KRAS pioneer and Stephenson Prize winner Frank McCormick aims to prevent all KRAS cancers with a pill

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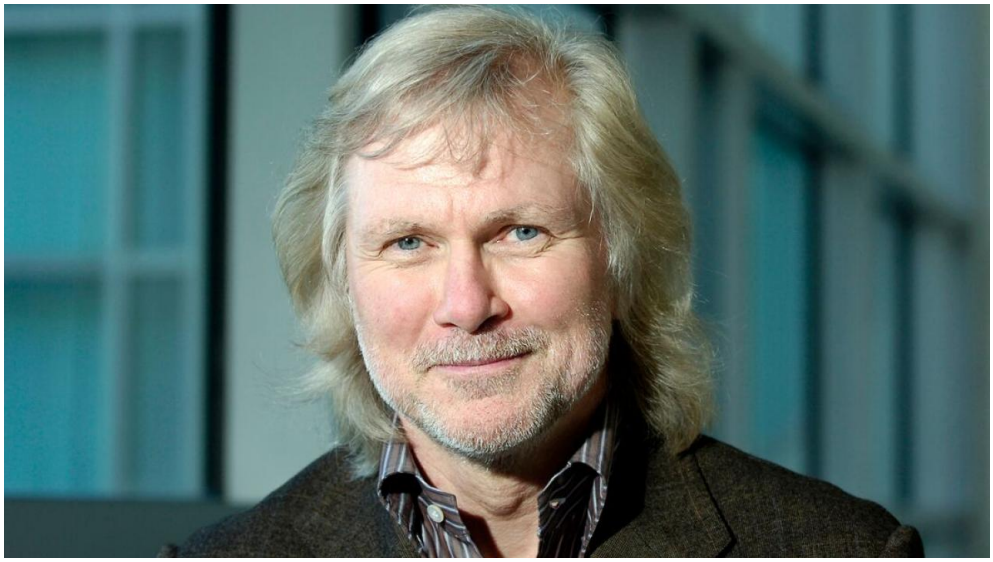

In 1988, Frank McCormick learned with the rest of the field that more than 90% of patients with pancreatic cancer have a mutation in the Kirsten rat sarcoma viral gene.

Immediately, the gene, which is also known as KRAS, triggered an obsession.

"For me, the first turning point was when [Manuel] Perucho discovered that KRAS is mutated in pretty much every pancreatic cancer. That was a shock to the field at that time," McCormick said to *The Cancer Letter*. "It's the only disease in which KRAS is completely—the only—driver. That was very unusual. That set the goal for me—pancreatic cancer is where KRAS drugs are the most effective."

Now, after a four-decade-long career focused on KRAS, McCormick has been awarded the inaugural $1 million Stephenson Global Prize for pancreatic cancer research. McCormick is the David A. Wood

Chair of Tumor Biology and Cancer Research and a professor in the Helen Diller Family Comprehensive Cancer Center and the Department of Cellular and Molecular Pharmacology at the University of California, San Francisco.

The Stephenson Global Prize is the centerpiece of a larger $150 million gift from entrepreneurs and philanthropists A. Emmet Stephenson Jr. and his daughter Tessa Stephenson Brand. The gift, awarded to City of Hope, also enabled the establishment of the Stephenson Global Pancreatic Cancer Research Institute (*The Cancer Letter*, Sept. 17, 2024).

The investment was given in honor of Toni Stephenson who died of pancreatic cancer in 2020.

The $150 million gift equals nearly two-thirds of the total annual research budget for pancreatic cancer from NCI and is intended to drive the trajectory for pancreatic cancer early detection and treatment.

The investment has been regarded as a signal of the growing role of philanthropy in funding biomedical research as federal support remains uncertain.

"Right now, students and postdocs are just bagging out and are not coming into academic science," McCormick said. "It was bad enough before Trump. I say that because funding hasn't kept up with inflation. Wages are low. It's tough, but now, for many young trainees, it's become too much."

