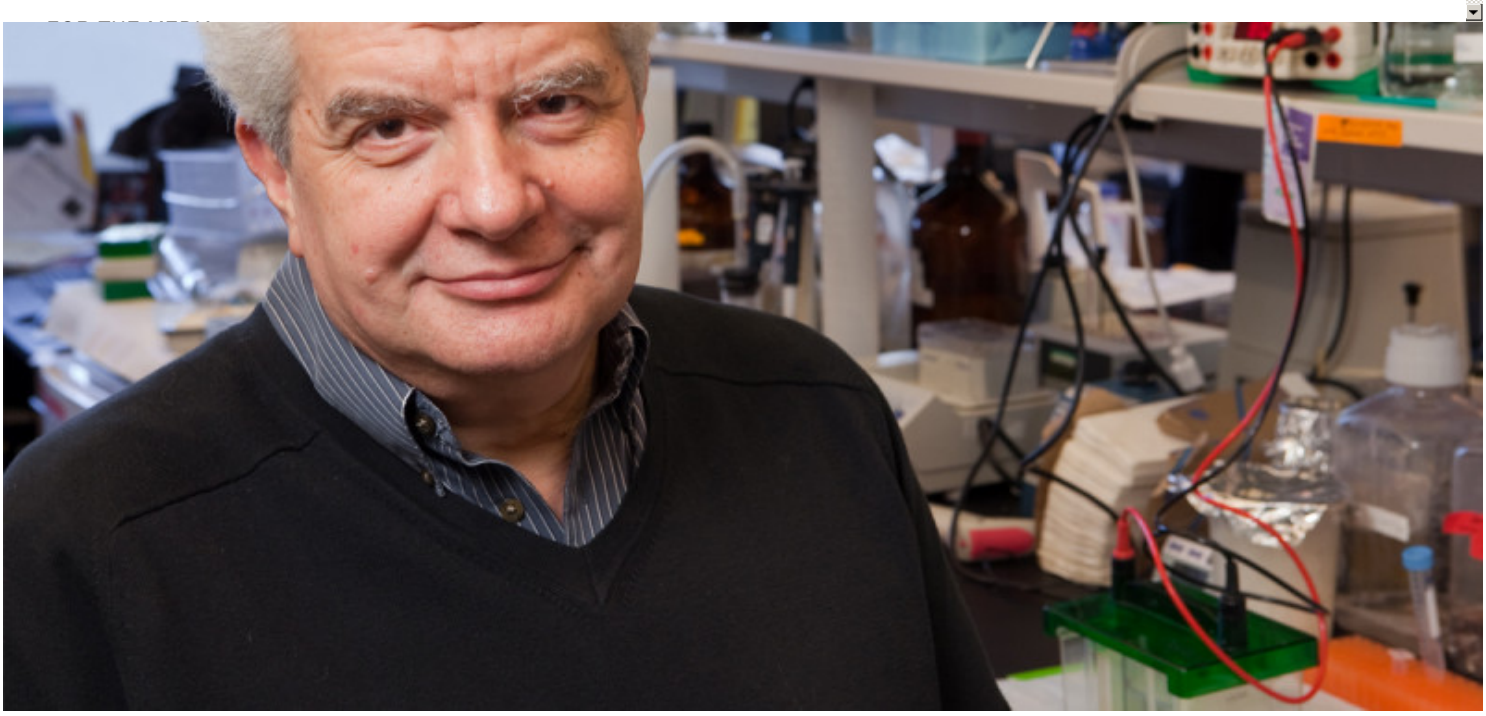

James A. Fagin

Physician-scientist James Fagin is an expert on the pathogenesis of thyroid cancer and the role of oncogenic kinases. We spoke to him in 2007.

I was born in Buenos Aires, spent most of my early years in Argentina, and went to medical school there. I then went to England where I completed my residency. I didn't originally envision working in a laboratory — I thought I would become a clinical investigator. But when I came to the United States in 1983, I wanted to have some experience in the lab and worked in one that was primarily focused on the regulation of gene transcription [the transfer of genetic information from the DNA molecule to the messenger RNA] in the pituitary. This was at a time when the early studies on mammalian oncogenes were being reported in the literature, and even though it was not directly connected to what I was working on, I was fascinated by the topic.

