“Generally speaking, two glioblastomas—one IDH-mutant, the other IDH-wild-type—may have the same grade [IV] and look very similar under the microscope, but the former tends to have a better clinical outcome,” says co–senior author Antonio Iavarone, MD, a professor of pathology and neurology at Columbia University Medical Center in New York, NY.

Given that IDH-mutant gliomas are frequently marked by the CpG island methylator phenotype (G-CIMP), or widespread DNA methylation, the researchers decided that epigenetic analyses would be a key part of their study. They were surprised to discover a subtype of IDH-mutant tumors “with lower methylation levels than would be expected, based on our traditional understanding of this phenotype,” Iavarone says. It turns out that not all IDH-mutant, G-CIMP gliomas are equally methylated; they can be further divided into “G-CIMP-high” and “G-CIMP-low” subtypes. Far from having the relatively favorable outcome of most IDH-mutant gliomas, G-CIMP-low tumors “displayed the molecular and clinical features of a more aggressive glioma,” Iavarone notes, “and were associated with significantly worse survival.”

The researchers also observed that, after treatment, recurring IDH-mutant gliomas that were previously G-CIMP-high could emerge as G-CIMP-low tumors. “It suggests that demethylation is a marker for disease progression, although we haven’t figured out if it’s a cause or a consequence,” says co–senior author Roel Verhaak, PhD, an associate professor of bioinformatics and computational biology at The University of Texas MD Anderson Cancer Center in Houston. “We only looked at 10 recurrent gliomas in this study. It would be interesting to see how often this curious loss of methylation occurs in a larger, longitudinal analysis.”

Iavarone, Verhaak, and their colleagues also discovered another subtype, this time in the IDH-wild-type group. Most IDH-wild-type gliomas are grade IV and highly aggressive, but the researchers found a small percentage that, instead, resembled pilocytic astrocytoma—a curable (through surgical resection) pediatric brain tumor with a far more favorable prognosis. They dubbed this new subtype “PA-like.”

“These two glioma subtypes we’ve uncovered represent clinically actionable information that will help identify [G-CIMP-low] IDH-mutant patients who need stronger drugs, and [PA-like] IDH-wild-type patients who can be spared unnecessarily intensive treatment,” Iavarone says. “It’s not that pathology is no longer important in grading gliomas. Rather, by molecularly segregating these tumors as well, we can characterize and treat them more accurately.”

This study, which was co-led by Houslan Noushmehr, PhD, from the University of São Paulo in Brazil, “makes the case for DNA methylation profiles as a real diagnostic tool,” Verhaak adds. “That’s what I’m hoping to achieve at MD Anderson within the next 2 years. I’ll also gladly be a little optimistic and predict that within, say, 10 years, methylation profiles will be standard in clinics nationwide.”—Alissa Poh

Fish Reveal Origins of Melanoma

Although researchers have discovered numerous cancer-causing mutations, they have not determined why not all cells with these alterations develop into tumors. A study of zebrafish suggests an explanation: individual skin cells are able to grow into melanomas because they return to an embryonic state (Science 2016;351:aad2197).

The BRAF V600E mutation, a key melanoma driver, is also frequently found in benign nevi, or moles, that do not become cancerous. To find out why, Leonard Zon, MD, of Boston Children’s Hospital, MA, and colleagues tracked the early events of melanoma formation in zebrafish carrying BRAF V600E and lacking p53 in their melanocytes, cells that arise from the embryonic neural crest and can develop into melanoma. Although every melanocyte carries the cancer-promoting mutations and could potentially give rise to a melanoma, each fish grows only one to three tumors during its lifetime.

Having previously observed that zebrafish melanomas reactivate expression of crestin, a gene whose expression is normally restricted to neural crest progenitor cells in the developing embryo, the researchers engineered transgenic zebrafish that express GFP under the control of crestin-regulatory elements. By tracking GFP-positive cells, they determined that only individual melanocytes that reactivated crestin initiated melanomas.

“We are seeing cancer at its beginnings, at the single-cell state,” says Zon. “The cell, to start the process of becoming a cancer, has to reprogram itself to become more neural crest–like.”

Zon and his colleagues also found that a transcription factor involved in neural crest development called Sox10 helps orchestrate this reprogramming of melanocytes to an embryonic state. When the team spurred zebrafish melanocytes to overexpress Sox10, the fish developed tumors much earlier, whereas using the CRISPR/Cas9 system to delete Sox10 delayed tumor onset.

