Molecular Imaging: A Triad of Technologies

By Tim Friend

Completing a three-city interview tour with three prominent molecular specialists in Boston, Los Angeles, and Knoxville on exciting new developments in molecular imaging, reminded Siemens journalist Tim Friend of the challenges of a triathlon. And indeed, his explorations proved that successful players in the field must excel in three important areas of expertise in molecular medicine – in vitro diagnostics, imaging, and information technology. Just as a triathlete must perform equally well in swimming, biking, and running, the combination of the three is what makes a good athlete.

Until recently, many physicians solely associated molecular imaging with imaging technologies like PET, SPECT, ultrasound, or MRI. But to leaders in the field, it has come to mean much more. Today, molecular imaging is revolutionizing everything from drug discovery and preclinical studies of disease to clinical research and daily medical practice. "Molecular imaging has evolved into an academic field, with diverse technology, preclinical, and clinical research, and it has been deeply integrated into biology and medicine," says Michael Phelps, Ph.D., Norton Simon Professor and Chair of the UCLA Department of Molecular and Medical Pharmacology, Los Angeles. "I think it is clear now that molecular imaging has come of age." As a lead inventor of the first PET scanner and one of the founders of the Academy of Molecular Imaging, Phelps, one of the founders of CTI Molecular Imaging, is well qualified to make such a statement.

As an evolving academic field, molecular medicine has become truly interdisciplinary, attracting specialists from widely diverse areas, including biology, chemistry, cardiology, genetics, genomics, immunology, neurology, nuclear medicine, oncology, pharmacology, and radiology. Its overarching purpose is to provide disease-specific molecular information through diagnostic imaging studies, according to Ralph Weissleder, M.D., Ph.D., Professor of Radiology, Harvard Medical School, and Director of the Center for Molecular Imaging Research, Massachusetts General Hospital, Boston.

But more specifically, molecular imaging is aimed at detecting the origins of disease-related pathways and targets in the human body by combining the use of molecular biomarkers and probes with the gamut of whole-body imaging techniques. "Molecular imaging as we understand it is the visualization of specific molecular targets or entire pathways and cells in living experimental animals or ultimately in the clinic," Weissleder explains. "Current molecular imaging techniques essentially allow us to do three things and do them much better than we were able to do them a couple of years ago. One of them is to detect disease much earlier. The second one is to stage cancer and some other diseases much more accurately and noninvasively, and the third is to facilitate and speed up the drug development process."

Michael E. Phelps, Ph.D., is Norton Simon Professor and Chair of the UCLA Department of Molecular and Medical Pharmacology at UCLA, where he holds six academic positions. In addition to serving as the Departmental Chairman and holding an endowed professorship, he is also the Director of the Crump Institute for Molecular Imaging and the Director of the Institute for Molecular Medicine.

The elegance and beauty of molecular imaging is its unique ability to visualize the human body in vivo for the first time as a dynamic biological system, rather than as a scaffold of bone and tissue. Newer hybrid technologies that combine the best qualities of PET, SPECT, ultrasound, and MRI with each other and with increasingly sensitive and specific biomarkers are making this possible in spectacular ways, according to Phelps: "As part of the evolving concept of molecular medicine, molecular imaging technologies are being developed to examine the integrative functions of molecules, cells, organ systems, and whole organisms. The organisms range from viruses and bacteria to higher order species, including humans, but in each case molecular imaging is used to examine the structure and the regulatory mechanisms of their organized functions." Three of the factors driving the evolution of molecular imaging to its new status as a medical discipline are the dramatic advances made in the past five years in imaging technologies, the rapid development of enhanced biomarkers and new molecular targets, and, most importantly, the merging of some of the best minds and efforts of leaders from academia, industry, and government. "Today is a changing time," says Phelps, "and it's interesting to look at what were the defining moments that occurred. Certainly a recent one was the Molecular Imaging initiative by the National Cancer Institute (NCI). On the other side of the Atlantic, the European Commission's Sixth Framework supports such activities as well."

