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Frontiers of Biomedical Imaging Science 2009: Workshop Report and Research Opportunities

Thomas E. Yankeelov^{1,2,3,4,5,9}, **Malcolm J. Avison**^{1,2,6,9}, **Bruce M. Damon**^{1,2,3,8,9}, **H. Charles Manning**^{1,2,3,7,9}, **Todd E. Peterson**^{1,2,4,9}, and **John C. Gore**^{1,2,3,4,8,9}

¹Institute of Imaging Science

²Department of Radiology and Radiological Sciences

³Department of Biomedical Engineering

⁴Department of Physics and Astronomy

⁵Department of Cancer Biology

⁶Department of Neurology

⁷Department of Neurosurgery

⁸Department of Molecular Physiology and Biophysics

⁹Program in Chemical and Physical Biology

WORKSHOP GOALS

The second “Frontiers of Biomedical Imaging Science” conference was held at Vanderbilt University in Nashville, Tennessee from June 2nd – 5th, 2009. The impetus for the “Frontiers” conferences is that current specialized meetings focus mainly on a single modality, and/or disease entity, limiting the opportunities for cross-fertilization across different imaging methods and biomedical research areas. Furthermore, most conferences encourage short presentations of new research but do not synthesize these into clear presentations of the state of each field, and the meetings are usually so large that close interactions are not easy to foster. To make the “Frontiers” series of greater value, attendance is limited to 300 people, and the state-of-the-art of various sub-fields of biomedical imaging science are reviewed in a didactic fashion, along with future opportunities, so that experts in any one modality find the meeting informative. It is hoped that this design allows for imaging scientists from magnetic resonance imaging (MRI) and spectroscopy (MRS), optical imaging, computed tomography (CT), positron emission tomography (PET), single photon emission computed tomography (SPECT), and ultrasound (US) to connect and appreciate advances in other specialties. Focused and emerging applications of imaging are also selected for in depth coverage. In particular, the “Frontiers” conferences are excellent opportunities for trainees in imaging science to extend their knowledge, which otherwise can be difficult as trainees tend to be highly focused in specific areas.

The goals of the second “Frontiers” meeting were to provide a forum that cuts across imaging modalities to present the latest advances and specific applications of imaging science and to emphasize how imaging contributes not only to radiological diagnoses but also to novel insights into problems in biology and medicine. Towards this end, 27 speakers were invited to present

40 minute reviews of the 1) recent advances; 2) current state of the field; 3) anticipated advances and future opportunities in their area of expertise. Talks were grouped thematically within sessions to complement and build on each other, providing attendees with a comprehensive picture of each area.

MEETING SESSIONS

The first day was dedicated to advances in the physics and engineering aspects of Imaging Science, while the rest of the conference emphasized specific applications. The conference began with five presentations that covered advances in PET and PET/MRI (Simon Cherry, University of California, Davis, CA), CT and hybrid (SPECT/CT and PET/CT) imaging (Bernard Bendriem, Siemens Healthcare, Knoxville, TN), US (Gregg Trahey, Duke University, Durham, NC), MRI (Adam Anderson, Vanderbilt University, Nashville, TN), and optical imaging (Eva Sevick-Muraca, University of Texas Health Science Center, Houston, TX). Highlights of this session included Dr. Cherry's description of the latest advances in dedicated PET/MRI scanners, and the possibility of performing between-modality correlation to understand the physiological status of tissues more comprehensively. These were further illustrated by the survey of new commercial hybrid scanners presented by Dr. Bendriem. He concluded his presentation with recent efforts at improving PET resolution and sensitivity. Dr. Trahey stressed the recent developments in ultrasound technology that have led to its portability and subsequent possible applications at the bedside, in an ambulance, or remote locations. Dr. Anderson described the potential advantages and current limitations of MRI at 7T and above, and showed how the higher signal-to-noise ratio can be used to provide higher resolution images of the brain. Dr. Sevick-Muraca discussed advances in optical imaging applications in humans including her recent work in imaging the lymphatic system in breast cancer patients using optical agents already approved for human use.

The afternoon of the first day included sessions on Image Assessment and Perception and New Microscopies. Maryellen Giger (University of Chicago, Chicago, IL) discussed current approaches to computer assisted detection (CADe) and diagnosis (CADx) and stressed the need to move past morphologic evaluation and incorporate functional imaging techniques into CAD algorithms. Matt Kupinski (University of Arizona, Tuscon, AZ) and Philip Judy (Brigham and Women's Hospital, Boston, MA) described the theoretical and practical aspects of image perception and assessment. Niels de Jonge (Vanderbilt University, Nashville, TN and Oak Ridge National Laboratory, Oak Ridge, TN) and Warren Warren (Duke University, Durham, NC) concluded the first day with discussions on electron microscopy and nonlinear laser imaging, respectively. Dr. de Jonge began with an overview of electron microscopy (EM) before discussing EM on biological samples. In this last section he highlighted his work imaging whole eukaryotic cells in liquid using a flow cell with electron transparent windows and the use of aberration corrected scanning transmission electron microscopy (STEM). Dr. Warren concluded the session by discussing the use of nonlinear signatures to address the limitations of spatial resolution and molecular contrast using optical imaging.

