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Pharmaco-Imaging in Drug and Biologics Development

Fundamentals and Applications



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Brian R. Moyer: To my wife, Carol, who has been an ever-strong influence in my life to always produce excellence, to our daughters, Lauren and Alycia, who always know that the dinner conversation will take a strange twist when Dad talks “science,” to my parents Harold and Shirley, for the way of life they taught me, and, to my mentor in imaging, Dr. Thomas F. Budinger, who taught me the true art of “seeing” science and to really love the imaging world.

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Tom C.-C. Hu: To my wife, Vivian, for her understanding for numerous late evening writings, reviews, and evaluations. To our kids, Abigail and Joshua, for all the joys and blessings they bring to our lives. Being a parent is truly a humbling experience. To my family, Kuo-Chieh Hu, Mei-Tsen Li, Chih-Kao Hu, and Chih-Ching Hu for the unending support to my pursuit of scientific knowledge. To my mentors, Drs. Alan P. Koretsky, Chien Ho, Guy MacGowan, and Miguel Llinás,

Preface

Imaging sciences applied to medicine could be regarded as starting when the first histologic section was viewed or when Roentgen accidentally took a picture of his hand by interfering with photons hitting a photographic plate. In the 1990s applications of PCR in gene mapping along with novel methods and automated systems for protein expression helped define the molecular basis of several pathologies and has led to many new ideas on how to track, treat, and follow disease. The revolution in how we look at disease has now created a time where “Pharmacology, and indeed pathology itself, is *Visible*.” What do we mean by this statement? Alongside the development of such technologies as PCR and molecular biology revolution was another engineering and mathematics revolution, which when combined with the molecular biology advances has pushed the proverbial “Physician’s Black Bag” into a whole new tool chest that opens up diagnostic and therapeutic potentials we only thought was possible in science fiction a few short years ago.

In this new twenty-first century, we are witnessing the creation of an expanding “biomarker” library, tools to “see” pathology as a dynamic, i.e., as it is progressing in situ, and not simply under the microscope on histology slides, the ability to measure treatment responses in vivo and to give doctors as well as patients a way to understand what their disease is and how it is responding to therapy. Consider the ultrasound image that is now a common “souvenir” of a pregnancy. The image used to be a blur of sound echoes translated to an electronic display and printed on a recording film, and now, due to better understanding of sound wave physics, mathematical computations providing high-resolution electronic signals and translated into high-definition displays (or “maps”), we not only recognize “a fetus,” but the image created today introduces us to seeing a recognizable “brother or sister.”

The late 1900s saw the revolution of 2-D (photo-type imaging) to 3-D projection imaging. The ability to create “bread slicing,” otherwise known as “tomography,” or serial projections of the body has revolutionized and personalized medicine. One can use x-ray computed tomography (CT) for anatomy, positron emission tomography (PET) and single photon emission computed tomography (SPECT) for functional distribution of radiotracers, magnetic resonance imaging (MRI) and magnetic

resonance spectroscopy (MRS) for metabolic and very high resolution (near micron resolution) of the “state of water” (fixed in place or flowing plus “seeing” the chemical state) and even ultrasound to view internally as if we were actually there such that we can rotate about “inside” as if we are in situ ourselves. The utility of the human-sized instruments we use in the clinic applied to small animal research is, however, poorly translatable, impractical, as well as cost prohibitive. While pharmaceuticals are generally developed first from animal models to the eventual testing in the clinical subject or volunteer, imaging has recently reversed this path to head back to the laboratory to develop systems which are designed specifically, but with full clinical translational intent, for use in small animals.

Clinical development within “Pharma” (the collective pharmaceutical business) has fostered the need to miniaturize the practical imaging field for human to that useful for small mammals such as the mouse. Accomplishing technical reductions of human-sized imaging platforms to accommodate animal models has fostered, indeed required, technical advances in material and computational sciences. Novel new materials for scintillation detection has allowed for smaller platforms but indeed higher efficiency in photon capture. In nuclear medicine, smaller detectors and tight packing has led to very high resolution systems. Modern micro-electronics to improve signal separation, reduce signal cross-talk (i.e., random event errors, etc.), and high speed processor electronics for digital as well as analog computational activities, has allowed for very small animals to be imaged with very useful image quality. Computational improvements include complex algorithms which can collect and frame digital data, construct and statistically correct the image, translate to visual media (screen, film, digital, contrast variables, and signal intensity correction (isobar color pallets)). These platform improvements provide the investigator with highly sensitive analytical tools to witness drug actions in small animals. The utility of quantifying anatomic regions and volumes of interest (ROI and VOI, resp.) in serial image collections can provide for dynamic assessments (time variance of a signal) in the test system (animal model). One can also perform dual mode imaging, i.e. co-positioning of two imaging platforms, to collect, for example, anatomy with function (i.e. CT with PET, MRI with PET, etc.). Multi-platform imaging can provide the pharmacologist with a novel “view” of drug or biologic targeting and/or response over the course of an ever-changing landscape related to a pathophysiology.

MRI (magnetic resonance imaging), MRS (magnetic resonance spectroscopy imaging; imaging of metabolites), optical probes of luminescence (luciferase based) or fluorescence (Quantum Dots, near infrared (NIR), and BRET imaging (self-illuminating probes) are all adding to the novel drug development armament. Laser excitation of in vivo sites of optical probe uptake allows for small animals (e.g., nude mice with modest translucence due to thin skin and target-to-light distance is minimally interference by scatter), and excitation of a probe by an outside light source can make the localized probe emit a response light at a different wavelength for remote ex vivo detection. The internal scatter and reflectance within the animal body can be determined in a semi-quantitative manner to provide a scatter- and attenuation-corrected uptake value to compare against controls.

