Summary

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For Simon N. Powell, research and medicine have always been joint pursuits. Dr. Powell joined Memorial Sloan Kettering in 2008 as Chair of the Department of Radiation Oncology with a joint appointment in Sloan Kettering Institute's Molecular Biology Program. He has 18 years of experience leading basic and clinical research, first at Harvard Medical School and most recently at the Washington University School of Medicine.

Growing up in Manchester, England, I wanted to become a scientist like my brother, who now is a physicist, and my sister, who is a science teacher.

Neither of our parents pursued an academic career — very few people in England had that privilege before the Second World War.

I studied neuroscience at the University of Oxford and initially planned to pursue a PhD degree in that field. But at one point, it occurred to me that the science I was most interested in was closely connected to medicine, so I changed my mind and went to medical school instead, at the University of London.

Because of my interest in neuroscience, I initially thought I would become a neurologist. However, an elective studentship with Sir Michael Peckham, a professor of oncology at the Royal Marsden Hospital, changed my perspective. It was my first encounter with a physician who was so strongly committed to science. Inspired by his ability to combine clinical and basic research, I decided to follow in his footsteps and specialize in oncology.

Many years later, after completing my specialty training in internal medicine and oncology, plus receiving a PhD degree from the Institute for Cancer Research, in London, I gave a lecture at a teaching course for oncologists. Afterward, Herman Suit, who was the head of radiation oncology at Massachusetts General Hospital, came up to me and said, “That was a good talk. Do you want to come to Boston?” Until then, I had never considered leaving England. But I did, and never moved back.

Here in the United States, my clinical practice became more focused on radiation therapy, the principle of which is to kill cancer cells, or prevent them from dividing, by damaging their DNA. Ideally, the treatment is delivered in such a way that it damages as many cancer cells as possible while sparing the healthy tissue surrounding the tumor. My laboratory research is focused on the molecular mechanisms that underlie a cancer cell’s vulnerability to DNA damage, and how these can be exploited therapeutically.

Normal cells protect their genome by repairing breaks in the DNA strands as they occur. If a cell’s DNA repair functions are weakened, its genome will start to accrue alterations that may eventually lead to cancer. For example, people who inherit mutations in the genes *BRCA1* or *BRCA2*, which are important for DNA repair, have an increased risk for developing breast or ovarian cancer . However, the same mutations can make radiation or chemotherapy more effective since they make tumors more susceptible to DNA damage.

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Recently, my co-workers and I developed a simple test to determine if cells isolated from a breast cancer patient’s tumor have DNA repair defects. In the future, we hope this test will help doctors predict how a patient will respond to radiation and guide treatment decisions. The test could also be used to predict individual responses to certain drugs such as PARP inhibitors, which are designed to exploit repair deficiencies in cancer cells. At Memorial Sloan Kettering, we are now exploring the clinical application of the test in a number of diseases, including breast, ovarian, and pancreatic cancers .

If a group of patients is treated with the same dose of radiation, the patients will show a range of responses. Hundreds of genes are involved in DNA repair, and their activity varies among individuals. Together with investigators in Memorial Hospital’s Clinical Genetics Service and SKI’s Computational Biology Program , we are launching a genome-wide association study, in which subtle genetic differences among people will be analyzed on a large scale. Such knowledge will be critical to developing new treatment methods in which radiation will be tailored to each patient’s genetic profile.

One of my incentives for joining Memorial Sloan Kettering was the great opportunities that exist here for translational cancer research. With an outstanding hospital and an equally renowned research institute, we are in the fortunate position of being able to do research that can benefit our patients directly. Our most imminent challenge is to link our basic and clinical science programs, making the transition of discoveries from the lab to the clinic as effective as possible. One step toward this goal is to increase the number of clinician-scientists on our team who have research plans that embrace basic science and clinical radiation oncology.

Together with the Departments of Radiology and Medical Physics, we are also making big investments in developing technology for custom imaging in radiation therapy. In the past, doctors would image a patient’s tumor during one visit and then perform radiation treatment during subsequent visits. To make sure we treated the whole tumor — and to account for the possibility that its position might have shifted since the patient’s last visit — we had to irradiate a substantial margin of healthy tissue around it, which required us to use lower doses of radiation. Today, our radiation units have incorporated CT scanners, which have increased precision enormously. By imaging the tumor while the patient is on the treatment table, we can position the beam optimally before switching it on and target the tumor with higher doses.

Imaging has also made it possible to evaluate how effective the radiation therapy is, both during and after a patient’s treatment. With sophisticated methods, we now have access to a lot of information about how a tumor is responding, often as early as after the first treatment. For example, we are

planning to install a magnetic resonance simulator in the radiation oncology suite at Memorial Hospital and will use it to explore whether a new treatment approach, known as high-dose single-fraction radiotherapy, can induce changes in tumor blood vessels. According to animal studies by Memorial Sloan Kettering clinician-scientists Zvi Fuks and Richard Kolesnick , high doses of radiation can make blood vessels collapse — and ultimately cut off the tumor's blood supply — in addition to killing cancer cells. We are now testing this concept in patients by delivering a single, high dose of radiation instead of many lower doses given over several weeks, which is the current standard of treatment.

With a wide spectrum of initiatives underway — from basic research to technology development to treatment innovation — this is a very exciting time to be at Memorial Sloan Kettering. As we find new ways of bringing all these activities together, I expect we will soon enter a new era of radiation oncology.