Day Two included Imaging in Mental Health, Imaging in Diabetes, and a Young Investigators Symposium. Topics in the Mental Health session included the role of imaging in schizophrenia (Anissa Abi-Dargham, Columbia University, New York, NY), post-traumatic stress disorder (Douglas Bremner, Emory University, Atlanta, GA), developmental disorders (Bradley Peterson, Columbia University, New York, NY), depression (Wayne Drevets, National Institute of Mental Health, Bethesda, MD), and development (Jay Giedd, National Institute of Mental Health, Bethesda, MD). Using results from large cohort studies, Drs. Peterson and Giedd illustrated the importance of understanding the variable trajectories of brain development across regions within and across subjects, and how different regional disruptions provide insights into structure/function relationships in behavioral and psychiatric disorders.

Dr. Abi-Dargham showed how PET methods can interrogate specific molecular components of dopamine neurotransmission and reviewed current understanding of the role of dysregulated dopamine signaling in schizophrenia. Drs. Bremner and Drevets reviewed the central role of imaging in identifying the structural and functional correlates of depression and post-traumatic stress disorder.

Following the Young Investigators Symposium, Craig Malloy (University of Texas Southwestern Medical Center, Dallas, TX) reviewed the role of MR spectroscopy in characterizing the defects in muscle and liver metabolism associated with insulin resistance and diabetes. Alvin Powers (Vanderbilt University, Nashville, TN) reviewed the state of pancreatic islet cell imaging, highlighting the limitations of current methods, as well as opportunities in development. Gene-Jack Wang (Brookhaven National Laboratory, Brookhaven, NY) reviewed recent PET and fMRI findings that dopamine brain circuits associated with reward may have similar disruptions in obese subjects as those seen in drug abuse disorders, and showed how these data will be used to better understand the role of these brain circuits in normal feeding and their disruption in eating disorders and obesity.

The final day's session highlighted recent developments in "Imaging Cancer Biomarkers".

Many of the emerging anti-cancer therapeutics are directed against particular tumor cell signaling pathways. Consequently, measures such as the Response Evaluation Criteria in Solid Tumors (RECIST), which are based on unidimensional size changes (1), may not be the most appropriate method of assessing response. Furthermore, assessment of therapeutic efficacy is typically evaluated in terms of "clinical endpoints" which reflect long term outcomes such as how a patient feels, functions, or survives. What are required are indices of outcome that can be applied noninvasively and early in the course of therapy so that ineffective therapies can be changed. The ability to provide earlier indices of outcome is the goal in developing surrogate biomarkers that are intended to substitute for a clinical endpoint. The cancer imaging community has developed many such candidates for this task and Thomas Yankeelov (Vanderbilt University, Nashville, TN) began the session with a summary of emerging techniques that may potentially serve as biomarkers for assessing the early response of tumors to therapy. His talk addressed the state-of-the-art in physiological, metabolic and molecular imaging, including both qualitative and quantitative descriptions of methods. Physiological and metabolic imaging techniques included dynamic contrast enhanced MRI (DCE-MRI, 2), ^{18}F -fluorodeoxyglucose PET (FDG-PET, 3), and ^{18}F -fluoromisonidazole PET (FMISO-PET, 4). Imaging measurements reporting on cellularity and other features that were discussed included ^{18}F -fluorodeoxythymidine (FLT-PET, 5), diffusion weighted MRI (DW-MRI, 6), and Annexin-V SPECT (7). Dr. Yankeelov concluded with an introduction to tumor cell surface receptor imaging, which is useful in selecting therapy, as well as for monitoring treatment response.

Building on these ideas, David Mankoff (University of Washington, Seattle, WA) discussed, "Molecular Imaging of Cancer: From Clinical Trials to Clinical Practice". Using ^{18}F -Fluoroestradiol (8) as an illustrative example, Dr. Mankoff discussed the use of molecular imaging to select therapy and monitor pharmacodynamic changes as well as response. He also stressed the need for multi-site standardization and assessment of reproducibility of emerging imaging techniques so that they can be incorporated into clinical trials—a necessary step on the path to adoption in clinical practice. The National Cancer Institute, the Radiological Society of North America, the Society of Nuclear Medicine, and the American College of Radiologist Imaging Network all have programs addressing these issues.