McCormick was chosen as the recipient of the Stephenson prize—which aims to recognize "a lifetime of achievements that have significantly advanced pancreatic cancer research"—for his work establishing how mutations in the KRAS gene lead to oncogenesis. His work led to the field's understanding of the detailed molecular biology driving the KRAS pathway, and his research laid the groundwork for the development of KRAS inhibitor therapies.

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>
> *— Frank McCormick*

McCormick received the prize and gave an award lecture at the AACR Special Conference on Advances in Pancreatic Cancer Research Sept. 30 in Boston.

Early years of his career, as he chased opportunities to study RAS, McCormick bopped between academia and the biotech in dustry. In 2013, then-NCI Director Harold Varmus called McCormick and asked if he wanted to lead the NCI-sponsored RAS Initiative at the Frederick National Laboratories for Cancer Research (*The Cancer Letter*, Jan. 30, 2009).

The initiative "mobilizes the cancer research community to develop ways to treat cancers driven by the mutant RAS gene in an open model of collaboration among government, academic, and industry researchers," according to the program's website.

About one-third of all human cancers—220,000 new cases every year—are driven by mutations of the RAS family of genes.

McCormick said "Yes"—even though the job requires regular travel between Frederick, MD, and his California home.

"A week every month, for ten years," McCormick said. "I know the best dining opportunities in Dulles Airport."

Under McCormick's leadership, three KRAS cancer treatments co-discovered by the RAS Initiative along with BridgeBio Oncology Therapeutics and Lawrence Livermore National Laboratory have entered clinical trials:

- BBO-8520: Targeting most common KRAS variant in lung cancer
- BBO-10203: Blocking cancer-driving RAS-PI3K pathway
- BBO-11818: 'Pan-KRAS' drug

"So, three drugs in 10 years from an NCI-based project is, I think, much more than anybody expected," McCormick said.

The RAS Initiative is an "absolutely awesome" place to work, McCormick said. McCormick is still a program adviser at the RAS Initiative.

"It's up there with working with Marge [Foti, CEO of AACR] at the AACR in terms of awesomeness," McCormick joked. He served as president of AACR from 2012-2013.

McCormick credits the unique composition and structure of the NCI Frederick laboratory for the initiative's success.

"This is a group that's between academia and industry," McCormick said. "They're not hardcore biotech people, and they're not academics, but they're just professional scientists that do great work and haven't got the egos tangled up, because they're all in one team.

"So, that's pretty rare."

The NCI RAS Initiative at Frederick has lost about 10% of its staff due to reductions in force, cuts, and firings carried out by the Trump administration, McCormick said.

Demoralization is a real issue and a tangible harm, McCormick said, "but compared with everybody else at the NIH, we can't really complain too much."

RAS's unfounded and damaging reputation as an "undruggable target"

Many cancer researchers are familiar with the notion that KRAS is an "undruggable target." Even McCormick's lab members have used the phrase.

However, this notion is baseless and it has cost the field years of research efforts, McCormick said.

"It kinda makes me mad," McCormick said.

Calling KRAS undruggable "just means, to me, it is more difficult than some of the kinases, which were relatively easy because they have a pocket and they are classic enzymes. RAS doesn't have that," McCormick said "But there are other drivers in cancer which are just as difficult as KRAS."

The misunderstanding is rooted in an unfortunate quirk of history, McCormick said.

Said McCormick:

> The first targeted therapies were actually farnesyltransferase inhibitors against RAS, way back.
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> Well, it turned out, for historical reasons, everybody used HRAS [Harvey Rat sarcoma virus] as their model systems, because it was the first oncogene identified in cancer.
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> So, everybody used HRAS models, not KRAS.

And it turns out the HRAS models are actually very sensitive to farnesyltransferase drugs. So, mouse models look great.

And then they went to clinical trials and they didn't work.

And then it was realized later that KRAS is not sensitive, because it has a backup system.

But, if people had selected the HRAS mutants back then, we'd have had drugs for RAS in 1992. But that was before you could do selection of patients by sequencing. So, you couldn't do it in those days.

And also, no one knew about the prevalence of H versus K. So, I've often made the case that if any of our target therapies were tested on an unstratified patient population, it would fail in a clinical trial—including Herceptin and all those targeted drugs.

