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OUR PANEL OF  
EXPERTS DISCUSS  
BLENDED MODELS



Charles River's Corporate Vice President, **WILLIAM BARBO**, and Director **PATRICK MCCONVILLE** discuss the benefits of preclinical imaging for the discovery process

# .future image



**D**espite being a relatively new technology, preclinical imaging has already begun to play an important role in research and drug development, and that role will only become more vital and more encompassing in the future. Depending on the modality and the study parameters, imaging has the potential to dramatically increase the efficiency of lead candidate selection by providing better quality and unique data. That is why Charles River has invested in becoming one of the few companies in North America to offer Quantitative Whole-Body Autoradioluminography (QWBA) as a tool for pharmaceutical clients to evaluate drug metabolism and pharmacokinetics. It is also why Charles River recently added the capability to offer clients the use of all of the major *in vivo* imaging modalities, including Magnetic Resonance Imaging (MRI), Computed Tomography (CT), Positron Emission Tomography (PET) and biophotonic imaging.

These tools can help better assess anatomy and disease morphology, physiological and functional parameters (e.g., blood flow and tissue oxygenation) and molecular and cellular processes (e.g., cellular proliferation, metabolism and metabolite levels). Preclinical imaging enables the most powerful and clinically translatable methods for monitoring disease progression currently possible. These imaging methods are also more easily applied than traditional methods in the newer, more realistic models of human disease that are becoming increasingly prevalent, such as models of invasive disease in the tissue

of origin, as well as transgenic mouse models. Imaging biomarkers and surrogate markers are rapidly becoming the most powerful methods that can be applied to drug discovery, drug development and clinical trials.

## MORE EFFICIENT

The increasing use of clinical imaging modalities has been attributed to efficiency. For example, by having an MRI or CT scan performed on a patient, a doctor can quickly receive trustworthy data to produce an accurate diagnosis and treatment plan, which in turn helps patients avoid the costs, both physical and fiscal, of undergoing and recovering from invasive exploratory surgery. In addition, the patient receives the benefit of starting treatment sooner, due to earlier detection and knowing quickly whether a given therapy is working. In clinical trials, early image-based indicators are being used increasingly for effective enrollment of patients or efficient switching of treatment paradigms, leading to enormous time and financial savings for the patient and the pharmaceutical company.

In the world of drug discovery, the efficiency benefits are analogous. One of the most important goals of a pharmaceutical company attempting to bring a product to market (as well as one of the most important mandates for a contract research organization) is to streamline the drug-discovery phase of its products. The more efficient the process, the quicker a company can invest resources into the most viable candidate without wasting them on

less promising compounds. Preclinical imaging is ideally suited to helping accomplish that goal.

For instance, the time benefits of imaging over surgery and terminal endpoints such as histology and *ex vivo* tissue biomarker analyses are substantial, due to significant reduction in the number of animals required to capture information at a set number of time points. Furthermore, preclinical imaging offers the capability, in many cases, to image multiple small animals at once, leading to an even higher throughput with a much lower time investment.

The focus on imaging endpoints in clinical trials further motivates the need for preclinical imaging as a tool for validating and optimizing imaging protocols used for a given agent or class of agents. By focusing on imaging earlier in a preclinical development program, the best-suited imaging biomarkers can be determined and validated, leading to tremendous increases in efficiency and cost savings in later-stage clinical development.

In addition, preclinical imaging allows for the combination of what have traditionally required separate cohorts/analyses to gather more data from a single study. For example, imaging modalities can be combined in a single study, or a single modality can be leveraged to obtain multiple physiological or functional parameters and endpoints, in addition to anatomical information. Increasingly, manufacturers are combining traditionally separate modalities, further facilitating this approach and optimizing the power and efficiency of each study.

For example, Charles River is routinely using combined MRI (e.g., tumor vascularity) and PET (e.g., metabolism and cellular proliferation) readouts to obtain the most powerful data for clients. The client then benefits by obtaining a powerful, multifaceted dataset from a single study that provides key information about the action of their drug at the functional level, in addition to traditional information for efficacy readout (e.g., tumor growth rate). This enables earlier and more informed decisions in the drug-development process and enables optimization of image-based biomarkers for use in concurrent or future clinical trials.

### MORE ACCURATE

The more realistic the models of disease, the better the quality of data that can be gathered from them, and the more effectively the possible effects of a compound or device can be known. Preclinical imaging can help achieve optimal use of those more realistic models in a variety of ways to provide more accurate and more unified data.

