Cancer's Dead End

There is a way to restore p53's tumor-suppressing prowess.

AT FIRST GLANCE, THE TUMOR SUPPRESSOR GENE *P53* WOULD SEEM like an ideal weapon against cancer. It puts the brakes on cancer progression and is impaired in about half of human tumors. ¶ In mouse models of cancer, HHMI investigators Tyler Jacks and Scott Lowe restored p53 activity in tumors and the tumors regressed.

However, p53 activation kills some cancer cells, but not others, and no one knows why. HHMI early career scientist Joaquín Espinosa has set his sights on finding an answer, and with it, a strategy for making p53-based therapies effective. It's a goal he's pursued with relentless passion.

"He's an extremely creative thinker," says former HHMI President Thomas Cech, who is an HHMI investigator and colleague of Espinosa's at the University of Colorado at Boulder. Where a traditional approach might focus entirely on the *p53* gene itself, Espinosa has adopted a broader and far more ambitious target—he aims to inventory all the genes and pathways that govern how cells react to p53 activation.

Espinosa's approach grew from his realization that if you want to harness p53's tumor-squelching effects, you also need to block the myriad pathways that tumors use to circumvent p53's killing orders. Espinosa sought to identify all of the p53-disarming pathways and the genes that control them with a technique called functional genomics. "This is a very new technology which allows us to interrogate the function of every gene in the human genome as it relates to p53," Espinosa says. "With functional genomics, we can ask—which genes influence the programmed cell death mediated by p53?"

To do functional genomics requires expensive equipment and huge libraries of costly reagents, and only a few such facilities exist in the world. Espinosa wanted one at the University of Colorado at Boulder. He had a vision for a functional genomics facility in Colorado that would not only advance his own research, but also put his colleagues at the forefront of biomedical research. "Joaquín enjoys doing things for the benefit of the scientific community," Cech says. "He's more than a team player, he's an instigator of teamwork."

Espinosa's first proposals to fund his functional genomics experiments were rejected by the National Institutes of Health and private foundations. But he persisted, eventually securing support from HHMI, the BioFrontiers Institute, and the University of Colorado Cancer Center. The Functional Genomics Facility at the University of Colorado at Boulder began operations in May 2010 with Espinosa at its helm. "We could finally do our dream experiment," Espinosa says.

In a series of investigations published online June 3, 2012, in *Nature Chemical Biology*, Espinosa's group identified genes that, when inhibited, allow p53 to kill cancer cell types that wouldn't otherwise respond. They accomplished this using an experimental drug called Nutlin-3, which activates the p53 protein, yet fails to induce cell death in most tumors. Using functional genomics, Espinosa's team screened thousands of genes and identified a few hundred whose inhibition made Nutlin-3 effective at killing cancer cells. To their delight, they discovered that compounds to inhibit the protein products of two of these genes, *ATM* and *MET*, were already available.

When they combined the ATM or MET inhibitors with Nutlin-3, the treatment destroyed cancer cells that didn't respond to any of the drugs individually. "If you treat cancer cells with one of the drugs, nothing happens, but if you treat them with both drugs, the drugs kill them," Espinosa says. The drug combination delivered a one-two punch—Nutlin-3 turned on *p53*, then the ATM or MET inhibitor blocked

