Translation, please

Matthew Kulke, MD, (left) and Ramesh Shivdasani, MD, PhD, discuss their findings.

Curiosity, money, and a mother's anguish help inspire neuroendocrine cancer research

By Debra Ruder

Ramesh Shivdasani, MD, PhD, has something under his microscope to show his Dana-Farber colleague Matthew Kulke, MD.

The pink-and-purple blotches on the stained slide are not merely cancerous cells removed during surgery and frozen for research. When combined with information about this patient's health history and the cells' DNA, the slide may offer another clue about a family of rare and little-understood cancers.

Neuroendocrine tumors, which arise in hormone-making cells throughout the body, have brought together these two physician-scientists – one focused on laboratory discoveries (Shivdasani), the other on clinical care (Kulke) – in an alliance that would have pleased Institute founder Sidney Farber, MD, who sought to bridge "patient bed and laboratory bench" in the quest to combat cancer.

Although this kind of collaboration is occurring more and more at Dana-Farber, it often takes a few sparks to ignite. In this case, the fuel took several forms, namely, recent advances in genetically targeted therapies, several hundred cooperative patients, financial gifts from private sources, and a mutual interest in the digestive tract, where these cancers most often lurk.

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therapies," says Shivdasani, who set up a laboratory specifically for this kind of translational work.

The pair, teaming with colleagues at Dana-Farber and its affiliates, has already made inroads in understanding the causes of these illnesses, which include carcinoid cancer and pancreatic endocrine cancer. Powered by recent knowledge about the genetic and biological behavior of neuroendocrine cells, Kulke and others have tested new combinations of drugs, among them angiogenic inhibitors that thwart the development of blood vessels around tumors.

An estimated 3,000-5,000 new cases of neuroendocrine tumors are diagnosed in the United States each year, many of them in the gastrointestinal tract, but some in the lungs and other organs. By contrast, more than 234,000 new prostate cancer diagnoses are expected nationally this year. Neuroendocrine cancers often grow slowly, are adept at outsmarting conventional chemotherapy, and are usually fatal when diagnosed at a late stage.

From anguish to hope

That's hardly news to Nancy O'Hagan, a 35-year-old Harvard graduate from Cambridge, Mass., who learned six years ago that she has carcinoid cancer. Since then, she has dedicated herself to finding help and hope for others with this disease, named in 1907 by the German pathologist Siegfried Oberndorfer for being "carcinoma-like."

O'Hagan had experienced fatigue, flushing, and abdominal pain for years, but doctors attributed her symptoms to stress and overwork as a corporate tax attorney. "I would get extremely hot, and my face would turn as red as a tomato," she recalls. "Then I'd look at my thighs and saw that the flushing was a full-body thing. As a lawyer meeting with clients, it was very debilitating."

One day, en route to her job at a prestigious Boston law firm, O'Hagan collapsed on the train and was taken by taxi to Massachusetts General Hospital. The flushing episodes turned out to be carcinoid syndrome, an uncommon side effect caused by tumors releasing large amounts of hormones into her bloodstream. Physicians warned her she might not have long to live.

Shunning self-pity, O'Hagan began educating herself about carcinoid and enrolled in some clinical trials to slow progression of the disease, which had spread to her liver and bones. She also underwent two embolization procedures to block blood flow to her liver and help contain her metastasis.

There seemed to be little hope for remission, however, and O'Hagan believes a bleak prognosis from doctors outside Boston offering second opinions contributed to her mother's suicide shortly before Mother's Day in 2001. "I think she had very little hope that I would get better or last as long as I have," says O'Hagan. Compelled by her late mother's anguish, O'Hagan and her husband, Patrick, launched the Caring for Carcinoid Foundation in December 2004 to help increase understanding of neuroendocrine cancers. The nonprofit medical research foundation awards grants to scientists performing cutting-edge, genetically based research,

"I consider myself fortunate to have the life that I do, the family that I've had, and so many wonderful friends," says Nancy O'Hagan, who was diagnosed with carcinoid cancer in 2000 and was told she didn't have long to live.

among them Kulke, Shivdasani, and others at leading cancer centers. It has awarded more than $2 million since its founding.

"There is very little public funding for these diseases because of their rarity," the slight, stylish O'Hagan reflected last spring. "So we're investing all our donations in fostering scientific collaboration and basic research, and accelerating drug development."

Caring for Carcinoid is one of several sources of private funding for the Shivdasani-Kulke partnership, enabling them to build the tumor/specimen collection and translational laboratory, as well as to carry out gene-chip analyses of neuroendocrine tumors. Among the others are philanthropists Dr. Raymond and Beverly Sackler of Greenwich, Conn., who have supported medical and educational institutions around the world and who, with their sons, have in recent years targeted research funding to carcinoid and related neuroendocrine cancers. The Sacklers have sponsored a yearly scientific meeting in the field and invited O'Hagan and another advocate for this work, Stephen Kaufer, who lost his wife to neuroendocrine cancer in 2005.