The advent of hundreds of new, highly specific, target-oriented animal models of disease has allowed us to optimize both the performance of imaging platforms as well as the opportunity to optimize the animal models. Imaging scientists now have the molecular biology revolution to help define diseases not through the microscope but through the visualization of a pathology's pharmacodynamics, i.e., tracking and localizing disease processes using patho-specific biomarkers, probes, and chemical state. The recent additions of optical imaging with self-illuminating quantum dots (QDs), the advances in the libraries of knockout/in animal models, chemical analytical methods now applied to autoradiographic as well as in vivo imaging (MALDI and SIMS-MS and MRS imaging), have all made small regional in vivo sampling possible. The drug development paradigm is now shifting from the formalism of the pharmacology and toxicology paths of the last century that has served us well to a potentially revolutionary path which will reduce animal usage and obtain time rate of change of biomarker and physiologic responses to drugs and biologics and create new interventional strategies.

This book is intended to be a contribution to the understanding of imaging as may be practically applied to the regulatory advancement of drugs and biologics. The enormity of the subject matter, the diversity of imaging platforms, and the daily addition of biomarkers and imaging agents makes this volume "out of date" as soon as it is published. However, we invite the reader to delve into this subject matter with imagination and to take the knowledge collected from this volume to apply these technologies toward the regulatory approvals of his or her own diagnostic or therapeutic products.

The book is for practical purposes divided into the specific platforms used currently in nonclinical imaging and especially as applied to drug and biologics development. That is, following a general introduction to the imaging platforms of nonclinical imaging (Moyer; Chap. 1) we describe the laboratory environment (Stout; Chap. 2) and practical setup considerations (Klaunberg and Morris; Chap. 3) that must be examined to establish a functional and economical asset to the company or academic laboratory for investigations into the pharmacology and toxicology of new chemical entities. In Chap. 4, we introduce the reader to a large Pharma company's philosophical and practical uses of imaging (Freedman). We step away from imaging per se in Chap. 5 for a short lesson on the concept of animal dosing and allometric considerations in imaging studies (Moyer). Solon and Moyer (Chap. 6) takes us through a very old but still highly applicable imaging technique called "autoradiography" and he introduces many new applications and analytical approaches using NIMS, MALDI, and MRS in tissue slice analyses. Chapter 7 (Bradley and Wyant) takes us to a favorite topic in the imaging world: Oncology. The authors provide examples of several animal models as well as inform on the limits of imaging oncology targets and measurement of therapeutic efficacy endpoints in small animal models. They have provided examples of molecularly engineered imaging probes (i.e. Mabs, etc.) and animal models that may potentially show target specificity losses from genetic change in the tumor or in the genetics of the host animal. Chapter 8 (Loutsios et al.) discusses the imaging of labeled cells and methods to maintain functionality with the perturbation of radiolabeling.

Golding and Zaitseva (Chap. 9) discuss the role of imaging in infections and their studies using bioluminescent technologies. Keith et al. (Chap. 10) introduce us to the very difficult work of imaging in the BSL3 and BSL-4 environments where pathogens must be controlled and imaging systems must be isolated for maintenance as well as operator protection. Moyer et al. (Chapter 11) take us through the physics of MR and how images are produced but more importantly the limitations of MR in resolution, time rates of change of any given pharmaceutical, contrast agent or biomarker, and the high signal requirements needed for quantitative imaging in small animals. Chapter 12 (Venter et al.) discusses the principles and technologies of magnetic resonance spectroscopy imaging (MRSI) and how we can image in situ a chemical entity's metabolomics as a consequence of disease or pathology. Lastly, we offer a regulatory chapter (Chap. 13, Moyer et al.) where we cite the regulatory implications of image sensitivity, specificity, quality and reproducibility, core laboratory image reading, image charters, receiver-operator characteristics (ROC) analysis of sensitivity and specificity of an imaging technique, and examine the regulatory guidance documents that are written mostly for the development of imaging agents and contract agents but where we are attempting to "turn the coin over" and examine the other approach, e.g., use known imaging agents that are functionally related to a pharmaceutical to advance that drug or biologic to their own regulatory approvals.

We invite you to read these chapters not as "facts to take back" to the laboratory but rather as "ideas to apply" to your own specific situation, your animal model and pathology and clinical indication that you are investigating. The primary goal of the book is to strip down the complexities of imaging (the physics, computational requirements, and limitations), the assortment of nuclear, optical, MR, and other probes that may be applicable, and the assessment of "practicality" in bringing an imaging platform (or more than one as in combined modalities, i.e., PET and CT) into your own laboratory setting. Imaging can offer so much "visibility" to pharmacology and we do believe imaging technologies will offer any investigator an actual vision or understanding of the pathology they are studying. Use of imaging should result in more defined pathways toward regulatory approvals. The future advancements and improvements in imaging systems that are expected in the next few years will certainly move drug and biologics development with even more "clarity of next steps" for more rapid drug or biologic advancement to approval.

To our imaging colleagues, respectfully.

Bedford, NH, USA
Hazelwood, MO, USA
Washington, DC, USA

Brian R. Moyer
Narayan P.S. Cheruvu
Tom C.-C. Hu

Quotes

“We are experiencing a paradigm shift from anatomic towards biomarker (molecular imaging) as the primary means for assessing treatment response in Oncology”

quote from Dr. Steven Larson, 2005.

“The source and center of all man’s creative power ... is his power of making images, or the power of imagination.”

Robert Collier, American motivational author, 1885–1950

“Logic will get you from A to B. Imagination will take you everywhere.”

Albert Einstein, American Physicist, Nobel Laureate 1921, 1879–1955

“You cannot depend on your eyes when your imagination is out of focus.”

Mark Twain, American Humorist, Author, 1835–1910

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