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Bridging the Preclinical - Clinical Divide in Translational Imaging: The Push, Pull and Pitfalls

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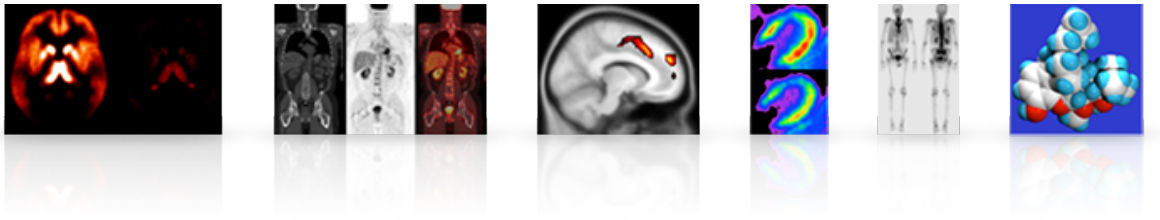

Introduction

The primary goal of translational imaging is to predict which new drug candidates will become the future blockbusters. A secondary goal is to tailor the use of newly approved drugs for individual patients using diagnostic biomarker imaging. Some believe, however, that the blockbuster epoch will be replaced by the advent of the 'niche busters' as the biological and molecular diversity of human disease is increasingly elucidated. Here, molecular imaging plays a role in defining the spectrum of relevant targets for drug development across therapeutic areas, for example serotonin receptor subtypes in depression or the diverse PI3K-AKT signaling pathway in cancer. Thus, extending the utility of imaging probes across the preclinical-clinical-diagnostic pathway should be a goal of biomarker and molecular imaging.

On average only 8% of new molecular entities (NMEs) make it to launch from the preclinical candidate selection stage, costing an average of $1.8 billion per NME (Paul et al., 2010). Since approximately 63% of the cost for each NME is spent in the clinical development phases I-III, improving the clinical success rate and reducing costs is a major goal. This low success rate is, in part, a result of efforts to develop new drugs for mechanistically novel targets. This is critical for the pharmaceutical industry, but the risks are significant. While experimental animal models are essential for the drug development process, direct extension to human patients is not always straightforward, especially for psychiatric and neurological indications where mechanistic understanding is incomplete. Thus, the limitations of preclinical imaging for transitioning new drug candidates should be carefully evaluated for each therapeutic area.

Quantitative modeling of the drug development process suggests a fine balance between the number of NMEs coming into clinical development and the clinical success likelihood of each NME (Paul et al., 2010). Optimal transitioning of new drug candidates from the preclinical pipeline to clinical testing and rapid recycling of the resources from failed drugs back into preclinical investigation is critical. Correspondingly, the lessons learned from phase I-III successes need to be quickly applied to ongoing preclinical discovery efforts. Quantitative de-risking of each NME preclinically and through the clinical development process is essential to manage a company's pipeline and to help ineffective drug candidates fail quickly.

Imaging Biomarkers

Imaging biomarkers have the greatest value when they can be extended from preclinical development to the clinical development stage, constantly and correctly advancing new drugs towards approval. Not all preclinical methods and imaging modalities can, however, be readily translated to clinical imaging. Two primary biomarker classes in active use today are the target and the disease biomarkers. The use of imaging biomarkers for toxicity testing is receiving increasing attention and as new drugs proceed through clinical testing, treatment-monitoring biomarkers become important. Significant preclinical imaging activity also takes place for new target discovery, target validation,

lead chemical optimization, etc., without the intent to translate the findings to clinical trials, but these uses will not be highlighted here.

Target engagement by the drug is a necessary, but not sufficient, condition for efficacy. Qualitative and quantitative drug targeting is an active use of molecular imaging for both preclinical and clinical development. Although much industry data are not readily available, the existence of organ and target bioavailability in animal models is generally a good indication that the same will be the case in human subjects. Differences in drug metabolism, however, may be a pitfall in generalizing animal targeting data to patients. Quantitative measures of drug targeting are also important in order to establish the drug dose for optimal target occupancy needed to achieve efficacy without untoward side effects. In this case, target imaging in human subjects is required due to well-established PKDM differences in animal models and human subjects.