Dr. Peter Choyke (National Cancer Institute, Bethesda, MD) reviewed the challenges of translating promising imaging approaches into clinical practice. Outlining the development of

a hypothetical new PET agent that has shown promising pre-clinical data, he pointed out that imaging can accelerate the drug development process by guiding combination therapies, as well as identifying candidate compounds, the most appropriate subjects, unexpected adverse events, and early responders. He provided an informative description of the many obstacles that must be overcome for a promising imaging technique to be adopted in radiological practice, including intellectual property protections and regulatory issues, as well as the cost and duration of all phases of clinical trials. Dr. Choyke also identified post-approval hurdles to adoption, including insurance companies', led by Medicare's, reluctance to approve an agent for reimbursement, and the frequently overlooked resistance of clinicians to changes in existing paradigms.

Robert Gillies (H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL) spoke about his work on glycolysis and tumor acidity (9). He discussed MR approaches for assessing tumor pH and metabolism, including ^{31}P and ^1H MRS, as well as pH-sensitive contrast agents. Dr. Gillies described how high glucose metabolism of tumors combined with poor perfusion leads to an acidic extracellular-interstitial pH of tumors, and suggested that this glycolytic phenotype, present from early phases of carcinogenesis, may reflect selection for cells that can change the local environment, leading to invasion and enhancing metastatic potential. He postulated that many tumors consume more glucose mainly to produce acid, not because it is needed for other energetic demands.

The cancer imaging session concluded with Daniel Vigneron's (University of California, San Francisco, CA) review of the rapidly evolving field of hyperpolarized MRS. MRS imaging (MRSI) can provide valuable information on tumor metabolic status, but its utility has been limited due to low sensitivity. With recent technical advances, it is now possible to dramatically increase the nuclear polarization for some species, and this "hyperpolarization" can increase the MR signal by five or six orders of magnitude. Hyperpolarized ^{13}C MRSI has shown promise for directly and rapidly observing metabolic processes *in vivo* (10). Dr. Vigneron discussed a number of pre-clinical studies showing elevated ^{13}C -lactate in primary and metastatic tumors following bolus administration of ^{13}C -pyruvate, and this higher lactate correlated with higher tumor grade. Dr. Vigneron also discussed the latest MR methods and coils that have been developed for pending first human studies in prostate cancer patients.

PERSPECTIVES AND OPPORTUNITIES IN BIOMEDICAL IMAGING

By the conclusion of the conference, several themes had emerged. The first is that the state of basic, translational and clinical imaging science is extraordinarily active. Tremendous progress is being made in the development of new imaging hardware, biologically relevant probes, computer assisted diagnosis and detection, image quantification, and biomedical applications. These advances will continue to push biomedical imaging past anatomical and morphological assessment to physiological, cellular, and molecular assessment of cancer. A second important theme that emerged is that methods of quantification must be improved and made reliable. For example, there is a mature literature on methods to quantify the data provided by FDG-PET; however, there is no consensus on how best to acquire such data or perform the subsequent analyses. For these methods to deliver on their promise and gain general acceptance, reliable and reproducible techniques are required. This is especially true for the more recent techniques described above.

It was noted on several occasions that since most diseases of interest are multi-factorial, no single imaging measure will suffice to answer all relevant questions, underscoring the importance of multi-parametric and multi-modality imaging. Thus, there is a need to develop intelligent methods for combining and integrating their data. This requires expertise from image processing (registration and segmentation) as well as statistical and mathematical

modeling. These developments and realizations have the potential to spawn a new sub-discipline, “image synthesis”. This becomes particularly relevant in light of Dr. Giger’s comments concerning the enormous volume of data that a radiologist must sort through to make a diagnosis. If a typical standard-of-care CT study produces a 500 image data set, what are the best ways to summarize a multi-parametric, multi-modality study that might produce several thousand images? As these data become more available, better methods to synthesize them will be required.

SUMMARY

The Second “Frontiers in Biomedical Imaging Science” highlighted recent advances and applications in state-of-the-art imaging science. By covering all modalities in selected areas of application, it fills a void within imaging not met by other meetings. The major themes to emerge from this meeting centered on the need to advance quantitative imaging biomarkers to a point at which they can be incorporated into multi-center trials. In particular, the view was expressed that there are critical needs for: 1) establishing reproducibility in existing and emerging imaging biomarkers, 2) new imaging targets and associated probes, 3) improvements in quantification methods, and 4) practical and intelligent integration of multiple imaging modalities. Furthermore, these methods must be advanced to provide reliable, “turn-key” techniques so that multi-center trials featuring advanced imaging can become a reality. The interested reader is encouraged to visit the web site for more information¹.

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