenced circulating tumor DNA in plasma samples from 503 patients. Sequencing revealed a total of 413 KRAS and 89 PIK3CA mutations. Notably, almost half of the patients with KRAS mutations (41 out of 86) did not harbor the mutations at the time of diagnosis. These findings support the use of liquid biopsies prior to initiating a new treatment and to monitor the response to therapy.

Further, plasma DNA genotyping confirmed that regorafenib improved overall survival (OS) and progression-free survival in PIK3CA- and KRAS-mutant and wild-type subgroups compared with concordant archived tissue samples.
Researchers also analyzed 611 plasma samples for 15 proteins that play a role in angiogenesis and the pathogenesis of colorectal cancer, uncovering potential prognostic indicators for treatment with regorafenib. High baseline concentrations of circulating tumor DNA were associated with shorter median survival, regardless of treatment. In patients who received regorafenib, high concentrations of circulating TIE-1 were associated with improved OS. Among those receiving a placebo, higher concentrations of IL8 and PI GF were associated with poorer OS.

“With a large cohort, this study confirms the concept that molecular tumor profiles change over time, and surveying the plasma provides insight into the molecular features of the tumor at any given point in the disease course,” says Scott Kopetz, MD, PhD, a colorectal cancer specialist at The University of Texas MD Anderson Cancer Center in Houston. Kopetz estimates that about 10% of patients with colorectal cancer at MD Anderson already receive such testing, but he anticipates that number will go up as clinicians become more comfortable with the technique and as additional uses for it emerge.

“The only drawback to this method is that our technology advances more rapidly than our ability to act on it,” says Lenz. “Finding a new mutation doesn’t mean that we immediately have a new treatment, and not every mechanism of resistance is based on gene mutations.”

Overstimulation Fatal for Cancer Cells

Many cancer drugs inhibit oncogenes, but no approved therapies use the opposite strategy of overstimulating them. However, Bert O’Malley, MD, of Baylor College of Medicine in Houston, TX, and colleagues now report evidence that this counterintuitive approach may work.

The researchers were hunting for inhibitors of steroid receptor coactivators (SRC), a family of proteins that enable steroid hormone receptors such as estrogen receptor and progesterone receptor to switch on genes. SRCs benefit cancer cells by speeding growth, turning up metabolism, and promoting tissue invasion and metastasis. While performing high-throughput screening on 359,484 compounds to identify SRC inhibitors, O’Malley and his team uncovered more than 100 compounds that stimulate SRC-1, SRC-2, and SRC-3. Instead of tossing these molecules out, the researchers investigated their effects and noticed that one of them, MCB-613, killed cancer cells.

As the team reported in August, MCB-613 proved lethal in several cancer cell lines, including breast, prostate, and lung, but spared healthy cells (Cancer Cell 2015;28:240–52). MCB-613 triggered a surge in reactive oxygen species in tumor cells and initiated the unfolded protein response, a pathway that cells activate when they are under stress.

To confirm that MCB-613 works by overstimulating SRCs, the researchers measured whether the promoters for two of SRC-3’s transcriptional targets were activated. Treating tumor cells with MCB-613 dramatically increased activity of both promoters. The effect was smaller in cells with reduced levels of all three SRCs.

The two most common causes of cell death—apoptosis and autophagy—weren’t responsible for the demise of the MCB-613–treated cells. Instead, O’Malley and colleagues determined that the compound triggers paraptosis, an uncommon form of cell death that can occur during embryonic development and neurodegeneration and in response to some anticancer drugs.

“The researchers also tested MCB-613 in mice with breast tumors. After 7 weeks, tumor growth stalled in the 13 treated mice, whereas tumors tripled in volume in the 14 control animals.

A cancer cell can cope with the harsh conditions inside a tumor, but “it’s operating at its maximum compensation in terms of stress,” says O’Malley. By boosting levels of reactive oxygen species, MCB-613 might increase the amount of stress on cancer cells and push them over the edge. The study “shows that you can kill cancer cells by overstimulating an oncogene,” he says.

Potential side effects from this approach include driving normal cells to become cancerous and increasing the aggressiveness of any tumor cells that survive the treatment. O’Malley says that his team didn’t see any sign of these problems in their cell lines or animal studies.

“The concept that hyperactivation of an oncogene can be therapeutic is intriguing and worth further exploration,” says Myles Brown, MD, of Dana-Farber Cancer Institute in Boston, MA. However, he cautions that the researchers need to do more work on MCB-613 “to validate that SRCs are the only targets of its actions.”

Skin Cancer Drug Also Targets Brain Tumors

According to results from phase II studies conducted through the Pediatric Brain Tumor Consortium, a subtype of the brain stem tumor medulloblastoma may respond to vismodegib (Erivedge; Genentech)—approved for basal cell carcinomas—with less toxicity than current standard therapy. Both cancers arise from aberrant Sonic hedgehog (SHH) pathway activity; vismodegib inhibits a key protein, Smoothened (SMO), in this signaling cascade.

Medulloblastoma’s SHH subtype (SHH-MB) occurs in about 60% of adult and 25% of pediatric patients. Initial treatment involves a combination of surgery, radiation, and cytotoxic therapy, with a 5-year overall survival of 70%. However, patients are often left with severe long-term side effects, and a grim prognosis if the tumor recurs.

“We need a therapy that is less toxic and better honed to its target,” says corresponding author Giles Robinson, MD, a pediatric neuro-oncologist at St. Jude Children’s Research Hospital in Memphis, TN.

The studies enrolled 31 adults and 12 children respectively, all with recurrent or refractory medulloblastoma (J Clin Oncol 2015;33:2646–54). Following treatment with vismodegib, a total of 13 patients experienced prolonged disease stabilization for up to 16 months. Four of these patients had significant tumor shrinkage for longer than 2 months, while another four had shorter responses. All positive responses occurred in patients with SHH-MB, and none among those with non-SHH tumors. So “while vismodegib seems like a good drug with a huge amount of potential, it’s effective for only a select group,” Robinson notes.

Interestingly, the SHH-MB subtype didn’t guarantee sensitivity to SMO inhibition. Molecular analyses of 26
Liquid Biopsies Track DNA Changes in Tumors


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