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TARGETING CANCER

WHEN THERE'S NO TARGET

FOCUS: A small molecule that targets KEAP1-mutant cancers.

"To get a car to work, you need a lot of things to go right; it's much easier to get a car not to work." Dr. Rizwan Haq uses this analogy to illustrate the specific dilemma his lab faces in their work toward developing a drug that targets cancers.

The "car" in this parallel is a protein that drives the growth of cancer. The focus of Dr. Haq's work are cancers that are mutated for the Kelch-like ECH-associated protein (KEAP1), a mutation that exists in approximately 30% of all lung cancers.

"Most drugs work by suppressing or obstructing an overactive protein," Dr. Haq says. "KEAP1 is different—it is actually deleted in cancers, so there's no active protein to target. The mutation has rendered it functionless, so to reactivate it you'd have to fix the mutation in the gene, which is very challenging, perhaps impossible."

So Dr. Haq and his team set out to find a way of hitting other key proteins in the KEAP1 pathway. They screened more than 330,000 compounds, and one was found to have a strong connection to loss of KEAP1 activity, and to preferentially target and kill the KEAP1-mutant tumors.

Harrington Discovery Institute is collaborating with Dr. Haq to find derivatives of this compound with more favorable potency and toxicity properties. In addition, beyond being a potential therapeutic for various cancers, the drug has also shown promise for some rare pediatric cancers where no effective therapies exist.

"It is validating that our expert Harrington advisors can envisage the possibility of our work leading to a drug that helps fight cancer."

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