In a way, I came to oncology research through the window rather than the front door — I was trained in a basic science lab and learned many tools of the trade, but the discipline I was involved with initially wasn't related to what I ended up wanting to do. I'm not saying that I am a self-taught cancer

researcher, because one learns so much from so many people, but in terms of having the traditional training in a lab that did cancer research, I didn't have that. So now, at a later stage of my career, being at Memorial Sloan Kettering surrounded by so many talented cancer researchers is a particular treat, and I'm really excited about the future.

The Endocrinology Service at Memorial Sloan Kettering has a tradition of excellence in clinical research in thyroid cancer and in the care of patients with the disease. We are fortunate to collaborate with a superb group of head and neck surgeons, world-renowned for their work in this area, and an equally outstanding nuclear medicine group that has done much important research on the use of radioiodine in thyroid cancer.

Many patients with thyroid cancer can be successfully treated with surgery, and sometimes no further treatment is necessary. However, some patients need additional therapy involving the ingestion of radioactive iodine that selectively targets thyroid cells, as they are one of the few types of cells that can "trap" iodine. The radioactive iodine travels throughout the body to anywhere thyroid cancer cells may be hiding and can destroy them without significantly affecting any healthy tissue — except the salivary glands, which are often damaged when higher doses are used. With this combination — surgery, radioiodine, and medication with thyroid hormone — we can take care of most patients. Unfortunately, there are still about a quarter of patients who have frequent recurrences.

Recurrent thyroid cancer presents a number of treatment challenges. Further surgery and external beam radiotherapy have a limited role, but are often not the solution. Standard chemotherapeutic drugs have been quite disappointing; and, in recurrent disease, thyroid cancer cells often lose their avidity for radioiodine, so they no longer respond to that form of treatment. In coming to Memorial Sloan Kettering, I decided to shift my focus toward these patients — those with more advanced thyroid cancer and more aggressive types of the disease.

> My research is dedicated to understanding how thyroid cancers develop on a genetic basis, understanding the biology of the disease, and identifying potential targets for new molecular-based therapies.
>
> James Fagin
> Endocrinologist

My research is dedicated to understanding how thyroid cancers develop on a genetic basis, understanding the biology of the disease, and identifying potential targets for new molecular-based therapies. One of the opportunities one has as a researcher here is that there is a rich archive of tumor samples that one can mine to try to identify genetic abnormalities — the mutations or other disruptions of genes — that lead to cancer. [Memorial Sloan Kettering pathologist] Ronald Ghossein is the Endocrinology Service's primary pathologist. Dr. Ghossein has developed a large database of thyroid cancer tissues that we are using to look in much greater depth at the genetic abnormalities that play a role in the disease's development.

When we or others discover genetic abnormalities, we want to understand their functional consequences and that is when we use different types of experimental models, including cell lines and mice.

In addition, we have started to work with Marc Ladanyi, Chief of the Molecular Diagnostics Service, to refine methods to genotype thyroid cancer samples in a way that will ultimately allow us to use the information to make decisions about patient treatment. [Genotyping involves identifying the specific mutation in a gene that causes a disease.] Dr. Ladanyi has a new piece of equipment that can genotype samples for many different known gene mutations rapidly, simultaneously, and cost-effectively. Our ultimate goal is to genotype patient samples and use this as a basis for determining which patients ought to be included in a clinical trial of a particular drug.

To advance the development of new therapies, we are looking at drugs that make sense in terms of what we know about the genetics and the biology of the disease and that are ready, or close to being ready, to be moved into clinical studies. We're fortunate to count on the expertise of David Pfister, Chief of the Head and Neck Medical Oncology Service, and Michael Tuttle of the Endocrinology Service, who will be planning and developing these studies. We hope to bring the most promising drugs into early phase clinical trials for patients with advanced thyroid cancer. It takes a lot of coordination and teamwork to put all this together, and we are just beginning the process. However, thyroid cancer is a disease that is ripe for this type of approach, and we're optimistic that we will be able to make a difference.

In addition to our focus on thyroid cancer, an important part of the mission of our service is to provide care for patients with other endocrine neoplasias. We are responsible, as well, for the care of patients with other cancers who have coexisting endocrine diseases — diabetes is the most common. Endocrinologists in a cancer center also treat patients who develop a disorder of the endocrine system as a result of their treatment. Some drugs used to treat cancer can affect metabolism and, therefore, the control of blood sugar. Other drugs may predispose patients to metabolic bone disease or thyroid disfunction. All these situations require the input of endocrinologists in order to offer integrated care to patients.

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