Ralph Weissleder, M.D., Ph.D., is Professor of Radiology at Harvard Medical School, and Director of the Center for Molecular Imaging Research, Massachusetts General Hospital, Boston, MA

Weissleder sees three forces that have had a critical impact on the evolution of molecular imaging. "Without doubt, one have been the National Institutes of Health and the FDA. The second one have been equipment manufacturers such as Siemens, and the third has been the pharmaceutical industry," he says.

Siemens and CTI Join Forces

Industry has played a key role in pushing the evolution of molecular imaging to its current potential. Siemens took center stage at the Society of Nuclear Medicine (SNM) conference in Toronto, Canada, in June with its molecular imaging booth and announcement of a newly unveiled division, Siemens Medical Solutions Molecular Imaging, which combines its nuclear medicine operations with CTI Molecular Imaging, Inc., the world's leading provider of PET imaging equipment and services, and now a wholly owned subsidiary of Siemens Medical Solutions.

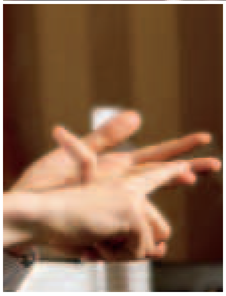
Michael Reitermann, President of Siemens Medical Solutions Molecular Imaging (former Nuclear Medicine Division), Hoffman Estates, IL

With the formation of the new division, Siemens strengthens its commitment to molecular imaging development, technological innovation, and the creation of new technologies, including the development and distribution of molecular bio-markers, preclinical imaging for research, and pharmaceuticals, as well as applications and postprocessing for molecular imaging.

"Uniting Siemens Nuclear Medicine with CTI to form a new molecular imaging division supports our vision to be the innovation trendsetter in the healthcare industry," says Erich Reinhardt, Ph.D., President and CEO of Siemens Medical Solutions. "By strengthening our leadership position in identifying disease earlier at the molecular level, we continue to transform the delivery of healthcare by improving patient care while reducing costs." Leading Siemens Medical Solutions' Molecular Imaging Division is Michael Reitermann, President of the former Siemens Nuclear Medicine Division in Hoffman Estates near Chicago. "Molecular imaging, in our opinion, is a very rapidly developing market opportunity," Reitermann says. "And I think it will change how we practice medicine on the diagnostic and therapeutic side. And we, of course, will be shaping that development."

Such statements about revolutionizing healthcare might have been hyperbole just a few years ago. But academic leaders such as Phelps and Weissleder, who also are collaborators with Siemens, agree that the science and technology of molecular imaging are rapidly reaching the critical mass necessary to fundamentally transform the medical and pharmaceutical landscape. That change has been fostered by heavy investment from both industry and government. In addition to investment by the NCI, Siemens has been a long-standing supporter of molecular imaging research at academic centers worldwide, including UCLA's Department of Molecular and Medical Pharmacology and MGH's Center for Molecular Imaging Research. The focus of the Siemens Molecular Imaging Division captures the essence of what academic researchers, government, and industry are achieving together.

"Our solutions for molecular imaging consist of various elements, one being the clinical solutions that are composed of PET, PET/CT systems, SPECT, SPECT/CT systems, and clinical applications that are supporting these systems and help us to actually diagnose and visualize the results," Reitermann explains. "Then we have preclinical imaging solutions – the microPET, microCT, bonSAI, a fluorescent small animal imaging device, as well as ClinScan, a microMRI device jointly developed by Siemens and Bruker – they are new developments in the preclinical area. And we have biomarker solutions, which are basically the production systems, the cyclotrons that allow you to create radioisotopes, and a development team that looks out for new biomarkers. We also have the distribution solution with PETNet that allows us to actually bring the existing biomarkers and the new molecular diagnostic markers to the marketplace."



