

Guest Editorial

Toward Molecular Imaging

RECENTLY, molecular imaging has attracted great interest and been widely recognized as a major trend of biomedical imaging. According to Weissleder and Mahmood [1], “*The term molecular imaging can be broadly defined as the in vivo characterization and measurement of biologic processes at the cellular and molecular level.*” While traditional biomedical imaging techniques are anatomically/functionally oriented that reflect structural features and physiological/pathological phenomena, the purpose of molecular imaging is to detect, capture, and monitor molecular/cellular abnormalities *in vivo* that cause diseases and associated symptoms. Hopefully, sensitive, specific, and quantitative imaging of such molecular/cellular targets would revolutionize life sciences and clinical practice from the most fundamental level, and bring enormous healthcare benefits in the future. This special issue is an initial response of our journal to the grand challenges in molecular imaging. Ten papers [2]–[11] were selected from 21 submissions as a snap-shot of its state of the art (The last paper [11] was handled by Associate Editor Erik Meijering).

Small animals, including genetically engineered mice, are popular models to study human diseases and evaluate therapies. In the post-genome era, the genome is being linked to phenotypic expressions in forms and functions for development of systems biomedicine. Hence, all medical imaging modalities have been downscaled over past several years. The resultant miniatures include micro-CT, micro-MRI, micro-PET, micro-SPECT, and micro-ultrasound scanners as well as optical imagers of different types for small animal imaging. With molecular imaging of small animals, physiological processes and pathologic progression can now be studied in a compressed period under controlled conditions with various probes. As a result, seven papers [2]–[5], [7]–[9] in this special issue are directly related to small animal imaging.

As the first medical tomographic modality, X-ray CT is not only extensively used for anatomical imaging but also important for physiologic imaging. In the work by Krishnamurthi *et al.* [2], functional micro-CT was evaluated for monitoring therapeutically induced changes at the cellular level. Based on a compartmental model, they determined the scanning protocols for mouse contrast studies on renal blood flow, glomerular filtration rate, fractional plasma volume, fractional tubular volume, and urine formation rate. Then, Surti *et al.* [3] assessed the performance of a small animal 3D PET scanner. This micro-PET camera of an axial length of 11.9 cm can achieve a resolution of 1.9 mm and a sensitivity of 3.6% in the range of 250–665 KeV. For micro-SPECT imaging, Metzler *et al.* coupled a commercial triple-head SPECT scanner with pinhole collimation and external transport for high magnification and helical scan-

ning [4]. They used this cost-effective micro-SPECT system to image radio-labeled molecules in phantoms and animals with a spatial resolution of 1.6 mm. Goertzen *et al.* replaced the parallel hole collimators of a human SPECT scanner with a multi-pinhole collimator array [5]. Their approach allows a balance between resolution and sensitivity, and may be improved for dynamic *in vivo* imaging. Furthermore, Brzymialkiewicz *et al.* tested the Cadmium Zinc Telluride detector-based 3D emission mammotomography for breast cancer studies [6]. They estimated signal-to-noise ratio and lesion contrast with/without a torso phantom background. Their data show that the 3D mammotomography can reveal tumors of <1 cm in diameter. As far as optical imaging is concerned, Zacharakis *et al.* developed a fluorescent protein tomography scanner working at the visible wavelengths to image fluorescent proteins deep inside a small animal [7]. They adopted multi-angle multi-projection illumination and highly sensitive detection strategies. Image reconstruction was based on the diffusion equation modified to accommodate relatively high absorption, producing sub millimeter spatial resolution in phantoms and tissues.

In a broad sense, biomedical imaging means not only data acquisition and image reconstruction but also image processing and analysis. In the paper by Jan *et al.* [8], three imaging modalities, X-ray CT, PET, and SPECT, were combined to map functional/cellular/molecular images at low resolution onto the corresponding anatomy at high resolution for small animal studies. For both the micro-PET-CT fusion and the micro-PET-SPECT fusion, the maximum errors along three axes were generally less than 0.5 mm. On the other hand, Marias *et al.* studied registration of fluorescent image sequences for monitoring genomics and proteomics over time on the same small animal [9]. Their method was based on computed surface landmarks, and compensates for differences in the posture and compression/stretch of the subject. In another hot area of molecular imaging—micro-array image analysis, Blekas *et al.* described a statistical approach for mixture model analysis [10]. They devised a girding method to localize individual spots, and assumed a Gaussian mixture model to analyze these spots. Their methodology was evaluated using synthetic and real data in comparison with existing techniques. It seems quite effective, flexible, and robust. Finally, the cells, as building blocks of the life, are of particular interest. Image analysis in this area quantifies cell morphology, growth, motility, and responses to perturbation. In the paper by Dong *et al.* [11], the problem of counting rolling leukocytes was solved using intra-vital microscopy and computerized post-processing. They proposed “*the gradient inverse coefficient of variation*” and a Bayesian classification scheme to discriminate leukocytes from their environment with a detection accuracy of 78.6%.