Before Caroline Kaufer's death at age 42, the couple gave $1.05 million to expand Kulke's clinical investigations at Dana-Farber.

"After my wife's diagnosis, funding neuroendocrine research became our top priority," says Kaufer, co-founder of TripAdvisor, an online travel information and planning resource based in Needham, Mass. "We were shocked to find out how little was being done for this cancer."

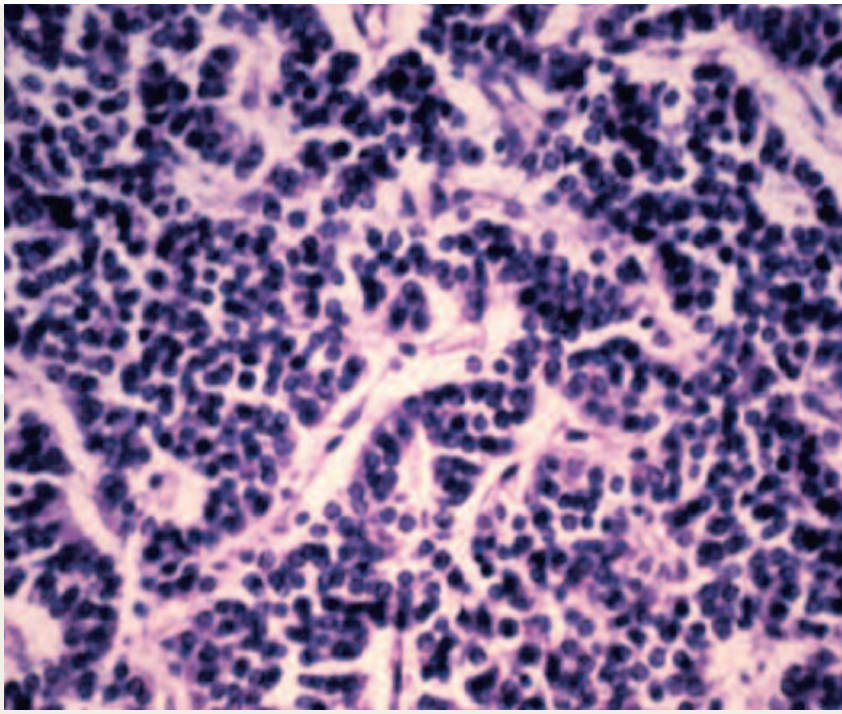
Such funding is critical for advancing research into a rare illness that doesn't pose a public health threat or stimulate much

Between a rock and a hard place

Some patients are more fortunate than others: Their neuroendocrine tumors never cause problems or are caught early and removed surgically. Others don't realize they have cancer in these hormone-making cells until it has spread. Medications can control some patients' symptoms and prolong life, according to the American Cancer Society, but they aren't very effective at getting rid of the disease.

"Carcinoid and other neuroendocrine cancers grow slowly, and that's also the reason they're so hard to treat," explains Dana-Farber's Matthew Kulke, MD. "Chemotherapy likes to attack rapidly dividing cells. And so it's like giving chemotherapy to a big rock; it doesn't care."

Unfortunately, neuroendocrine tumors are not unusual when it comes to being stubborn, notes Kulke's DFCI colleague Ramesh Shivdasani, MD, PhD. "They're hard to treat because all tumors are hard to treat," he says. "Our lack of genetic understanding of neuroendocrine cancers certainly doesn't make things any easier. That's what we're trying to change."



A slide showing carcinoid tumor cells, arranged in discrete and organized "nests" and separated by bands of surrounding tissue. The cells appear relatively uniform and grow slowly – one reason they may be less responsive to traditional chemotherapy agents than other cancers.

Clinical research coordinator Christine Frauenhoffer checks a frozen neuroendocrine cancer sample. "When you work with a disease that is less well-known," she says, "you have the potential to make great strides in the diagnosis and treatment."

interest among pharmaceutical companies, Shivdasani notes. "The seed money is vital," he says. "There's no way to get the big National Institutes of Health-sized grants without having some preliminary results. But that's the culture of the federal grant system: You don't get funded for an idea. You get funded for continuing an already-productive line of reasoning. So this support is not only vital, it's imperative."

Marking progress

On a mission to gather preliminary results, Dana-Farber investigators have probed the genetics of neuroendocrine cancers, launched several clinical trials, and established two tissue banks. Located at Dana-Farber across from Shivdasani's lab and at Brigham and Women's Hospital, these banks store blood, urine, tumor, and other samples gathered from some 400 men and women with this disease, representing a range of ages and backgrounds.