Historic Parallels, Future Promise

In many aspects, advances in molecular imaging, over a startlingly brief period in medical history, are analogous to advances in astronomy that occurred over the past 500 years. In the early 1500s, Galileo became the first person to view features on other worlds – craters on the moon, sunspots, the moons of Jupiter, and the rings of Saturn – through a pair of simple binoculars. A century later, Sir Isaac Newton revolutionized telescope design with the curved mirror, providing greater detail of our solar system and opening the galaxy to exploration through much more powerful magnification. In the 20th century, the development of infrared telescopes and X-ray astronomy made it possible to begin spectral analysis of the compositions and internal dynamics of stars and to study other galaxies. Now we can glimpse the most distant reaches of the universe and send probes to planets, moons, and comets to gather information on temperature, atmospheric and subsurface compositions, and the dynamics of planetary weather systems.

Röntgen's discovery of X-rays in 1895 might be compared to Galileo's binoculars, and Newton's telescope to the development of PET, CT, ultrasound, and MRI in the 1970s, which opened exploration of the molecular universe inside the human body. Like modern astronomy, 21st-century molecular imaging can now send targeted probes to the interiors of individual cells to study the dynamic systems of human biology – the interactions of cells, pathways of proteins, enzymatic reactions, and even the activity of genes as they are expressed or shut down in normal biological processes.

According to the Society for Molecular Imaging, of which Weissleder is cofounder and past president, molecular imaging holds the potential of simultaneously being able to locate, diagnose, and treat disease in vivo as well as the ability to depict how well a treatment is working early after therapy onset. This is the type of power that can and will transform daily medical practice from a system that reacts to disease and treats symptoms, often after it's too late for a cure, to one that detects disease at the beginning and treats its root cause. "Our ultimate goal with molecular imaging is to enable disease detection much earlier than is currently possible, which ultimately will obviate unnecessary surgeries and treatments. If an intervention is necessary nonetheless, molecular imaging may also be of help; e.g., by detecting tumor borders during the procedure. And in the best-case scenario, it will also result in more cost-effective treatments," says Weissleder. One of the most promising new technologies for this application is fluorescent imaging, which is being codeveloped by Weissleder's CMIR and

Siemens. The fluorescence is detected in the near-infrared light spectrum by a prototype handheld optical imaging device that investigates the target tissue during surgery with near-infrared sensors. The optical image is converged with MRI to reveal its precise location. Regardless of the imaging system being used or favored by research groups, the common thread linking them all is the need for new biomarkers and molecular targets that elucidate disease pathways. "One of the essential ingredients to molecular imaging, and in particular clinical molecular imaging, is the availability of imaging probes that allow us to report on these targets," Weissleder says. "So, it all boils down to the development of more imaging agents with different specificities that we could then use by nuclear imaging technologies (PET and SPECT), optical imaging technologies, and MRI."

Early Detection Broadens Treatment Options

According to both Weissleder and Phelps, the number of molecular imaging studies that have moved from the bench to the bedside has risen exponentially thanks to an expanding arsenal of imaging agents and constantly improving imaging technologies. Scientists at this year's SNM conference and at the Academy of Molecular Imaging annual meeting in Orlando presented dozens of new human studies from clinical research centers around the world. The same is expected from the scientists at the Society of Molecular Imaging (SMI) meeting that will be held in Cologne, Germany, this fall. Such studies, reports Phelps, clearly demonstrate that molecular imaging is the way of the future for the diagnosis, staging, and treatment of the most common diseases affecting the world's population, including cancer cardiovascular disease, various neuropsychiatric disorders such as depression, Alzheimer's, Parkinsons and other neurodegenerative diseases inflammatory and immun diseases.

"In cancer detection, subcentimeter cancer metastases that are missed by conventional, anatomically based imaging methods may be detected in patients by molecular imaging methods," says Weissleder. "Together with other biomarkers and emerging molecular tools (e.g., DNA screening, tissue proteomic and metabolomic analysis, serum markers), this information soon may be used for screening, diagnosis, detection of recurrence, and treatment assessment."

