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PAUL MISCHEL

CANCER'S CIRCUIT BREAKER

In 1938, a 13-year-old Theodore Mischel was, along with the rest of his family, frantically destroying all evidence of their Jewish heritage when his eight-year-old brother found a document showing their maternal grandfather had at some point become an American citizen. It sufficed to get them passage to the U.S. as refugees just after German forces swept into Austria to establish the *Anschluss*. Five years later, Theodore had enlisted in the US military and was *en route* to what would come to be known as the Battle of the Bulge when he came down with the mumps.

He was confined to a field hospital and, by the time he recovered, the tide had turned in favor of the Allies. So he was assigned to the intelligence corps, with which he served as a translator during the Dachau concentration camp trials. Having possibly dodged death twice before turning 20, Theodore went to college on the GI Bill, eventually becoming a professor of philosophy in upstate New York.

"He's living the American dream," recalls his son Paul Mischel, who is today a member of Ludwig San Diego, "and then, at 51, he gets diagnosed with stomach cancer. He dies in this absolutely excruciating fashion. I was 14, and it was heart-wrenching listening to people say, 'Well, at least we caught it early'. Of course, it's rarely caught early. I watched him become a human skeleton within six months and decided then that I would dedicate myself to doing something about this disease."

Mischel has picked as tough a quarry as you get in pursuit of that goal. He focuses on glioblastoma multiforme (GBM), an incurable brain cancer that typically takes the lives of patients within 15 months of their diagnosis. Working with his colleagues—most notably Web Cavenee, who today directs Ludwig's alliances in brain cancers, (see Box, page 37) and Frank Furnari of Ludwig San Diego—Mischel has over the past decade explored how the GBM cell's genome, metabolism and responses to the environment interact to support tumor growth and drug resistance.

Working with the laboratory of his Ludwig San Diego colleague Bing Ren (see story, page 9) in 2015, Mischel and his team charted in granular detail how an aberrantly activated mutant receptor alters the chemical, or "epigenetic," modification and reading of the GBM genome through a protein complex known to coordinate cancer cell metabolism. He also led a study that showed how two common nutrients, glucose and acetate, can drive drug resistance through that same complex, known as mTORC2. Both studies have clinical implications. The former unveiled a promising therapeutic strategy for GBM. The latter not only revealed a novel mechanism of cancer drug resistance but also exposed the potentially counterproductive effects of a drug often given to GBM patients.

Tracing circuits

Mischel went to medical school at Cornell University and then trained as a cancer pathologist before taking a fellowship in molecular neurobiology at the University of California, San Francisco. After joining the faculty of UCLA in 1998, he continued his studies charting the biochemical cascades responsible for signaling within cells. When distorted, such signals drive the uncontrolled growth of cancer cells, and the proteins responsible for transmitting them are the targets of many modern cancer drugs.

Though such targeted therapies have certainly improved outcomes for some cancers, they've been far less successful than was initially expected. GBM has, at any rate, shrugged off every targeted therapy thrown at it by researchers.

"What we've all learned," says Mischel, "is that there's a wide gulf between identifying a drug target and having a drug actually work."

Mischel wants to know why. Since moving to Ludwig in 2012, he and his longtime collaborators have uncovered seemingly inexhaustible mechanisms by which GBM cells adapt to those few therapies that actually make it into the tumor. They've found that GBM cells switch signaling circuits when a preferred pathway is blocked by a drug, that they change the cell surface receptors—think of them as the switches—that engage those circuits. Most bafflingly, they even found that GBM cells can "hide" the mutant genes that encode an aberrant receptor, EGF receptor vIII (EGFRvIII), until an EGFR-targeting therapy is halted.

Looking deeper

Such findings have inspired Mischel to look at the cancer cell and its genetic programs in a new way.

"We have had a mechanistic view of cancer genes," says Mischel. "We put them into models and see that they replicate tumors, but we don't really understand how they change the cell or what they do that causes cancer."

One place in which he is looking for that perspective is in the induction of the cancer cell's uniquely productive metabolism. Mischel and other researchers have shown that the protein complex mTORC2 is a central controller of the phenomenon. Its activation by such drivers of cancer as EGFRvIII cranks up, among other things, the import of glucose and acetate. These nutrients provide raw energy to cells and, through a metabolic sleight of hand known as the Warburg effect, furnish the molecular building blocks required to make new cells.

In one study, published in the *Proceedings of the National Academy of Sciences* in 2015, Mischel and his colleagues showed that in GBM cells driven by EGFRvIII, the boost in glucose and acetate uptake through mTORC2 activation has an additional effect: It induces drug resistance. They report that a

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shared metabolite of the two nutrients, acetyl-co-A, directly activates mTORC2 in cells treated with a targeted therapy against EGFRvIII. This effectively circumvents the blockade on signaling that the drug is meant to impose—and illustrates the ability of the cancer cell to adapt to its environment (the threat of a drug) in a manner that is not directly dependent on genetic change.

The finding is also of immediate clinical relevance. GBM patients are often treated with steroids to contain brain inflammation, and steroids tend to ramp up blood glucose levels. Such therapy, it seems, may inadvertently fuel the growth of GBM tumors.

A peek at the sourcecode

In a second study, published in *Molecular Cell*, Mischel partnered with Ludwig San Diego's Ren to examine how exactly EGFRvIII alters the reading of the GBM genome. Using technology developed in Ren's laboratory (see story, page 9), the researchers began by profiling EGFRvIII's epigenetic activation of DNA sequences known as "enhancers." These elements of DNA do not themselves encode anything. Instead, they boost the expression of specific genes.