To understand the mechanism whereby neural crest genes such as crestin and sox10 are reactivated, the researchers evaluated epigenetic marks at these loci and identified regions with broad enrichment of H3K27Ac histone marks known as super-enhancers. Consistent with these findings in zebrafish, the researchers also found that most human melanoma cell lines in the Cancer Cell Line Encyclopedia as well as human embryonic stem cell–derived neural crest cells express SOX10 and are distinguished by super-enhancers at this locus.

“What we’ve been able to identify is the initiating event” for melanoma, says Zon. Although other researchers had previously noticed that cancer cells often regress to a more embryonic state, they “haven’t been able to show that it’s...
causative,” adds Glenn Merlino, PhD, of the National Cancer Institute in Bethesda, MD, who was not connected to the study. Zon and his team are now trying to determine whether chemicals in the fish’s water or other factors trigger melanocytes to make this switch.

“It’s a tour de force in terms of technology application” that may lead to better diagnostic methods and techniques to halt melanoma formation, says David Fisher, MD, PhD, of Massachusetts General Hospital in Boston, who also was not connected to the study. “Once you have a system that can identify these early events, you can ask what the causes are and if there are prevention opportunities.”

Martin McMahon, PhD, of the University of Utah in Salt Lake City, gives the authors credit for “visualizing the early specification of cells that go on to become melanomas.” He emphasizes that researchers need to confirm that the mechanism also occurs in mouse models and human melanomas, not just cell lines. –Mitch Leslie ■

### UK Groups Plan Cancer Research Hub

Two major cancer research groups in the UK have announced plans to create a hub for cancer research and treatment to accelerate drug development and foster collaboration with industry. The $1.5 billion campus in south London is expected to house 10,000 scientists and clinicians and jump-start development of cancer drugs.

The proposed London Cancer Hub is a partnership between the London-based Institute of Cancer Research (ICR) and the Royal Marsden NHS Foundation Trust, as well as the Borough of Sutton. The plan calls for doubling the space at ICR’s Sutton campus to 265,000 square meters, including room for start-up biotechnology companies working on new drugs, medical devices, and digital technology, according to the project’s “roadmap,” available at www.icr.ac.uk.

“Since 2005, we’ve discovered 20 drug candidates and have been very successful in licensing those discoveries to big drug companies, but we’ve never been able to do that locally,” says Paul Workman, PhD, ICR’s president and chief executive. “There’s a strong argument that physical co-location of world-class basic research and healthcare with biotechnology enterprise creates a mutually beneficial triangle of innovation—that’s what we’re seeking to achieve.”

The hub will allow ICR to increase productivity by 40%, from five to seven new drugs every 5 years, he says. A center for drug discovery, to be built over the next 3 years, will facilitate that growth by locating ICR’s cancer therapeutics group alongside its Center for Evolution and Cancer, a multidisciplinary team that studies cancer from an evolutionary biology perspective.

“The idea is to have a diverse group of scientists thinking about the key challenges facing cancer now,” says Rajesh Chopra, MD, PhD, who heads up ICR’s Division of Cancer Therapeutics. “Those include understanding the basis of tumor heterogeneity, understanding the mechanisms that hasten the evolutionary process of cancer cells, and defining novel therapeutic targets.”

Other research priorities include studying genetic instability and DNA repair; small-molecule approaches to immunotherapy; and epigenetic mechanisms associated with drug resistance, says Chopra. The Sutton expansion will be rolled out over the next 20 years, starting with 20,000 square meters for drug discovery facilities and incubator space to be built in the next 3 years, according to the roadmap. Highlights beyond that include:

- **Years 3 to 6.** Creation of the London Cancer Hub Knowledge Center and expansion of Royal Marsden’s ambulatory care facilities.

- **Years 9 to 12.** Opening of facilities for private companies and expansion of Royal Marsden’s inpatient and outpatient departments.

- **Years 12 to 15.** Construction of a tram connecting the campus to downtown Sutton and central London, and additional life sciences buildings.

- **Years 15 to 20.** Completion of life science facilities, restaurants, hotels, and a school.

“The advantage of having start-ups and researchers in one place is it gives us the opportunity to be flexible and take on high-risk ideas,” says Chopra. “We will have enough critical mass and resources to conduct significant and expensive experiments—and a cadre of scientists who understand drug development and can support the growth of start-up ventures.” –Janet Colwell ■

### Potential Therapy for Refractory Colon Cancer

Patients with advanced RAS/BRAF-wild-type colorectal cancer typically develop resistance to two leading EGFR inhibitors, the monoclonal antibodies cetuximab (Erbilitux; Lilly Oncology) and panitumumab (Vectibix; Amgen). A recent study suggests that an investigational antibody mixture could provide a new therapeutic option for these tumors (Sci Transl Med 2016;8:324ra14).

Acquired resistance to cetuximab and panitumumab most often develops from mutations in genes downstream...