Phelps takes it one step further: "If you had microfluidic chips that showed a person's protein fingerprint simply by using a drop of blood, and if this fingerprint would reflect that person's health condition, this would mean a huge step forward." In 2004, Siemens was awarded the German Innovation Prize for their biochip technology – lab on a chip called Quicklab. Quicklab is a molecular diagnostic system that allows the integration of molecular in vitro diagnostics into the clinical workflow. Genetic material (DNA) and proteins are analyzed on a chip and can be instantly displayed for diagnostic purposes. Diagnosing cancers at their earliest stages has been a dream of scientists and physicians for decades. But conventional diagnostic techniques usually are unable to detect such miniscule tumors, and by the time many cancers are diagnosed, metastatic cells may have already begun to migrate from the primary site. Quicklab in conjunction with molecular imaging tools promises to transform the treatment of cancer by allowing for the earliest possible diagnosis and determining the best course of treatment, according to Weissleder. "Indeed, molecular imaging has changed the cancerstaging procedure. For example, using nanoparticles, an outgrowth of nanotechnology, we're now able to detect cancer metastases in non-enlarged nodes as small as one to two millimeters in size," he says. "And in some of the clinical trials in prostate cancer, the sensitivity for detecting disease nodal metastases was over 95 percent, approaching that of surgical intervention."

These applications benefit from MRI protocols and evaluation software, a joint MGH and Siemens contribution. The company also contributed by providing MR protocols and evaluation software. "This is a perfect example of how the development of contrast agents, hardware, and software must go hand in hand on an interdisciplinary level," says Weissleder. But this is just the beginning. Siemens is also engaged in other promising projects with the pharmaceutical industry and radiologists.

Staging, Monitoring, and Changing the Course of Therapy

Phelps stresses that molecular imaging is clearly superior to conventional diagnostic techniques, allowing physicians to better stage a patient's tumor, monitor responsiveness to treatment, and rapidly change course when therapy is not working. "In multicenter trials in twelve different cancers such as lung, colorectal, head and neck, breast and ovarian cancers, melanoma and lymphoma, PET was shown to have an 8 to 43 percent higher accuracy for detection, staging, recurrence and assessing therapeutic responses versus conventional workups in head-on comparisons, and changed the choice of therapy selected by conventional evaluations in 15 to 50 percent of patients, depending on the specific clinical question. About 65 percent of therapy changes occur because PET showed there was more extensive disease than originally determined by conventional tests, whereas in about 35 percent of patients, PET showed that previously diagnosed metastases were benign lesions, resulting in changes to simpler therapies, improved prognosis, and lower costs. It's quite miraculous, even to me, to realize that today."

Molecular imaging also is expected to change the way Alzheimer's disease and other slow-developing neurodegenerative diseases are diagnosed and treated. According to Phelps, longitudinal studies using PET found that Alzheimer's disease can now be detected three years earlier than with conventional clinical diagnostic methods employing years of repetitious tests – with an accuracy of 93 percent. The most effective existing drug therapies available for Alzheimer's work only in the earliest stages of the disease, so an earlier diagnosis should increase the chances that progression of Alzheimer's can be delayed. More recent research presented at an Alzheimer's disease conference in June 2005 by a team from New York University School of Medicine found that PET scans can predict the onset of Alzheimer's and mild cognitive impairment nine years before symptoms appear, confirming and extending earlier work at UCLA and Arizona State University showing Alzheimer's could be detected with PET five years before symptoms occur.

Hybrids Equal More Precise Treatment

PET, SPECT, ultrasound, and MRI all have unique advantages and abilities to unveil the human body's most intimate details. Not surprisingly, one of the first hybrid systems to show promise in clinical studies is the Siemens PET/CT biograph. "Hybrid imaging actually brings together all the information that is necessary," says Reitermann. "You have biological information from the PET or the SPECT side, and you can clearly understand what the metabolic activities are in the body, for example, but you cannot locate them exactly in the body. So what you do with the second element, the second modality – in this case, CT – is to actually bring precise anatomical information into the picture. And by merging the two, you have the metabolic information plus the exact anatomical information. And that, for example, for surgery or radiation therapy, gives you invaluable information for the treatment process."

