

# ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

Section Editor: Mark J. Ratain, MD

## Imaging in Drug Development

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### H&O How has the role of imaging in drug development changed in recent years?

**EA** The role of imaging in drug development has come a long way. Not long ago, imaging was considered by many to be mainly a decorative technology for drug development programs. Over the past few years, the potential contribution of imaging modalities such as magnetic resonance imaging (MRI) and positron emission tomography (PET) in drug development has become clearer, changing the perspective of many industry and academic researchers regarding their use. Currently, imaging is viewed as a key component to decision-making in drug development.

### H&O How was imaging initially used in drug development?

**EA** Some of the initial work involved microdosing. A drug was administered at very low levels, below 1/100th of the starting phase I dose. This microdosing enabled the biodistribution of a compound to be determined very early in the drug development process, answering certain questions that arise whenever a drug transitions from animal models to the clinical setting. This was one of the earliest uses of imaging, from a pharmacokinetic (PK) perspective.

From a pharmacodynamic perspective, imaging has always been part of clinical trials, particularly computed tomography (CT). More recently, PET has been implemented with increasing frequency. The use of fluorodeoxyglucose (FDG)-PET in the study of imatinib mesylate (Gleevec, Novartis) is a good example of the usefulness of imaging in drug development.

### H&O Could you describe this example?

**EA** FDG-PET scans were taken during the initial stages of the clinical trial process, some within 24 hours after imatinib dosing, and others at 8 days after dosing. In both cases, a dramatic reduction in FDG uptake was observed. One study found that most patients who showed early reductions in tumor FDG uptake also showed responses to treatment on CT scans taken approximately 8 weeks later.<sup>1,2</sup> These findings had an early impact in terms of knowing whether the drug was hitting its intended target.

The studies also highlighted the potential role of FDG-PET imaging in drug development. Of relevance to drug development, other types of PET studies are worth mentioning. First, demonstration that the test-retest reproducibility of FDG-PET in tumors was within 10% in imaging studies that preceded imatinib<sup>3</sup> allowed definition of the cut-off for metabolic response. Furthermore, studies in other settings at 2 weeks into treatment, and after the first or second cycles of chemotherapy or chemoradiotherapy have demonstrated that patients who show a reduction of tumor FDG uptake after treatment usually have a survival benefit.<sup>4</sup> However, the imatinib trials brought PET to the forefront in terms of drug development.

### H&O What is the exact information that imaging contributes to the drug development process?

**EA** In general, there are two main aspects to this contribution.<sup>5</sup> The first aspect pertains to PK and biodistribution. The drug of interest is radiolabeled and its distribution is followed throughout the body. It is possible to measure how much of the drug reaches the tumor and how much enters the heart, for example, where it could cause toxicity.<sup>6</sup> Such studies are allowed by the regulatory agencies, as they have the potential to aid optimization of a drug's pharmacologic properties prior to large clinical trials; see for instance the US Food & Drug Administration's guidance on exploratory IND applications.<sup>7</sup>

Another aspect pertains to their use as biomarkers. Here, the imaging probe is radiolabeled and is used to track modulation of a particular target or cognate biochemical

processes. This approach provides information on whether the target is being inhibited and to what extent, as well as how quickly the target recovers, if at all.

These are the two main uses of imaging in drug development. Together with profiling patients for a particular target, these data create the so-called pharmacologic audit trail, constituting a very rational approach to drug development.<sup>8</sup>

### **H&O** How does FDG-PET work in terms of drug development?

**EA** FDG is a glucose analog that is taken up via glucose transporters into the cell, where it is phosphorylated by hexokinase. Most tumors express high levels of glucose transporters together with high activities of hexokinase, and would therefore show high levels of FDG uptake. The generally accepted hypothesis is that most anticancer drugs decrease FDG uptake because of a reduction in cell viability through, for instance, increased cell kill or cell-cycle blockade. It is becoming increasingly clear that another mechanism exists that involves direct targeting of the glucose uptake mechanism. For example, it has been postulated that P13 kinase inhibitors might target the glucose uptake mechanism directly, and it has been demonstrated that imatinib does so.<sup>9,10</sup> As with imatinib, administration of active doses of this latter class of compounds is likely to cause a rapid reduction in tumor FDG because of direct targeting of the glucose uptake mechanism. With both classes of compounds—those that target the glucose uptake mechanism directly and those that inhibit proliferation or induce apoptosis—it is possible to see an effect on FDG uptake, usually 1–4 weeks after commencing treatment.

There is one caveat though: inflammatory response can confound FDG-PET measurements. For instance, when macrophages infiltrate tumors after therapy, there may be an anomalous increased uptake of FDG. This situation has led researchers to search for alternative approaches to using FDG-PET. Probes for imaging proliferation and apoptosis avoid this potential problem.

