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In February, **Thomas J. Lynch Jr., MD,** became director of Fred Hutchinson Cancer Research Center in Seattle, WA, replacing Gary Gilliland, MD, PhD. Most recently, Lynch was the chief scientific officer at Bristol-Myers Squibb. He has also served as director of the Yale Cancer Center in New Haven, CT, and chief of Hematology-Oncology at Massachusetts General Hospital (MGH) in Boston. Lynch specializes in novel therapies for lung cancer: While at MGH, he investigated gefitinib (Iressa; AstraZeneca) to treat *EGFR*-mutant small cell lung cancer.

Kenneth C. Anderson

Kenneth C. Anderson, MD, and **Riccardo Dalla-Favera, MD,** became editors-in-chief of *Blood Cancer Discovery*, a new journal of the American Association for Cancer Research (AACR). Anderson is the director of the Lebow Institute for Myeloma Therapeutics and Jerome Lipper Myeloma Center at Dana-Farber Cancer Institute in Boston, MA. He has served as president of the American Society of Hematology and editor-in-chief of the AACR's *Clinical Cancer Research*. Anderson's research, focused on developing treatments for plasma cell disorders, has led to the approval of bortezomib (Velcade; Millennium) and lenalidomide (Revlimid; Celgene) for multiple myeloma.

Columbia University Irving Medical Center

Riccardo Dalla-Favera

Dalla-Favera is the director of the Institute for Cancer Genetics at Columbia University in New York, NY. He is also a professor of clinical medicine, as well as pathology and cell biology, at Columbia. A member of the National Academy of Sciences, Dalla-Favera is interested in the pathogenesis of B-cell malignancies such as Burkitt lymphoma, diffuse large B-cell lymphoma, and chronic lymphocytic leukemia. His team studies genomic lesions that lead to the development of these diseases.

Alzheimer-Related Protein Suppresses Gliomas

Tau, the microtubule-associated protein linked to neurodegenerative disease, plays a critical role in brain cancer, too. Researchers report that mutant *IDH* triggers tau expression, which in turn inhibits EGFR signaling to impede glioma progression (Sci Transl Med 2020; 12:eaax1501).

The findings help explain why *IDH1/2* mutations are linked to prolonged survival—and *EGFR* mutations to poorer outcomes—in people with glial brain tumors. They also provide a scientific rationale for pharmacologically mimicking tau's function with microtubule-stabilizing drugs to treat *IDH*–wild-type brain cancers or low-grade gliomas lacking *EGFR* mutations.

Taxanes inhibit microtubule disassembly by binding the same site as tau. Most approved taxanes do not readily cross the blood–brain barrier, but some newer agents do. "If our data using mouse models translates into patients," says Pilar Sánchez-Gómez, PhD, of the Carlos III Health Institute in Madrid, Spain, who led the new study, "these drugs, at low concentrations, may put the brakes on the disease."

Over the past 15 months, independent teams led by Sánchez-Gómez and George Blanck, PhD, of the University of South Florida in Tampa reported that gliomas expressing high levels of *MAPT*, which encodes tau, have better clinical prognoses (Front Aging Neurosci 2019;11:231; Oncology Reports 2019;41:1359–66). Those findings were entirely phenomenological until Sánchez-Gómez's latest paper. "They were able to add mechanism," Blanck says.

Sánchez-Gómez and her team used tissue samples, cell lines, and mouse models to interrogate the connections between tau activity and favorable *IDH1/2* mutations or adverse *EGFR* mutations in gliomas.

In *IDH1/2*-mutant gliomas, they observed high levels of tau that decreased as tumors acquired aggressive properties. In *EGFR*-mutant gliomas, however, tau expression was negligible. Probing the molecular links, the researchers showed that mutant forms of IDH serve as epigenetic regulators of *MAPT* transcription. By increasing methylation at a particular site in the *MAPT* gene, the mutant enzymes disrupt the normal binding of a repressive transcription factor, leading to elevated expression.

Tau then—through its stabilizing effects on microtubules and the subsequent changes in intracellular trafficking of proteins and organelles—promotes EGFR degradation. Without active EGFR signaling, glioma cells do not undergo mesenchymal transformation and they stay in a less aggressive state.

Tau-induced repression occurred even when *EGFR* was amplified but otherwise unaltered—and the same effect could be achieved therapeutically with epothilone D (Bristol-Myers Squibb), a brain-penetrating taxane no longer in clinical development. However, gliomas with activating mutations in *EGFR* no longer responded to tau. As Sánchez-Gómez and her colleagues reported, the EGFR pathway—despite high levels of tau—remained in overdrive, spurring the growth of new blood vessels and decreasing the sensitivity of cancer cells to chemotherapy and radiation.

According to Sánchez-Gómez, the findings also provide a cautionary note regarding mutant-selective IDH inhibitors to treat gliomas (Cancer Discov 2019;9:992). These agents may stop oncogenic forms of the IDH enzyme from producing a cancer-causing metabolite, but they may also suppress tau activity—which could explain why *IDH1*-mutant cell lines treated with a precursor to vorasidenib (Agios) were less sensitive to other therapies.

"If you actually target IDH mutations you can make a tumor much more aggressive," Sánchez-Gómez warns. "That's a danger with these kinds of treatments." *–Elie Dolgin* ■

Cancer Mortality Lowest in Decades

The overall mortality rate from cancer declined by 29% in the United States between 1991, when it peaked, and 2017—reducing the number of lives lost to cancer by an estimated

2.9 million—according to a recent analysis (CA Cancer J Clin 2020;70:7–30). Although it's tempting to ascribe the mortality reduction to recent treatment advances, such as the introduction of immune-checkpoint inhibitors, the reality is more complex.

