Molecular Imaging in Oncology

Edited by
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Foreword

Molecular imaging can be traced back to France in 1896, when Henri Becquerel discovered that certain materials emitted energetic ''rays,'' a physical process that his graduate student, Marie Curie, later called radioactive decay. In 1929, American physicist Ernest Lawrence built the first cyclotron and was able to produce positron-emitting radionuclides. In 1931, the British physicist, Paul Dirac, had postulated the existence of positrons, based on an equation he developed in quantum mechanics. He postulated the existence of the positron as an antiparticle having the same mass as an electron but with a positive rather than negative charge. The proof of the existence of the positrons was proved in cosmic radiation by another Nobel prize winner, Carl Anderson, in 1932. That same year French physicists Irene Curie (Marie's daughter) and Frederick Joliot (Irene's husband) announced their discovery of artificial radio-activity. They showed that many different atoms could be made radioactive. With the Curie/Joliot publication, Lawrence immediately recognized the enormous potential value of being able to make ''radioactive tracers'' that made possible medically important as well as chemical and physical measurements. Subsequent pioneers recognized the great biological importance of the radioactive elements that a cyclotron could produce, including oxygen-15 and carbon-11. In the 1930s, chemist Martin Kamen, working with Lawrence, made the key discovery that the oxygen produced by the process of photosynthesis, and so important for living organisms, came from water, not from carbon dioxide, as had been previously assumed.

In the spring of 1945, the U.S. government made the decision to produce radioisotopes for civilian use. In June 1946, President Truman signed an executive order that made iodine-131 available from Oak Ridge National Laboratory to qualified physicians throughout the United States. The first shipment of carbon-14 was on August 2, 1946, to Martin Kamen at Berkeley, California. The shipment was kept secret because Kamen was falsely thought at the time to be a communist. The first announced shipment to a civilian institution was subsequently to the Barnard Free Skin and Cancer Hospital at Washington University in St. Louis. On December 7, 1946, the revolutionary announcement was made by an internist, Sam Seidlin and colleagues that radioiodine could not just ameliorate but cure metastatic cancer. According to Marshall Brucer at Oak Ridge, within days, every Congressman had heard from his constituency, and on Jan 1, 1947, the Atomic Energy Commission (AEC) took over the distribution of radioisotopes from the supersecret Manhattan District Project of World War II that had developed the atomic bomb.

In 1946, George Moore, a neurosurgeon at the University of Minnesota, used iodine-131-labeled iodofluorescein to localize brain tumors using a Geiger-Muller detector in 12 patients during surgery. In 1950 the FDA recognized iodine-131 as the first ''radioactive new drug''. By 1950, 3250 publications had been published on the use of radionuclides in medicine. Molecular imaging was not accepted immediately. Marshall Brucer wrote: ''Surgeons poo-poohed any thought of treating hyperthyroidism with some kind of fake iodine. Hematologists laughed at the P32 trials in the treatment of leukemias. Medical societies had no room on their agendas for radioactive isotopes.''

The public was excited by news of the use of radioiodine not only in the diagnosis of hypo- and hyperthyroidism, but in the treatment of thyroid diseases, in many patients eliminating the need for surgery. It was the first example of defining disease on the basis of a measured regional molecular process, that is, the accumulation of radioactive iodine.

''Radioisotope scanning'' was the name given to imaging of the distribution of radioactive tracers in the living human body at various times after injection of a radioactive ''tracer.'' New ''radiopharmaceuticals'' were developed in the 1950s and 1960s as a means of ''visualizing'' previously invisible organs, such as the liver, that could not be examined effectively by conventional X-rays.

A tremendous boost to molecular imaging, then called ''atomic medicine,'' and subsequently ''nuclear medicine'' was given by a speech delivered by President Dwight Eisenhower before the 470th plenary meeting of the United Nations in New York on December 8, 1953. He said:

''The more important responsibility of a new (atomic energy) agency would be to devise methods whereby fissionable material would be allocated to serve the peaceful pursuits of mankind. Experts would be mobilized to apply atomic energy to the needs of agriculture, medicine and other peaceful activities. I would be prepared to submit to the Congress of the United States, and with every expectation of approval, any such plan that would, first, encourage world-wide investigation into the most effective peacetime uses of fissionable material, and with the certainty that the investigators had all the material needed for the conducting of all experiments that were appropriate.''