### **H&O** How is proliferation imaged?

**EA** This is one of the most rapidly developing areas in PET imaging. Much work has been done with carbon-11–radiolabeled thymidine, a natural compound that is taken up by the classical nucleoside transporter and then phosphorylated and incorporated into DNA. By this method, it was possible to examine response by measuring the changes in thymidine uptake. Because carbon-11–radiolabeled thymidine is rapidly metabolized in vivo, there are limitations to this approach.

A new analog of thymidine, fluorothymidine (FLT; Figure 1), was developed,<sup>12</sup> which is a more metabolically stable probe for imaging proliferation. The mechanisms of uptake are slightly different from those of thymidine, but the method is fairly similar in that the probe enables measurement of the initial process of thymidine incorporation into the cell.

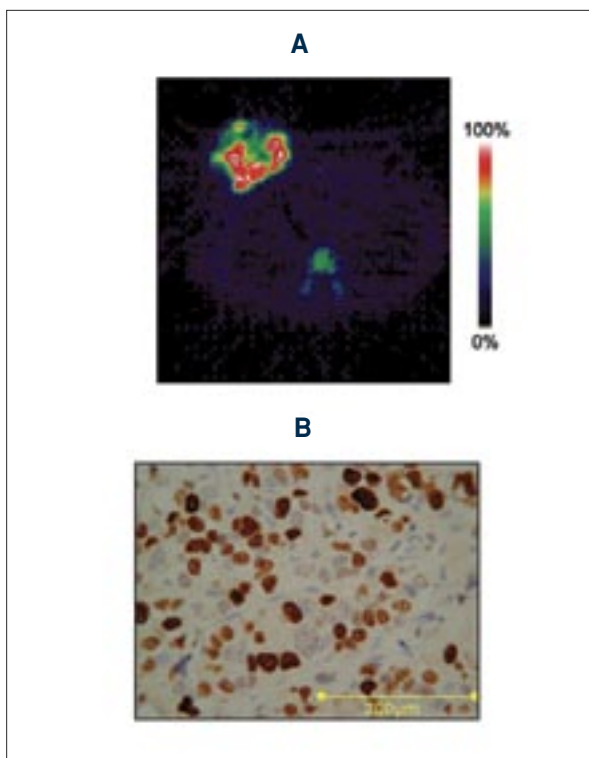
More recently, our group and others have been evaluating the utility of FLT for monitoring the effects of different compounds, including cytotoxic agents as well as some of the newer molecular therapeutics that have been developed, such as histone deacetylase inhibitors and receptor tyrosine kinase inhibitors. Preclinical studies are showing that FLT can be used to measure changes in proliferation that occur with treatment.<sup>13–15</sup> This approach may become a very important use of PET technology because it enables imaging of one of the key biologic pathways for drug response.

There are several other intriguing endpoints for which PET probes are being designed, including apoptosis, choline metabolism, and angiogenesis-regulated cell surface receptors. Existing probes are also being used in new trial designs to inform drug development. For instance, measuring blood flow with oxygen-15–radiolabeled water has shown some interesting results in the early clinical development of the antivascular agent combretastatin A4.<sup>11</sup> These techniques, in which one can study not just the overall toxicity of a compound but the actual direct effect on a target, have much to offer to the drug development process.

### **H&O** What other types of imaging have a role in drug development?

**EA** There are a number of other types of imaging. The use of CT scans to provide anatomic information is standard practice.<sup>16</sup> Now, new contrasts are available for CT that enable evaluation of tumor perfusion,<sup>17</sup> key data in the development of antiangiogenic agents. In addition, new methods for ultrasound, including ultrasound with microbubble contrast agents that enable measurement of blood flow are being developed; again, this technique could be very useful in the development of angiogenesis inhibitors and is likely to be cheaper than most of the other technologies.

A number of advances are being made with MR. Dynamic contrast-enhanced MRI is often used to study blood flow, blood perfusion, and permeability. These measures are all useful to the development of antiangiogenic and antivascular therapies.<sup>19</sup> MR spectroscopy can be employed to study tumor drug pharmacokinetics directly or to study response using proton MR spectroscopy or phosphorus MR spectroscopy.<sup>8</sup> These modalities



**Figure 1.** Imaging of cell proliferation by positron emission tomography (PET). (A) Transverse section of  $^{18}\text{F}$ -fluorothymidine PET image of a patient with grade III ductal carcinoma showing right-sided breast carcinoma with high uptake around the periphery. (B) Corresponding Ki-67 immunostain (45.2% labeling index). Such quantitative images can be performed before and during treatment to assess the efficacy of novel therapies.

have been used in a number of clinical trials to measure response and drug kinetics.

## H&O What is the potential effect of imaging on the drug development process?

**EA** Imaging can enhance the rational selection of the dose or schedule and can aid in the go/no-go decision-making process. Overall, it should reduce the attrition rate and improve our ability to select phase II doses. Many pharmaceutical companies have now integrated imaging into their drug development process. In general, it is thought that this approach will increase the cost effectiveness of drug development.

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