Evidence of molecular imaging's growing influence and importance in modern medicine was readily apparent at the recent 2005 SNM conference, where academia and industry showcased its remarkable power. Hybrid PET/CT images and molecular imaging studies were a hallmark of the conference, and Siemens presented first semi-conductor-based experiments with simultaneous phantom measurements at the ISMRM in Miami Beach. Says Heinrich Kolem, Ph.D., President of Siemens Medical's MRI division: "Today, clinical molecular imaging is dominated by nuclear medicine. But in the future, MRI will increasingly become an indispensable modality. Be it by providing anatomic landmarks (MR PET) or by the direct detection of molecular events."

Phelps is developing a truly revolutionizing technology that extends PET beyond FDG-PET: microfluidic chips with nanotechnology will allow researchers to create highly specific, designer biomarkers for PET and PET-hybrid systems in a matter of days using "click chemistry factories" inside a laptop-sized integrated microfluidics platform being developed between Hartmut Kolb, Ph.D., at Siemens Molecular Imaging, UCLA, and Jim Heath, Ph.D., at Caltech. Phelps' group at UCLA is also in hot pursuit of discovering novel imaging agents and targets, and is developing a new paradigm for synthesizing and testing them. Phelps views biology and the human body from a systems perspective, looking at molecular pathways in normal tissues as electronic integrated circuits, and the process of diseases as a malfunction in those circuits that can be fixed. "If you think about a system's biology view of disease, you have to begin thinking about how the body is organized into an integrated function in the cell and the networks of cells," explains Phelps. "You have to think about how disease can reprogram those circuits to gain and lose functions and do harm to us in a different configuration in the circuit. People in the field of systems biology don't believe in the old concept of what breast cancer is, or prostate cancer, or Alzheimer's disease. They believe that cells are being progressively reprogrammed into different configurations of cell circuits and intercellular networks throughout the developmental course of disease to gain and lose functions that do harm to the organ systems of the body and we must understand this so that we can deal with it effectively and therapeutically. All of that begins with molecular diagnostics, whether it's in vitro in cells and blood, or in vivo with molecular imaging, to identify the critical proteins that consolidate specific biological processes of disease that occur in the reprogramming process. Those are the therapeutic targets; we need to either push them or to drive them back to normal or to terminate them. This is a new world that we live in. And I think over the next five to ten years we will see dramatic changes – changes in the old world going down and changes in the new world coming up to resolve these issues."

The most significant breakthroughs in molecular imaging over the next few years are expected to come from increasing the accuracy of identifying the critical disease targets and development of specific molecular imaging probes that bind to those targets or that measure the biological process involving or associated with the target. When searching for new molecular targets, Weissleder believes scientists should follow a few basic principles. Overall, molecular targets should define disease status earlier than conventional imaging methods, identify the underlying molecular events that initiate disease and cause progression, distinguish between aggressive and indolent disease states, or represent downstream targets in an already well-characterized molecular network or disease pathway. Once a specific molecular target, its affinity ligand, and an imaging system have been identified, the next step is to synthesize a corresponding molecular agent for in vivo use.

With continued efforts from academia, industry, and government, experts in the field expect molecular imaging to become even more powerful and the technologies to become simpler and more widely available with diversity in biomarkers to match critical biological indicators of disease and drug targets. To achieve this goal, powerful IT solutions must be developed so that the large amount of data resulting from both in vivo and in vitro diagnostics can be analyzed. Measured values must be transformed into actual medical knowledge by means of high-capacity IT tools. Siemens, in collaboration with Weissleder's group, has taken preliminary steps in this direction by developing a data organization system called MIPortal (see also page 74).

Michael Reitermann describes the change from today's medicine to molecular medicine with 3 Ps: "Medicine is going to be predictive, personalized, and preventive." Weissleder and Phelps say practitioners are paying attention and are increasing the rate at which they adopt molecular imaging technology. Just look at the recent adoption rate of PET and PET/CT that lays the foundation for the clinical use of other molecular imaging technologies. Phelps is excited about the future of his field: "In medicine and biology there is a new playing field. It's all molecular. And it is going to change the world we live in."

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WIP – the information about this product is preliminary. The product is under development and is not commercially available in the U.S., and its future availability cannot be ensured.