The largest drop in age-adjusted mortality was seen between 2016 and 2017, making speculation about the role of the newest therapies particularly alluring, but the overall pattern is perhaps more noteworthy than the 2.2% decline. "It's very much a continuation of a long-term trend," says Kathy Cronin, PhD, MPH, deputy associate director of the NCI Surveillance Research Program.

These reductions have primarily been driven by a decrease in lung cancer deaths. "If you take lung cancer out [of the analysis for 2016 to 2017], that 2.2% goes down to 1.4%," says lead author Rebecca Siegel, MPH, of the American Cancer Society. Lung cancer is the leading cause of U.S. cancer mortality, accounting for more deaths than breast, colorectal, and prostate cancers combined, explaining its outsized influence on cancer survival.

In the 5 years leading up to 2017—even prior to the approval of immunotherapies—the lung cancer death rate fell by about 4% per year. Reduced incidence due to decreases in smoking accounts for part of the shrinking death rate, but improved treatments, including new surgical options, and other factors may play a role. Survival following lung cancer diagnosis is increasing, which hints at the importance of treatment advances. However, the study cannot pinpoint causality.

Major strides have also been made in treating pediatric cancers, with mortality slashed by 68% for pediatric cancers and 63% for adolescent cancers since 1970. "It's not new therapies," says Siegel—instead, the drop is primarily attributable to optimizing dosages and combining existing chemotherapies. The greatest success has been in childhood acute lymphocytic leukemia, which now has a remission rate nearing 100%. This steady decline comes even as the incidence of childhood and adolescent cancers has increased by about 0.7% per year since 1975, for unknown reasons.

In contrast, survival rates for cancers of the uterine corpus and cervix have not declined since the mid-1970s. Human papillomavirus vaccination will likely drive down cervical cancer incidence and mortality, but the lack of new treatments and effective screening methods for other uterine cancers does not portend mortality improvements. "We're going to continue to see increases in endometrial cancer incidence and mortality," says Ashley Felix, PhD, MPH, of the Ohio State University Comprehensive Cancer Center in Columbus. Incidence is likely to increase due to factors such as reduced hysterectomy rates, declining pregnancy rates, and rising obesity rates—the last of which is a contributor to many other cancers.

Further progress in cancer treatment may help maintain the downward trend in mortality, but advances may also be possible by other means. "There's much more opportunity to accelerate the progress by ensuring that all people, especially those who are low income, have access to high-quality care," says Siegel.

"I think the treatments are important, but I think also that the public-health initiatives to reduce smoking are really playing an important role, too," Cronin adds. *–Nicole Haloupek* ■

First EZH2 Inhibitor Approved—for Rare Sarcoma

The FDA has approved tazemetostat (Tazverik; Epizyme), the first EZH2 inhibitor to receive the agency's nod, and the first therapy specifically approved to treat epithelioid sarcoma. The accelerated approval greenlights the drug for patients who have locally advanced or metastatic tumors with *INI1* deletions.

Epithelioid sarcoma, which doctors often describe as "relentless," affects about three in 10 million people, usually teenagers and young adults. In one form of the disease, the tumors grow under the skin on the limbs, hands, or feet; in the other, they affect the trunk, head, or neck. Although epithelioid sarcomas typically grow slowly, they infiltrate surrounding tissues and frequently metastasize to lymph nodes. Surgery, often combined with radiation, is the standard treatment for localized tumors.

Patients with metastatic disease may receive doxorubicin or gemcitabine, but retrospective studies suggest that chemotherapy is effective only 15% to 20% of the time. Even then, tumors can recur years later and metastasize, notes Charles Keller, MD, of the Children's Cancer Therapy Development Institute in Beaverton, OR.

About 90% of patients with epithelioid sarcoma have lost INI1, a tumor supressor of the SWI/SNF complex. Tazemetostat inhibits EZH2, a component of polycomb repressive complex 2 (PRC2) that spurs histone methylation and gene silencing. These two complexes work against each other: SWI/SNF favors differentiation, whereas PRC2 prompts cells to retain their stem-cell characteristics and capacity for self-renewal. The loss of INI1 from SWI/SNF complexes may disrupt this balance and enable PRC2 to promote abnormal growth; tazemetostat may counteract this effect by blocking EZH2.

The data that led to tazemetostat's approval came from a phase II study that tested the drug in a range of tumors. Fifteen percent of 62 patients with INI1-negative epithelioid sarcomas had a complete or partial response. In 67% of these patients, the response lasted 6 months or longer. The three most common side effects were fatigue, nausea, and pain.

Approval of the drug "provides a well-tolerated treatment option for patients who have few options," says Robin Jones, MD, of The Royal Marsden NHS Foundation Trust and The Institute of Cancer Research in London, UK. "In patients who do respond, the drug gives durable clinical benefit as a single agent." Jones, who participated in the phase II trial, says that ongoing work on tissue samples from sequential biopsies will provide information on mechanisms of response and resistance.

Newly diagnosed patients appear more likely to benefit from the drug, Keller notes: Their response rate was 25%, versus 8% in patients who had relapsed. "The approval, in light of the low response rate, shows a commitment on the part of the FDA and Epizyme to cultivate drug development for soft-tissue sarcomas, even if the