What is the optimal time to initiate human target occupancy imaging studies? In most cases, studies are undertaken after complete safety data are obtained in phase I studies since drug doses leading to significant target occupancy are employed. An alternative is to initiate human targeting studies as part of phase I trials. In this manner, a targeting problem can be identified at the earliest stage of clinical development and lead to dose adjustments in the context of an adaptive trial design or early trial termination, in which case the trial resources could be rapidly re-channeled into ongoing preclinical development. This approach would be in accord with the economic model referenced above where resources are rapidly transitioned and back-transitioned in the preclinical-phase I space. Implementation of this strategy would require that an imaging agent is available or has been developed during phase 0 and is ready to be employed in the phase I safety trial. If a new imaging probe for a novel target needs to be developed and validated, sufficient time must be allocated in the development pipeline so that the probe is available at the time phase I studies commence. Fortunately, new FDA micro-dose and abbreviated IND mechanisms have shortened this timeline.

Disease-related imaging probes represent a larger and more diverse group, in large part because there are many ways to detect and monitor disease activity, whether by anatomic imaging, functional measures, or the molecular targets themselves. For example, in Alzheimer disease hippocampal atrophy, metabolic PET (^{18}F-FDG), and amyloid PET are available as disease biomarkers. In cancer imaging, CT and MR anatomic imaging, ^{18}F-FDG metabolic PET, ^{18}F -FLT DNA synthesis PET, and probes for many drug targets are available. An active area of current investigation is receptor tyrosine kinase (RTK) imaging (Tolmachev et al., 2010). RTK over expression in many malignancies mediates cell proliferation, suppression of apoptosis, and increased neovascularity. Accordingly, RTKs are active targets of drug development, using peptides and antibodies. Imaging RTKs can aid drug development, but also expand the personalized medicine space by selecting cancer patients for specific targeted therapies (Tolmachev et al., 2010).

Ongoing advances in small animal imaging hardware now permit multimodality CT, MR, PET, and SPECT animal imaging at increasingly high resolution and sensitivity. Thus, preclinical imaging technologies developed with these modalities can be readily extended

to clinical imaging at the appropriate time. For example, in the case of RTKs, multi-PET probe imaging of glucose metabolism, blood flow and VEGF binding in preclinical cancer xenograft models during sunitinib treatment has been developed (Nagengast et al., 2011). These results show that VEGF-PET imaging correlates with tumor growth and immunohistochemical vascular and tumor markers. Another example is preclinical SPECT imaging of the insulin-like growth factor 1 receptor (IGF-1R) (Cornelissen et al., 2008). The results demonstrate a correlation between the tumor uptake of 111In-IGF-1(E3R), IGF-1R density in breast cancer cell lines, and the resistance of these cell lines to trastuzumab. These approaches and the many other multiprobe, multimodality preclinical technologies using CT, MR, PET, and SPECT imaging can, in most cases, be readily extended to human clinical imaging as the preclinical models confirm targeting and anti-neoplastic properties of new drug candidates.

The same cannot be stated for other preclinical imaging technologies, such as optical, bioluminescence and fluorescence imaging, where human clinical imaging opportunities are very limited. Although these methods are clearly useful in the preclinical space and are less costly to set up and operate, their translational limits should be considered as new projects and programs are strategically evaluated. The lost opportunity from the inability to translate to clinical development or the added expense and loss time of developing a new clinical probe may be significant limitations for some programs.

Another factor to consider is the potential value of a new commercial diagnostic imaging agents that can be derived from clinical imaging research and development. A recent example of note is the purchase of Avid Radiopharmaceuticals for $800M by Lilly for Avid's amyloid imaging and other technologies. As personalized medicine grows and the dependence of individualized therapeutic strategies on molecular diagnostic imaging increases, the greater will be the diagnostic value and financial valuation of new molecular probes used in drug development.

Strengthening Preclinical-Clinical Translation Pathways

Molecular and biomarker imaging is most effective when used to efficiently "push" drugs candidates out of preclinical development and through the clinical development phases and then "pull" them and their resources back a function of the data at each development phase. As the Paul, et al model demonstrates, the primary drivers of high drug development costs are phase II and III attrition and therefore, biomarker imaging should be focused the factors that have been shown to be responsible for high phase II and III attrition for a given therapeutic area. Reducing phase II and III attrition through biomarker imaging requires a sustained effort as candidates migrate from preclinical to phase I investigation. Therefore, it is important to maintain continuity of the imaging technology over this period by ensuring a smart choice of the imaging modality and probe at the earliest preclinical time point. Managing and reducing cycle time within the development stages can be a key driver within the later phase attrition problem. As referenced above, biomarker imaging can reduce cycle time within each development stage by either terminating or accelerating trials as objective imaging data are obtained in

small subject groups, thus overcoming the limitations of large trials with purely clinical endpoints.