First, preclinical imaging helps provide a more comprehensive picture of the effect of therapy on a disease. Conventional methods of disease analysis run a greater risk of missing disease that has spread to unanticipated areas of the body or changed in ways that are difficult to physically observe without the use of exogenous markers in *ex vivo* analyses. With preclinical imaging, the entire body can be seen at once and disease can be visualized in its native state, mitigating the risk of overlooking certain results. Second, preclinical imaging allows the collection of data in real time, rather than after the fact through terminal endpoints. This provides the benefit of being able to observe the effect of therapy on a disease at the moment of most interest: its living, native state. Third, preclinical imaging permits researchers to follow a single animal over time to see how a disease changes. Without imaging, researchers are forced to sacrifice multiple animals at multiple time points to monitor disease progression. No matter how similar a group of rodents are assumed to be, they are still separate animals with unique biological characteristics that could distort or disharmonize data. Preclinical imaging allows the circumvention of that obstacle by measuring relevant endpoints in each animal over time. This also helps further the principles of humane care, as it reduces the number of animals necessary for a study.

An example where imaging provides greater accuracy is in metastasis models. There is increasing industry focus on preventing or treating

metastasis. However, metastasis models do not allow an accurate determination of the full extent of metastatic tumor burden using traditional life span or necropsy-based endpoints. Charles River is leveraging the power of optical imaging of reporter tumor cell lines in these models, which enables tracking of individual metastasis appearance and growth/response to treatment. In contrast, using traditional endpoints can limit accuracy, since survival may be coupled to tumors in non-relevant tissue sites, and necropsy may not reveal the full extent of tumor burden in a relevant tissue.

### UNIQUE DATA

Now that imaging technologies have evolved beyond the ability to reveal anatomy and can detect tissue function and molecular changes as well, preclinical imaging offers unique capabilities over more conventional testing and measurement methods.

For instance, dynamic contrast-enhanced (DCE) MRI is the only clinically proven method for quantitatively measuring the vascular permeability of a tumor. This is an important capability given the prevalence of vascular targets in a variety of diseases, including the widespread focus on anti-angiogenic and anti-vascular disrupting therapies in oncology. DCE MRI fills the need for a clinically translatable method for quantitatively determining vascular response to therapy. Preclinically, alternative methods to accomplish this largely rely on sacrificing animals and using invasive methods that can uncouple the readout from the disease property being measured, and therefore decrease the relevance of the data gleaned from it.

PET imaging is also becoming an increasing area of focus for drug discovery and development because of its unique capabilities. In oncology, the two most clinically relevant PET protocols involve use of fluorodeoxyglucose (FDG) for quantification of tissue metabolism and inflammation, and fluorothymidine (FLT) for quantification of cellular proliferation. PET is also playing a key role in quantifying receptor occupancy for new targeted therapies in several disease states. The future will bring a broad suite of new commercially available designer PET tracers, each a biomarker for a critical disease process. Many of these are already being used in clinical trials and preclinical studies.

These examples illustrate the ability of imaging to meet needs where traditional methods have not. Increasingly sophisticated imaging technologies, probes and biomarkers will further drive this uniqueness. Through imaging, researchers can obtain information *in vivo* that cannot be obtained in any other way. This is exactly why preclinical

imaging is necessary to accelerate the drug development process.

### THE FUTURE OF PRECLINICAL IMAGING

The future of preclinical imaging as a broadly employed technique is strong. In fact, the future of drug research and development is filled with tremendous potential for advancement because of the advent of preclinical imaging. Currently, imaging is used in almost every common human disease, and the development of increasingly sophisticated and powerful imaging protocols, technologies and tools is occurring at a rapid rate. While industry trends show reliance on preclinical imaging mostly in the later stages of the preclinical phase of drug development, imaging is increasingly being deployed earlier — saving time, money and effort on candidates that do not play out. This also helps ensure familiarity with image-based endpoints in a drug-discovery and development program, leading to its most optimal use and ultimate successful utilization in clinical translation.

One example of earlier deployment of imaging is *in vivo* biophotonic imaging (or bioluminescence imaging). In this modality, a luminescent protein or enzyme can be transfected into diseased cells that are then implanted into an animal or expressed in a transgenic animal. The light emitted from the implanted animal is then imaged. This can be used to track disease progression. In addition, expression of the light-emitting reporter can be tied to a conditional molecular process to enable imaging of the drug mechanism at the target level. This modality also allows the use of exogenous reporters that enable quantification of a molecular or cellular process. An increasing spectrum of these “smart” probes are becoming commercially available.

Biophotonic imaging also enables a high level of throughput, offers results in less than a minute, and can therefore be more cost-effective compared with modalities like MRI and PET. Furthermore, bioluminescence imaging can be conducted *in vitro*, before the use of animals. This allows screening assays to determine how cells react, so that more efficient judgments can be made before moving on to an *in vivo* stage, which again furthers a responsible approach to research from a humane-care point of view.

In summary, the opportunity for development and enhanced application of preclinical imaging is enormous because of its potential to increase the efficiency and accuracy of the discovery process. Technological advancements — such as the availability of multiple integrated modality imaging systems — will soon see preclinical imaging grow at unprecedented levels. **FP**