The researchers are using the samples to decode the genetic patterns of neuroendocrine tumors, and they're exploring the diets, lifestyles, hormone levels, and other aspects of these patients to compare them with cancer-free individuals.

It's not uncommon to find Shivdasani and Kulke conferring about neuroendocrine cancers on the 11th floor of the Dana building, where they both see patients on Tuesdays, or in Shivdasani's lab, where they meet formally on Thursday mornings. Three research assistants working on gastrointestinal cancer projects ferry blood samples from the clinic to the lab almost daily for analysis. And on a recent afternoon, Kulke and Shivdasani continued hunting for carcinoid's genetic underpinnings by examining a pink-and-purple-stained slide with tumor DNA that had been purified in Shivdasani's lab and sent to the Institute's Molecular Diagnostics Laboratory for "whole genome analysis."

"In the past few years, there's been a shift in approach to clinical research," Kulke observes. "In addition to taking a disease and implanting it in a mouse, we're taking actual tumors from an individual, analyzing them, and trying to find out what makes the tumors tick. We're looking at patients' DNA to figure out, 'Is there something about their genetic makeup that makes them more prone to neuroendocrine cancer?' If we figured that out, it would presumably point us to the genes that are making these tumors work and show us how to attack them."

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How Kulke wound up pursuing this specialty is – as with many professional interests – a story of chance encounters and an inspiring mentor. During his medical training, Kulke saw a patient with carcinoid cancer and realized the disease was both fascinating and frustrating: "It's very different from other cancers because you can develop these hormonal symptoms, like flushing and diarrhea," he says. "And even though it tends to grow slowly, there didn't seem to be much known about it."

After he and Institute physician Robert Mayer, MD, published a paper about carcinoid cancer in the *New England Journal of Medicine* in 1999, Kulke recalls, patients with this illness began seeking out Dana-Farber for treatment. The first few clinical trials (using traditional chemotherapy drugs) were not terribly successful, he says. But two advances provided more options. One was the development of therapies, such as Gleevec and Iressa, targeting specific genetic mutations and biological signaling pathways associated with cancer. A second was the advent of antiangiogenesis agents, which prevent tumors from developing new blood vessels to nourish them. Carcinoid appears to be more "blood-thirsty" than other forms of cancer.

In recent years, Kulke and his colleagues have tested the effectiveness of several angiogenic therapies, including Sutent, originally developed for gastrointestinal stromal tumors. Other clinical trials have combined traditional chemotherapy (such as temozolomide) with drugs that thwart blood-vessel formation (such as thalidomide or Avastin). The temozolomide-thalidomide pair shrank neuroendocrine tumors in one-quarter of study participants and was biochemically active against malignancies in 40 percent of them – with fewer-than-usual noxious side effects. "We're very excited about extending these findings further," Kulke says.

The young clinician's inroads and enthusiasm helped draw in Shivdasani, a basic researcher who has long been fascinated by the digestive tract. He knew the neuroendocrine tumor bank and database would complement his desire to connect laboratory findings with cancer treatments.

Shivdasani and O'Hagan met at a gathering of Dana-Farber's Gastrointestinal Cancer Center Visiting Committee two years ago, after Shivdasani gave a brief talk on his work. Nancy O'Hagan serves on the committee and approached him during a break. "Nancy told me she'd been impressed by what she heard," he recalls. "That support was an important catalyst for me."

Motivating force

As much as she wants to change the prognosis for patients like herself, O'Hagan believes this kind of collaborative research will have ramifications for diseases beyond the one that has changed her life, including diabetes, stroke, Alzheimer's, and lung and prostate cancers.

"I'm confident this work will give us a greater understanding of how neuroendocrine cells, which are everywhere in the body, function – as well as what happens in the gut," she says. "I hope it will also benefit people who have carcinoid but don't know it. In my case, I wasn't diagnosed for years."

By bestowing research grants; by jetting across the country to confer with scientists and fellow advocates; by providing a website and blog; and by tapping friends to support the foundation (including taking part in the Pan-Massachusetts Challenge bike-a-thon and Boston Marathon®Jimmy Fund Walk), O'Hagan is out to kindle optimism and soothe family members' hurting hearts by working toward improved treatments and, eventually, a cure for carcinoid cancer.

"I don't feel sorry for myself," she says. "I consider myself fortunate to have the life that I do, the family that I've had, and so many wonderful friends. For a long time, I didn't even want to tell people that I had cancer; I didn't want them to look at me differently.

"But the thing is," O'Hagan adds, "I have to get out there and do what I can to make a difference." ■