President Eisenhower's speech led to the creation of the International Atomic Energy Agency (IAEA), which made possible research with radioactive tracers all over the world. The types of studies include measurement of regional blood flow to organs and lesions, measurement of the regional bioenergetics, and molecular processes involved in intercellular communication.

Since the 1950s molecular imaging has encompassed much more than the peaceful use of radioactivity. Although radiopharmaceutical-based techniques tend to dominate clinical molecular imaging presently, molecular imaging is not really about any specific modality. It is about uncovering physiology noninvasively by probing specific cellular and molecular processes in vivo. What has made molecular imaging so exciting now is the introduction of efficient, high-sensitivity devices for preclinical (animal model) as well as clinical imaging. Hybrid imaging devices, which combine the high resolution of anatomic imaging with the physiologic techniques, are also becoming standard in clinical practice and enable determination of a metabolic or receptor defect with pinpoint accuracy within minutes. Increasingly relevant imaging targets are being uncovered due to protein arrays and high-throughput methods by which to interrogate human biopsy specimens. Mice that can be genetically manipulated not only help validate those targets but also provide excellent models in which to test new molecular imaging probes. The introduction of current molecular biological techniques—as they evolve in real time—to imaging science will only make molecular imaging increasingly relevant to study physiology and disease in the coming years.

Oncology is perhaps the most fruitful domain of molecular imaging at present, particularly because of the information provided in measuring the energy supply of lesions, the abundance of unexploited tumor markers, and intra- and intercellular

communication pathways amenable to imaging. This book describes the development, principles, and uses of molecular imaging in answering the questions raised in the practice of medicine, with an emphasis on oncology: (1) What is the problem? (2) Where is the problem? (3) What is going to happen? (4) What is the best course of action and treatment? (5) Is the treatment effective? A graded approach is taken whereby there will be a brief introduction to basic principles in biology and molecular imaging, then to the modalities available on through clinical molecular imaging of cancer. Medicine has moved from whole body to organs to tissues to cells and now to molecules. We are indeed in a revolutionary time in the history of medicine.

Henry N. Wagner, Jr., MD

Preface

Although a relatively new aspect of imaging science and practice, molecular imaging is beginning to make its presence felt. It has done so because it involves the collaboration between two rapidly evolving fields, namely, molecular biology—including genomics, proteomics, and the use of transgenic animal models—and high-sensitivity imaging devices to probe cellular and molecular phenomena in vivo. Those two fields are powerful in their own right, but together they can generate considerable new knowledge about normal cellular processes and disease and, in particular, cancer.

This volume is dedicated to the molecular imaging of cancer, taking a graded approach to the subject by first introducing concepts of basic molecular biology (sect. 1) and the operation of the various imaging modalities (sect. 2). We felt it was necessary for the reader to understand the challenges in the development of imaging probes (sect. 3) and in performing imaging in animal models—the mainstay of current molecular imaging research (sect. 4). More directly germane to the molecular imaging of cancer are chapters dedicated specifically to molecular-genetic imaging (sect. 5), imaging cellular migration and other processes (sect. 6) and clinical translation (sect. 7), where examples from several key clinical challenges are provided (sect. 8). The final chapters highlight imaging in anticancer drug development and how to move into the future through collaboration with industry and the government (sect. 9).

Although molecular imaging is evolving rapidly, due to the incorporation of nanobiotechnology, microfluidics, and other rapidly advancing fields, we have tried to maintain relevance for the practicing clinician—who will be the ultimate arbiter as to whether molecular imaging will actually prove useful for and adopted into clinical practice. Nevertheless, sufficient detail is provided so that graduate students and established practitioners in allied fields, e.g., chemistry, imaging physics, and cell biology, can become acquainted with molecular imaging in cancer and begin incorporating imaging beneficially into their work, likely generating new ideas previously unseen by dedicated imaging scientists.

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