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Chemical biologist targets 'undruggable' proteins linked to cancer in quest for new cures

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Why is a cure for cancer so elusive? Brent Stockwell, an associate professor with a joint appointment in chemistry and biological sciences and an Early Career Scientist with the Howard Hughes Medical Institute, believes the main culprit is “undruggable proteins”—the 85 percent of the proteins in the human body that are not treatable with traditional drugs. Unfortunately, many of them are associated with the most insidious illnesses, from cancer to neurodegenerative diseases such as Huntington’s and Alzheimer’s.

These undruggable proteins feature prominently in Stockwell’s new book, The Quest for the Cure: The Science and Stories Behind the Next Generation of Medicines (Columbia University Press, June 2011). Stockwell, who grew up in Bayside, Queens, had wanted to write a book for the general public for some time; his desire to do so was shaped in part by his mother, a longtime editor of the newspaper for physicians *Oncology Times*. The book explores the history of drug development, the challenges facing scientists and promising research approaches, including some in his own lab, that may help lead to cures.

The focus of Stockwell’s research lies in the intersection of biology, chemistry and computer science, as he and his colleagues search for substances that can bind to a nook or cranny in disease-causing proteins and render them harmless. Unfortunately, some of the proteins associated with cancer or neurodegenerative diseases have smooth, flat

surfaces to which drugs can't easily bind.

He cites the disturbing fact that the 20,000 or so pharmaceutical products that have been approved to date by the U.S. Food and Drug Administration interact with just 2 percent of the proteins found in human cells.

One focus in his lab in the Northwest Corner Building is the RAS gene, which is associated with unchecked cell proliferation. It occurs in 20 to 30 percent of tumors and is especially prevalent in pancreatic and lung cancer.

"Each tumor has a specific set of mutations," says Stockwell. "But there is a lot of overlap. Disease cells may contain several key mutations. If we can find ways to target some of those specific mutations—such as RAS—we can attack the cancer in a specific way."

He has devised new screening technologies, including the development of paired cell lines, identical except for the presence of a single cancer-causing mutation. Using a liquid-handling robot that can screen molecules in a fraction of the time it would take a human, his team can test hundreds of thousands of small molecules and look for the ones that kill the cancer-causing cell lines and leave the others intact. His efforts have already paid off. He has so far identified two molecules out of more than a million tested that go after the RAS gene.

His hope is that targeting so-far undruggable proteins will one day lead to an era of personalized medicine in cancer treatment. It's an attractive alternative to chemotherapy, which is often almost as toxic to the body as the disease itself. "The idea is to match the medicine to the mutations in the patient," he says.

Stockwell, who received his Ph.D. at Harvard and was an independent fellow at the Whitehead Institute for Biomedical Research, affiliated with MIT, traces his research interest back to his undergraduate days at Cornell. There, after staying up late into the night studying the conversion of one molecule into a completely new one, he realized he'd found his passion.

"I realized that all of these diseases were essentially complicated puzzles involving molecules," he says, "and that if I could help to solve these molecular puzzles, it could make a big impact on people's lives."

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