Clinical phase successes can also represent lessons learned for the preclinical space as validation of current approaches or as indicators for future improvements across probes, modalities and image analytics. At one major pharmaceutical company approximately 30% of the translational work is "back translation", feeding the knowledge from the clinic back to the discovery investigators for the next generation of drugs (Spinella, 2007). This model, of course, requires tight integration and communication between the preclinical and clinical domains of drug development.

Another factor is the number of compounds in preclinical development necessary to supply the clinical development path in order to have the requisite number of new launches per year (typically 2-5). Thus, it is important to not only to efficiently utilize imaging in the preclinical space, but also rapidly reinvest resources for terminated clinical development back into new preclinical imaging research. Key in this process is keeping costs down, particularly for expensive imaging technologies. Fortunately, preclinical imaging domestic and international outsourcing opportunities are increasing as the value of imaging is increasingly recognized and at the same time pharmaceutical companies migrate from the Fully Integrated Pharmaceutical Company (FIPCo) to the Fully Integrated Pharmaceutical Network (FIPNet) model. Clinical molecular imaging is much less developed at the CRO level, but some companies are beginning to migrate their business strategies from lucrative phase III, multi-site models to earlier phase studies that will better position pharmaceutical companies for successes in the efficacy trials.

The adequacy and validity of the experimental animal models used for preclinical imaging are key determinants for correctly advancing drugs into the clinic. For cancer and cancer imaging research there is a multitude of experimental animal models that have demonstrated high utility and predictability for new drug development. In contrast, in psychiatric disorders, were disease mechanisms are incompletely understood, clinical imaging is paramount. Nonetheless, development of animal models of psychiatric disorders, including depression and schizophrenia, continues to be pursued (Nestler and Hyman, 2010) and may offer new drug development opportunities. Nonhuman primate and mouse transgenic models of Alzheimer disease also have significant limitations. For example, mouse, beagle, and monkey models suffer from the fact, among others, that extant PET amyloid imaging probes bind poorly to brain amyloid in these models, likely due to differences in the structure and aggregation pattern compared to human amyloid (Delatour et al., 2010; Sur, C personal communication and presentation at 2010 World Pharmaceutical Congress).

As the drug development process is increasingly modeled from a quantitative economic standpoint, it will be increasingly important to estimate the likelihood of a positive set of preclinical imaging data predicting downstream efficacy. Here, back-translation will be important to better understand the false positive rate of advancing drug candidates based on preclinical imaging results. The quality of the preclinical model will also determine

the amount of time and resources dedicated to preclinical imaging versus proceeding quickly to early-stage clinical imaging. In the absence of exquisite communication and information sharing between preclinical and clinical investigators, too many resources and too much time may be dedicated to preclinical imaging and a significant opportunity cost within the clinical imaging domain. Inadequate internal attention to creating a strategy for seamless transition between preclinical and clinical imaging, and the higher cost of clinical imaging studies may also be barriers. The more favorable regulatory environment for new imaging probes and the expanding availability of new technologies for rapid synthesis and testing of new probes argues strongly for early-stage expansion of clinical imaging and diminished preclinical resource allocation where animal models are limited.

Conclusions

Molecular and biomarker imaging continues to play an active and even vital role in accelerating drug development and reducing associated costs. Although imaging is a complex and costly technology itself, drug development economics creates a strong case for further implementation in order to reduce phase II-III attrition, reduce cycle time, right size the preclinical pipeline, maximize technical success, and increase value. A seamless integration of imaging technologies across the preclinical-clinical-diagnostic divide creates maximum long-term value, but careful planning and deep insight are needed to take full advantage of the benefits of imaging in the areas of discovery, safety testing, drug targeting, molecular disease mechanisms, personalized medicine, and treatment monitoring. Fortunately, improvements in the regulatory environment, enhanced CRO service offerings, outsourcing opportunities, imaging technologies, pre-competitive industry collaboration, economic insight, and broadened education are strengthening the bridge to lower cost and higher value pharmaceuticals.

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