Despite the impressive results published in this special issue and other peer journals, molecular imaging is still at its infancy.

To meet the requirements of individualized molecular medicine, current molecular imaging techniques must be dramatically improved in sensitivity, specificity, resolution, accuracy, and other indexes. Most importantly, issues specific to molecular imaging must be addressed using innovative ways, related to solution nonuniqueness, numerical instability, rather low signal-to-noise ratio, complicated heterogeneity and dynamic processes [12]–[14]. Although the future is difficult to predict, we believe promising research paradigms should involve novel probes, sensitive data acquisition, multi-modality multi-mode fusion, advanced reconstruction methods, prior knowledge based regularization, sophisticated image analysis, and/or optimized system integration. There is no doubt that molecular imaging will play an increasingly more important role in basic and clinical research. Toward that goal, we hope that more junior and established investigators will join us to advance this interdisciplinary field of unprecedented promises.

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Dr. Wang serves as Editor-in-Chief for the *International Journal of Biomedical Imaging*, and Associate Editor for IEEE TRANSACTIONS ON MEDICAL IMAGING and *Medical Physics*, among others. He is an AIMBE Fellow. He has been honored by the 1996 Hounsfield Award from Society of Computed Body Tomography and Magnetic Resonance, the 1997 Giovanni DiChiro Award for Outstanding Scientific Research from the *Journal of Computer Assisted Tomography*, the 1999 Medical Physics Travel Award from American Association of Physicists in Medicine, and the 2004 Herbert Stauffer Award for Outstanding Basic Science Paper in *Academic Radiology* from Association of University Radiologists.



Ronald J. Jaszczak (M'75–SM'91–F'93) received the B.S. degree with high honors in physics from the University of Florida, Gainesville, in 1964, ranking 4th in a class of 980. In 1968, he received the Ph.D. degree in nuclear physics from the same university.

He was awarded a U.S. Atomic Energy Commission Postdoctoral Fellowship at Oak Ridge National Laboratory in 1968 and remained in the Physics Division at ORNL as a Staff Physicist until 1971. He then joined the Research Department at Nuclear Chicago Corporation as a Principal Research Scientist and became Chief Scientist in 1977. In 1979, he was recruited to Duke University as an Associate Professor in the Department of Radiology. He is currently a Professor of Radiology and a Professor of Biomedical Engineering. He has contributed to the development of single photon emission computed tomography (SPECT) and is credited with coining the term SPECT. In 1981, he and his wife, Nancy, co-founded Data Spectrum Corporation, Hillsborough, NC, a leading manufacturer of quality assurance and research phantoms for the nuclear medical imaging community. He has authored or co-authored over 300 peer-reviewed journal articles,

conference proceedings and book chapters.

Dr. Jaszczak has held several appointed and elected positions on the NPSS Administrative Committee (AdCom) including, for example, NPSS President and V.P. He has served as an Associate Editor of IEEE TRANSACTIONS ON MEDICAL IMAGING. In 2000, he received the Paul C. Aebersold Award from the Society of Nuclear Medicine for his outstanding achievements in basic sciences applied to nuclear medicine.



James P. Basilion received the B.A. degree in biochemistry from the University of Pennsylvania, Philadelphia, in 1984, and entered the doctoral program at the Graduate School of Biomedical Sciences, University of Texas Health Science Center at Houston.

Following his graduate studies he took a Postdoctoral Fellowship at NIH-NICHD in the Cell Biology and Metabolism Branch. During his postdoctoral work he began a series of studies with investigators at the Center for Molecular Imaging at Massachusetts General Hospital (MGH) to exploit iron metabolism for molecular imaging. This work resulted in the creation of a transgene and magnetic resonance imaging probes suitable for imaging gene transfer and changes in endogenous levels of internalizing receptors *in vivo* both noninvasively and in real time with magnetic resonance imaging. In 1996, he left the NIH to take a position as a Senior Scientist at a small genomics/anti-cancer biotech company. In 1999, he joined the Faculty of Harvard Medical School and MGH as an Assistant Professor of Radiology. With the Director of the Center for Molecular Imaging, he formed the NFCR Center For Molecular Analysis and Imaging and has

been attempting to mine the rich genomic databases with an eye on informing molecular imaging technologies. Currently, he heads a small group of Ph.D.s and physicians that are attempting to identify informative markers and molecular signatures of disease and are developing imaging agents suitable to image simultaneous expression of multiple markers.

Dr. Basilion is a member of several societies, has held several offices in the Society for Molecular Imaging, has written numerous reviews on molecular imaging and genomics and holds editorships on three imaging or imaging related journals. In September 2005, he will join the Case Center for Imaging Research as an Associate Professor of Radiology and Biomedical Engineering at Case Western Reserve University.