If you didn't pre-select the patients, they wouldn't work. The same is true of farnesyltransferase. We just couldn't do the selection because the technology wasn't there.

So, in fact, HRAS is druggable and was druggable years ago. It's just there aren't that many HRAS tumors.

So, I think that's a mistake.

And then the field got burned by that. Because every pharma company jumped in with farnesyltransferase inhibitors for about five to 10 years. That consumed so much energy. And because it didn't work, people sort of said, "Well, hell with RAS, let's do kinases."

Because kinases came along around the late nineties. So, that became the focus of pharma. That's why no one focused much on RAS.

What McCormick plans to do with $1 million

With his recent infusion of $1 million, McCormick plans on funding the project he is most excited about: Developing a perfectly "clean" KRAS inhibitor that, ideally, would be administered to everyone over a certain age, have no side effects, and prevent all KRAS-mutated cancers.

That would include 90% of pancreatic cancers, 45% of colorectal cancers, and 25% of lung cancers.

"If you're 50 or 60, you've got a one in 15 chance of getting a KRAS cancer, which is going to be really bad," McCormick said. "If it didn't cost that much and didn't have any side effects, why wouldn't you take a preventative pill? I think that's the way to go. I'd take it.

"And then all the technology for early detection? You could preempt that just by just going straight to everybody over a certain age."

McCormick thinks prevention is the way to go in pancreatic cancer, since the disease has proven difficult to catch early.

"Early detection is really, really hard. And to me, it's kind of pointless if you don't have drugs to deal with it," McCormick said. "I know it's better to treat early and so on, but why not just treat everybody with a drug as a preventative, so that you haven't got to spend a lot of time identifying people?

"Just like aspirin. If you take aspirin for colon cancer, why not take a pill and prevent pancreas cancer? People take aspirin to reduce the risk of heart disease and colon cancer, and they take vaccines obviously, even though they have side effects."

> What I'm proposing is that maybe like 10 people get together and just go through a workshop to sort of see: Is this B.S., or not?
>
> *— Frank McCormick*

With the money from the Stephenson Prize, McCormick plans to sponsor a workshop to stress-test his idea.

"What I'm proposing is that maybe like 10 people get together and just go through a workshop to sort of see: Is this B.S., or not? And Marge [Foti] has generously offered to host it at the AACR offices in Philadelphia."

McCormick is confident.

"That's where we're going. I'm going to do it," McCormick said.

If his idea is deemed "not B.S.," the development of the pill will proceed.

"The KRAS drugs that are the kind of thing that I think we want are already in the clinic, in phase I trials," McCormick said.

McCormick is not particularly concerned about the potential uptake of his chemoprevention idea, but he does understand that it is a question that would need to be dealt with—particularly since he proposes recommending the prescription of a drug to a healthy population.

"People take pills all the time," McCormick said. "There is no shortage of interest in taking a pill. But that's all the kind of stuff we need to work through; right? How many people would actually do it?"

McCormick has faith in his idea.

"That's my idea. Maybe not a good one," he said summing up.

"But I haven't heard a reason not to do it yet."

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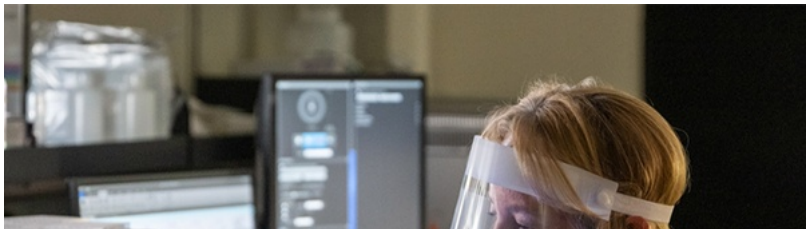

IN BRIEF

UNM's Kimberly Leslie awarded $12.9M NCI grant to study endometrial cancer

Kimberly Leslie, a professor at the University of New Mexico Comprehensive Cancer Center, was awarded a 5-year, $12.9 million grant from NCI. Leslie and her research team, which includes scientists from the Universities of Iowa, Utah, Kansas, Virginia, and California at San Diego, will study all available hormonal regimens to prevent and treat endometrial cancer.

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