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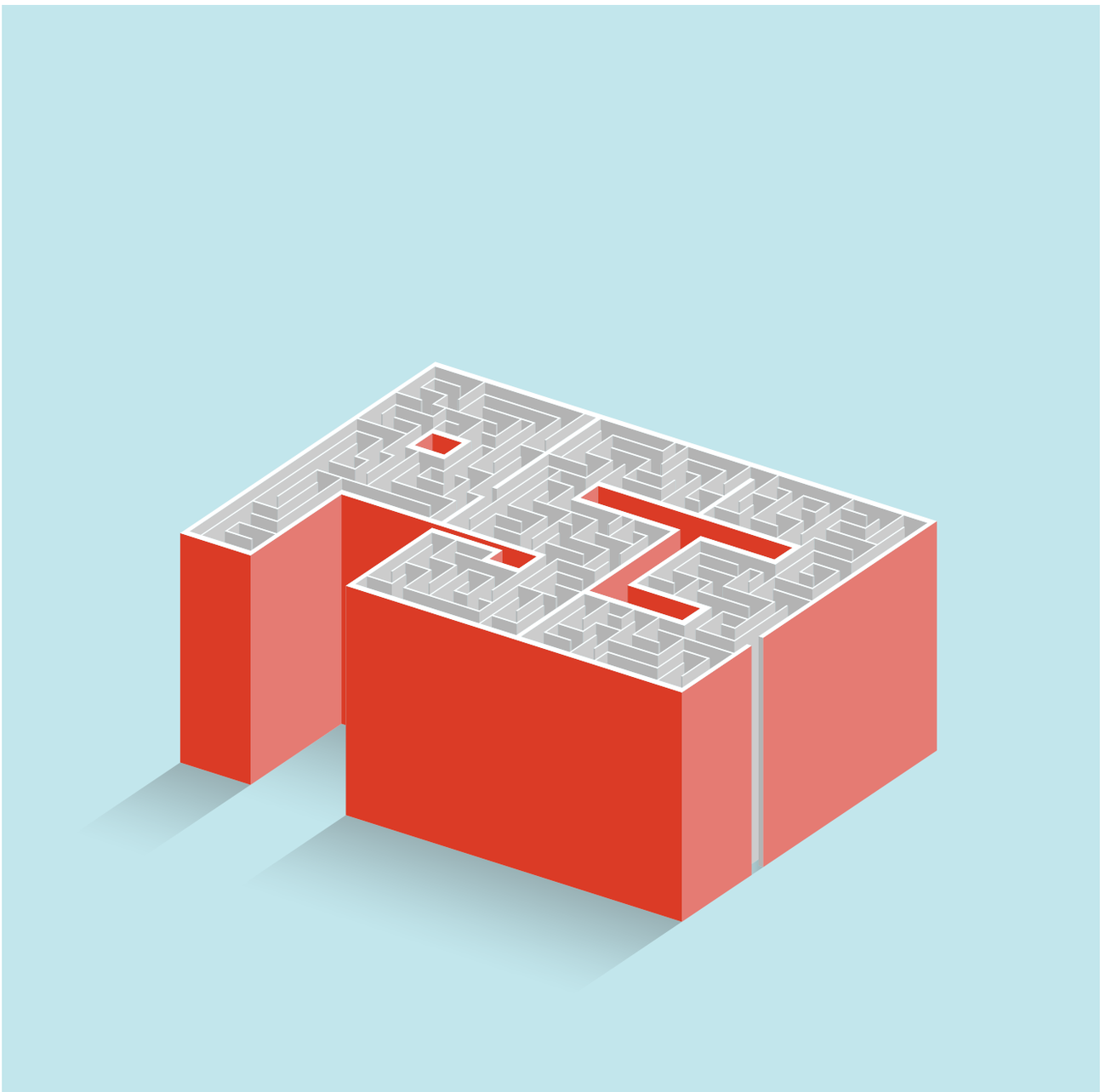

the proteins that would allow the cancer cell to thrive despite *p53* activation. "With one genetic screen, we identified a combination of drugs that will kill tumors that otherwise resist them," Espinosa says. His team is collaborating with clinical investigators to test these drug combinations in animal models and human tumors grown in mice.

By hitting multiple genetic targets, Espinosa hopes to drive cancer cells into a dead end. "You can block resistance genes before they ever have a chance," he says. With this strategy, new treatments can be designed to overcome a tumor's natural work arounds. "The future is not in isolated drugs, but rather in combinations of drugs," Espinosa says.

Clinical trials are costly and time-consuming, and Espinosa hopes his studies can help drug researchers predict and anticipate how their p53-related treatments will work in the clinic, long before they've spent millions on trials. "These are very basic experiments we can do in the lab to get ahead of problems we'll see in clinic."

■ –CHRISTIE ASCHWANDEN