Yale Cancer Center

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MAGAZINE

Pinpointing Oncogenes to Destroy Cancer

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Making Cancer Quit Cold Turkey

Colleen Shaddox **writer** Peter Baker **photographer**

A cancerous tumor might contain 50,000 mutations. Professor of Molecular, Cellular & Developmental Biology Frank Slack found that turning off a single oncogene – microRNA21 – was enough to cause tumors to completely regress in mice in just a few days. The study was the first to establish a phenomenon being referred to as "oncomiR addiction," though Slack said that "dependency" might be a better term. In his experiments, lymphomas could not survive without this particular microRNA. "Their 'cold turkey' is to die," he said. He recently published these findings in the journal *Nature*.

Slack cautioned that treating cancer in humans is a far more complex endeavor than treating it in mice. There is no certainty that the therapy will have human applications, which would take years to develop. But the finding is promising because microRNA21 has already been found in unusual levels in many common human cancers and because scientists already know how to stop its expression.

"Frank's cutting edge research provides convincing evidence that microRNA21 can drive tumorigenesis and is necessary for maintaining tumors in an animal model," said Curtis C. Harris, MD, Chief of the Laboratory of Human Carcinogenesis at the National Cancer Institute. "These preclinical studies support the potential of targeting certain microRNAs in cancer prevention and therapy."

MicroRNAs were not discovered until 1993. As the name implies, they are small RNAs. At about 20 nucleotides long, they are so minute that for most of human history we lacked the technology to detect them. Scientists found microRNAs have the ability to regulate genes, meaning they signal genes to become active or remain dormant. Only in the past six years have some microRNAs been shown to play a role in cancer. Slack's research focuses on these and other microRNAs. He is trying to answer fundamental questions about how microRNAs function while also looking at ways to harness them to address cancer and aging.

microRNA21

Frank J. Slack, PhD, Director of the Yale Cancer Center Genetics and Genomics Program and Professor of Molecular, Cellular & Developmental Biology.

In the case of these overabundant microRNA21, Slack explained, a potential cancer therapy could involve "binding" the microRNA to stop its activity. MicroRNA function by fitting together with given spots on the genome – much like the pieces of a puzzle. That action can be stopped by introducing another agent that is a perfect fit for the microRNA, thus blocking it from latching onto the genome. Academic medical centers and private biotech firms are active in developing these synthetic puzzle pieces, said Slack.

Many of his experiments use *Caenorhabditis elegans*, transparent roundworms that are a favorite of scientists because they are so easy to manipulate.

"It was a risky program because we didn't have any prior indication, except that the microRNA was over-expressed in cancers," said Slack.

He spent four years on the project, which was funded by the James S. McDonnell Foundation and Yale Cancer Center. It

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answered two key questions: Is microRNA21 an oncogene? And can tumors survive without it?

While microRNA21 is over-expressed in many cancers, that does not mean it causes cancer. Slack tested this by working with mice genetically engineered to over-express microRNA21 but otherwise perfectly normal. They went on to develop an aggressive disease reminiscent of pre B-cell lymphoma and displayed clinical symptoms of lymphoma/leukemia, including enlarged lymph nodes, enlarged spleens and labored breathing. This demonstrated that the over-expression of microRNA21 was not simply a sign of their disease; it was the cause. The tumors could be transplanted to mice without the genetic modification and continued to grow. This indicates that the tumors were malignant.

When he "shut off" microRNA21, the tumors shrank rapidly, in large part due to apoptosis, programmed cell death. The tumors literally could not live without microRNA21. His next step is to determine if a treatment to knock out microRNA21 has any toxicity in mice. Slack's hope is that in three to four years the research will lead to clinical trials in humans and to targeted cancer therapies. Though much work remains to make that happen, the progress of microRNAs from a newly discovered factor to a potential drug target has been rapid.

"Some of the most amazing discoveries have been basic science discoveries," said Slack, who added that as technologies are developed to do biology on ever-smaller subjects more such discoveries would follow. "We have to keep looking. We're exploring a part of the cell that was dark before," he said. He recalled how in the 1980s and 90s, scientists believed that many parts of the human genome served no purpose and deemed these regions *junk* DNA. But as microRNA research illustrates, close examination can prove that unlikely bits of biology can be overwhelmingly useful.

"Maybe there's no junk in the genome," said Slack. "We just have to keep looking."