of New Jersey in New Brunswick, and Stephen J. Elledge, PhD, a professor of genetics at Brigham and Women’s Hospital in Boston, MA, shared the 2015 Albert Lasker Basic Medical Research Award for their studies illuminating the fundamentals of the DNA-damage response. James P. Allison, PhD, chair of Immunology at The University of Texas MD Anderson Cancer Center in Houston, received the 2015 Lasker-DeBakey Clinical Medical Research Award for the discovery and development of a monoclonal antibody therapy that releases the brakes on the immune system so that it can combat cancer.

Witkin began her work in 1944, studying the basis for radiation resistance. X-rays and ultraviolet light were known to cause inherited mutations, but the question of how remained a mystery. Working with bacteria, she exposed 50,000 cells to a very high dose of UV light, killing all but four. Those cells, Witkin discovered, overcame sensitivity to radiation by initiating what is now known as the DNA-damage response, which detects anomalies in DNA as well as genetic processes, such as DNA copying during cell division, that have gone awry. Alerted to the problems, cells trigger protective mechanisms to make repairs and ensure their survival.

Working with yeast four decades later, Elledge began to build on Witkin’s work by elucidating a signaling system that spurred multiple genes to produce proteins that contribute to DNA repair. He went on to detail the molecular pathway by which cells in more complex organisms, including humans, detect and fix damaged DNA, an essential ability for the prevention of cancer.

Rather than prevent cancer, Allison wanted to attack cancer that had already been diagnosed. He showed that the protein CTLA-4 limited T-cell activation, reiniging in the immune system. By suppressing CTLA-4, he found that disease-fighting T cells could be unleashed and destroy malignant cells. That discovery led to the development and approval of the CTLA-4–inhibiting drug ipilimumab (Yervoy; Bristol-Myers Squibb), a treatment that has prolonged the lives of countless patients with metastatic melanoma. Researchers are now studying the drug as a treatment for other malignancies, including lung cancer and renal cell carcinoma.

The Lasker winners “have opened up new frontiers,” said Lasker Foundation President Claire Pomeroy, who bestowed the awards during a ceremony in New York, NY, on September 18. “They remind us all that investing in biological sciences and medical research is crucial for our future.”

Established in 1942, the Lasker Foundation strives to improve health by advocating for support of medical research. For 70 years, its eponymous awards have recognized “the contributions of scientists, clinicians and public servants who have made major advances in the understanding, diagnosis, treatment, cure, or prevention of human disease.”

High-Affinity PD-1 Protein Has Potential

A small, engineered protein that selectively binds to PD-L1 was more effective in shrinking tumors and synergizing with other immunotherapies than conventional PD-L1 antibodies in a preclinical study, according to data presented at the CRI-CIMT-EATI-AAAC International Cancer Immunotherapy Conference in New York, NY, in September.

The high-affinity PD-1 protein may overcome some drawbacks of existing antibody-based immune checkpoint inhibitors, says study corresponding author Aaron Ring, an MD/PhD student at California’s Stanford University School of Medicine who will soon join the faculty at Yale University School of Medicine in New Haven, CT. “It is approximately 10 times smaller than an antibody and it lacks the antibody ‘Fc’ moiety that is recognized by Fc receptors on cells like macrophages,” he says. “Consequently, the high affinity PD-1 protein penetrates deeper into tumors and, unlike antibodies, does not cause unwanted depletion of PD-L1–positive T cells that mediate antitumor immunity.”

Ring and his colleagues used directed evolution to design the small protein. Using this technique, they first created a library of over 100,000,000 different PD-1 variants that they displayed on the surface of yeast. They then used magnetic and fluorescence cell sorting techniques to select for the tightest binders to recombinant PD-L1 protein. Through increasingly more difficult binding conditions, they zeroed in on one variant that bound to PD-L1 about 50,000 times more tightly than wild-type PD-1.

To assess its effectiveness in penetrating solid tumors compared with anti–PD-L1 antibodies and our high-affinity PD-1 protein penetrate tumors, and there was a striking difference,” says Ring. “The antibody is mostly found close to blood vessels and at the tumor periphery, whereas the smaller PD-1 protein spreads more extensively throughout the tumor.” They also found that the small protein was more effective at treating larger tumors than PD-L1 antibodies.

Both therapies shrunk tumors 50 mm³ in size, but only the small protein was effective against tumors measuring 150 mm³. Adding an anti–CTLA4 antibody to anti–PD-L1 therapy in the larger tumors did not improve the efficacy of anti–PD-L1, whereas combining an anti–CTLA4 antibody with the small protein resulted in greater efficacy compared with either treatment alone.

“Our hypothesis is that as tumors grow larger, the need for effective penetration by the therapeutic agent becomes more important,” says Ring.