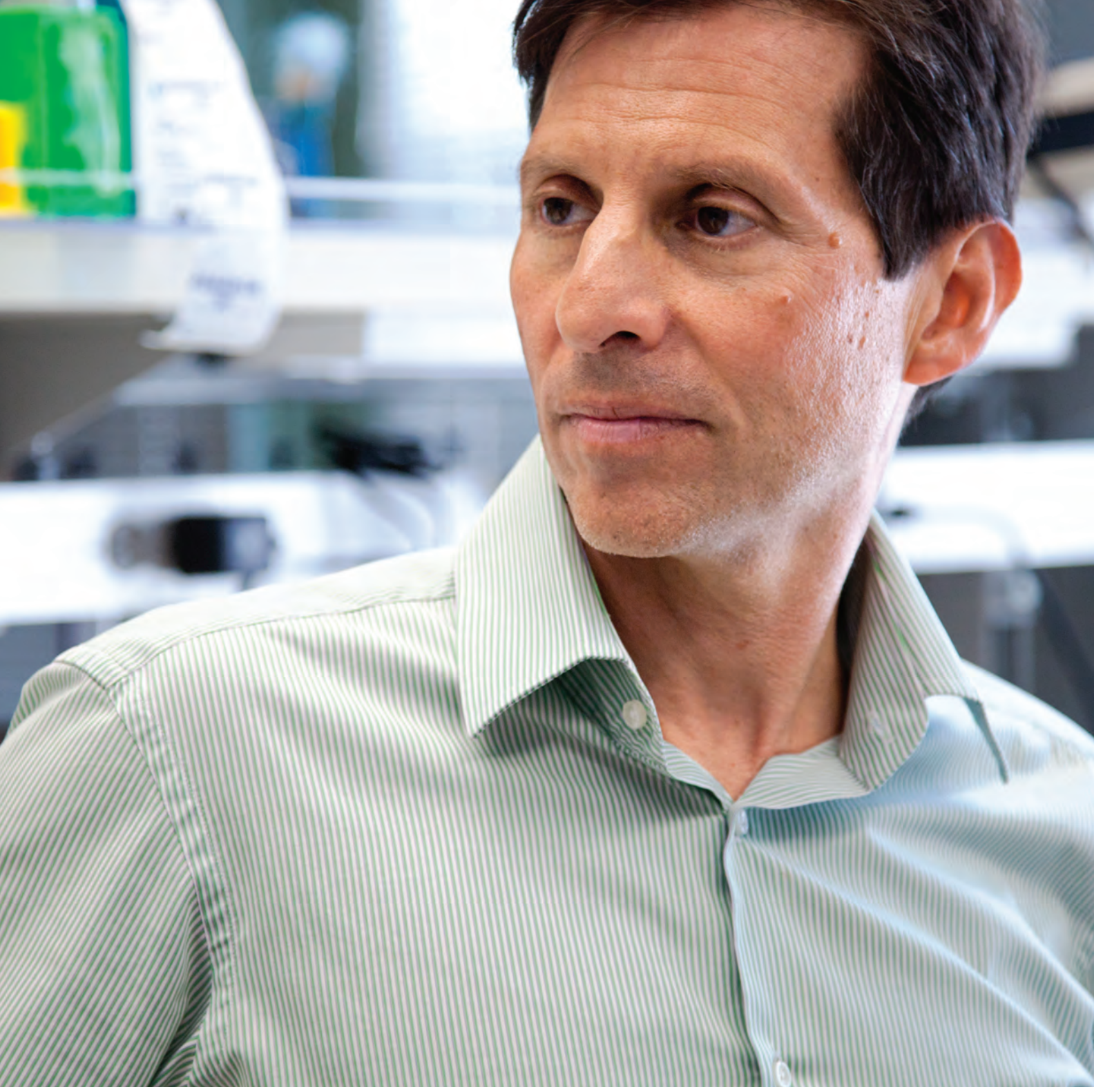
Most of the enhancers they identified bore signature DNA sequences that are bound by dozens of transcription factors—regulators of gene expression—expressed at high levels in GBM. Two of the signatures stood out: those for the transcription factors SOX9 and FOXG1. Notably, their silencing in experiments stopped tumor growth, both in cell cultures and in an animal model that mimics GBM.

The researchers next examined the genes whose expression is controlled by SOX9 and FOXG1. One of those genes turns out to be a protein named BRD4, which in turn is known to control the expression of another transcription factor named c-Myc, a molecular lever that links signals driving growth to those that control metabolism. Working with Cavenee and Furnari, Mischel has uncovered several distinct mechanisms by which mTORC2 induces the aberrant activation of c-Myc in GBM.

"Our studies are converging to show how EGFRvIII is reprogramming the metabolism in GBM cells through c-Myc," says Mischel. "This suggests that if we could target c-Myc, or some of the players along the way that regulate c-Myc, like BRD4, we might actually be able to make a real difference for patients."

To test that hunch, the researchers tapped the expertise of the Ludwig Cancer Research Small Molecule Discovery Program, headed by Andrew Shiau (see story, page 13). Together, they showed that an experimental drug named JQ1, which is currently in clinical trials for another cancer, could kill EGFRvIII-fueled GBM cells and shrink tumors in a mouse model.

Mischel and his colleagues are digging deeper into how the epigenetic changes they've



Paul Mischel
Ludwig San Diego

mapped drive GBM. They're also working on developing novel molecules to target c-Myc activation as possible drug candidates.

"We're actively asking how changes in the environment change the levels, the activities and the consequences of cancer genes," says Mischel. "We hope and expect that this work will connect to some intelligently designed clinical trials and, perhaps, bring new hope to patients diagnosed with this cancer."