The RAS oncogene has been extensively studied for over 30 years, and for good reason: RAS mutations are implicated in as many as 30 percent of all human cancers, including 95 percent of pancreatic, 45 percent of colorectal, and 35 percent of lung cancers. Past attempts to develop effective treatments against RAS have failed, leading many researchers to deem it “undruggable.”

An intense effort to better understand RAS and discover its vulnerabilities is beginning to show progress. The Frederick National Laboratory leads the National Cancer Institute’s RAS Initiative, an international flagship mission that has reignited the search for an effective RAS inhibitor. The Initiative has made substantial advancements, including three major milestones that have reshaped the field of RAS research.

The first milestone was to produce full versions of KRAS, not just a portion. Until recently, most RAS studies were performed on the G domain, the first 169 amino acids of the KRAS protein. This portion of the protein was easier to produce and contained several important functional pieces, but it was incomplete. On the other hand, the full-length protein—while it required specific modifications and was challenging to produce—gave researchers a valuable glimpse into how KRAS binds to cell membranes.

**KRAS “Floppy Tail” Discovered**

The second major milestone capitalized on protein production capabilities, including fully processed KRAS, to determine a crystal structure of previously unidentified mutations as well as a previously unidentified region of the RAS molecule. The “floppy tail” of RAS had not been determined until Frederick National Laboratory’s Dhirendra Simanshu, Ph.D., and his team used the full-length KRAS in complex with a protein known as a chaperone to capture a crystal structure that showed the floppy tail in its entirety. Alongside that work, the Initiative has determined the structures of all the major RAS mutants and some of the RAS-interacting protein complexes, which

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**Targeting the “Undruggable” Oncogene**

Until recently, finding an effective RAS inhibitor seemed impossible. Today, there’s hope.

Story by Christopher Worthington
Design and Layout by Joe Meyer and Al Kane
Frederick National Laboratory for Cancer Research
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Frederick National Laboratory for Cancer Research
have revealed potential new pockets and new ways to attack RAS. Advances have been made in drug discovery, as well. One of the Initiative’s newest projects is improving screening capabilities for a method called tethering that searches libraries of compounds for small-molecule drug fragments that may bind directly to RAS and could be further developed as KRAS inhibitors. Tethering may also help researchers uncover compounds that disrupt protein–protein interactions, such as those between RAS and effector proteins.

**Assays Bolster Search for Inhibitors**

So far, the RAS Initiative has developed more than a dozen assays to look for potential inhibitors and has created reproducible tests that allow them to screen numerous candidate compounds simultaneously. These assays have garnered growing interest from pharmaceutical companies. Under a Cooperative Research and Development Agreement with the Frederick National Laboratory, the companies are using these tools to screen their chemical libraries to identify compounds that might react to KRAS.

“Whether we discover an inhibitor here or, through our commitment to basic biology and increasing the knowledge base make it possible for others elsewhere to discover an inhibitor, both would be considered equally successful,” said Dwight Nissley, Ph.D., head of the Cancer Research Technology Program, which hosts the RAS Initiative at the Frederick National Laboratory.

**Fragments Bind to KRAS**

One particularly promising lead comes from a group led by Anna Maciag, Ph.D. Her team, in collaboration with the University of California, San Francisco, has identified several fragments that exhibit desirable binding characteristics, and they’ve developed those fragments into compounds that may prevent KRAS from being modified into a cancerous version. Better yet, they discovered that these compounds are KRAS-specific, meaning they don’t interfere with the other forms of RAS. This is an important development for two reasons—first, because most cancers with a mutated RAS have KRAS mutations, and second, because wiping out all RAS activity could result in a highly toxic compound.

A KRAS-specific inhibitor could be the key to attacking RAS-mutation-driven cancers, and these compounds are being optimized with the intent to develop them for clinical application.

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**Collaborate with the Frederick National Laboratory**

The Frederick National Laboratory for Cancer Research is a shared national resource whose mission is to enable solutions to biomedical research questions and overcome challenges to progress. We actively establish partnerships among our scientists and external researchers in government, academia, industry and the nonprofit research community.

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