Several issues should be addressed before the high-affinity protein is ready for clinical testing, the researchers emphasize. For example, due to its small size, it is excreted from the body more quickly than antibodies, and...
therefore it may need to be administered more frequently. Furthermore, like any protein drug, there is also a risk of immunogenicity.

However, the study achieved its aim, says Ring. “Beyond the specific molecules that we made, we demonstrated the potential for small proteins to complement traditional biologics in cancer immunotherapy.”

A Vulnerable Side to MYC-Driven Cancers

Despite efforts to quell hyperactive MYC in cancer, this oncogene remains remarkably resistant to therapeutic targeting. However, a new study suggests that MYC-driven cancers do have an Achilles’ heel: To survive, the cells require a fully functional spliceosome—the multiprotein complex that prepares immature mRNA for translation by joining together coding sequences called exons after first removing introns, or intervening stretches of noncoding DNA (Nature 2015;525:384–8).

“MYC is aberrantly activated in a third of cancers, and has the unusual function of ramping up transcription across much of the cancer cell genome,” says senior author Thomas Westbrook, PhD, an associate professor at Baylor College of Medicine in Houston, TX. “This stimulation of widespread RNA synthesis may be protumorigenic, but it also places a heavier burden on the spliceosome. Basically, oncogenic MYC comes at a cost to cancer cells.”

Westbrook and his team began uncovering the spliceosome’s importance in MYC-driven cancers when a genetic screen revealed synthetic lethality between MYC and a gene called BUD31. They went on to confirm that in the absence of BUD31, human mammary epithelial cells with hyperactive MYC ceased proliferating and underwent apoptosis. Rather than zeroing in on BUD31 as a key culprit and potential therapeutic target, the researchers decided to find out more about this little-known protein.

“We cataloged all the proteins associated with BUD31, and what we got, essentially, was the spliceosome,” explains Tiffany Hsu, an MD/PhD candidate at Baylor and the study’s lead author. When the researchers systematically inactivated or reduced the function of not only BUD31, but also other core components of the spliceosome, “we saw the same effect each time—MYC-hyperactive cells simply couldn’t tolerate such perturbations, however small,” Hsu adds. These cells suffered widespread defects in mRNA maturation that led to the deregulation of essential processes like DNA replication, mitosis, and metabolism.

“So, the key here isn’t BUD31,” Westbrook emphasizes, “but rather that the survival of MYC-driven cancer cells depends on the spliceosome operating at maximum efficiency. We showed that normal cells, on the other hand, are fine with modest reductions in spliceosome function.”

The researchers also showed that SD6, a new small-molecule inhibitor targeting a core spliceosome protein called SF3B1, was effective in a mouse model of triple-negative breast cancer, an aggressive subtype largely fueled by aberrant MYC activity. SD6 impeded the growth of both primary tumors and lung metastases in the mice, without obvious toxicities. Targeting the spliceosome could therefore be an indirect way to prevail over this recalcitrant oncogene, and SD6 is just the tip of the iceberg, Westbrook points out. With more than 100 core spliceosome proteins in all, “there’s lots of room to maneuver in this therapeutic space.”

“We’re far from understanding all the ways hyperactive MYC confers vulnerabilities even while spurring cancer cell growth,” he adds. “The more we learn, the better we can selectively target these cancers, by finding ways to exacerbate their oncogene-induced collateral stress.”

Implantable Devices Could Monitor Tumors without MRI

To determine if a cancer therapy is working, physicians often use MRI to gauge tumor size. However, it can take weeks or months to see MRI evidence of tissue loss or disease progression. Rather than zeroing in on SD6 as a key culprit and potential therapeutic target, the researchers decided to find out more about this little-known protein.

To explore that question, several years ago the researchers built an injectable oxygen sensor by enclosing a contrast agent within a polymeric matrix (Proc Natl Acad Sci 2014;111:6588–93). Although the system prevented dispersion of the contrast agent, it still required MRI—a costly, specialized procedure—to distinguish signals coming from the contrast agent from those of the surrounding tissue.

Now, to resolve that problem, the researchers incorporated electronics into the implanted sensor so it could measure local changes in oxygen concentration or pH without an MRI scanner. Instead, signals from the implanted sensor, which measures about 2 mm wide by 6 mm long, are detected by an external reader coil.

The team first tested its sensor in vitro in solutions with a known pH, as well as in gas flow tubes where oxygen concentration could be controlled. In vivo, the sensor measured pH when placed into a xenograft tumor model in mice and sensed changes in dissolved oxygen when implanted into the calf muscle of a rat subjected to ischemia by constricting the hind leg.

The system is not yet ready to be tested in larger organisms. Detecting signals from the sensor implanted deep inside a human patient would require an external reader with larger magnets than in the current design, says Vassiliou.