

# Advances in Drug Development

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*Current Developments in Oncology Drug Research*

## Imaging in Drug Development

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### **What benefit does imaging offer in the process of drug development?**

The idea behind employing imaging in drug development research is to find out early in the research process whether an agent is having a measurable effect on the biologic endpoint. Some of the techniques now available, such as dynamic contrast magnetic resonance imaging (MRI), offer measurements that cannot be obtained as effectively in any other way.

### **Why are surrogate markers needed in drug development research?**

Many of the compounds now being developed are not going to lead to tumor shrinkage; the best response may in fact be stable disease. While pure antivasular and antiangiogenic agents might be effective against new vessels, there might be little effect against inducing blood vessels. However, it would still be important to quantify any effect on the vasculature, be it on blood flow, the leaking of molecules, vessel permeability, or some other surrogate feature. Imaging provides an alternative to biopsy, which is fraught with problems. Because tumors are so heterogeneous, a biopsy will yield different findings depending on the location. In addition, biopsy is an invasive technique, which has obvious disadvantages. Imaging provides a picture of the entire tumor, and can enable identification of tumor sites that might be useful for biopsying. Imaging also provides a measure of blood flow and volume, and there are a number of imaging techniques available for this purpose.

### **What are the potential drawbacks of using imaging to measure surrogate markers?**

The challenge with using imaging in this setting is that there are often not enough patients to validate the findings, and also the results are not as useful when disease is stabilized. In other words, if a tumor shrinks as a result of treatment, imaging will show this change fairly early on, but if a tumor remains stable, it is difficult to know whether this is due to the agent or whether the tumor would have stabilized without treatment.

### **What is dynamic computed tomography?**

Dynamic computed tomography, or dynamic contrast MRI, as it is sometimes called, uses a high molecular weight contrast

agent that is radio opaque. This technique does not measure blood flow directly but enables an investigator to extrapolate blood flow from nuclear magnetic imaging. The contrast is followed through the blood and is visible through the vessels.

### **In what situations would positron emission tomography be the appropriate imaging modality?**

Positron emission tomography (PET) is the gold standard for measuring blood flow and would be applicable in most situations.

### **Is 3-dimensional ultrasound useful in drug development research?**

Blood flow can be measured with ultrasound, but because this is a surface probe, it is useful only if the blood vessel through which flow is being imaged is close to the surface. This modality is useful but needs to be very close to the target area with nothing in the way. Ultrasound may be most appropriate for studying surface tumors, and perhaps liver lesions, which are measurable through the skin.

### **How is laser scanning cytometry used alongside imaging?**

While imaging is useful to measure blood flow, the findings need to be validated with tissue. With laser scanning cytometry, a biopsy could be taken and stained for different immunocytochemical markers. For example, blood vessels might be given one colored marker and dying cells another. Then, a double-labeled overlay could be done in order to count populations of cells.

### **Are different imaging modalities appropriate for different types of targeted agents?**

Yes. The choice of imaging depends upon what pathway is being targeted. For example, if an agent were working directly on the tumor cell, affecting tumor cycling and metabolism, then fluorodeoxyglucose PET, which is metabolic, would be an appropriate imaging modality to use. For a vascular endothelial growth factor inhibitor, since these agents affect permeability and flow, a contrast MRI would be an effective approach. For a more obscure angiogenesis blood flow inhibitor, PET might be the most appropriate choice of imaging modality. Overall,

the imaging modality should be selected in accordance with the effect that one wants to measure.

### **With the current direction of drug development in oncology, is imaging becoming more important?**

Absolutely. Drug development is such an exciting area, and many agents are being studied. However, patient numbers are limited, as are resources. Therefore, it is important to find some way to choose which agents to move forward in the development process. Imaging is a necessary part of this selection process.

### **Is the technology keeping up with the need for effective imaging modalities?**

Yes, the technology is current with the need. Companies such as General Electric and Amersham are working to develop new tracers and compounds to better assess the various factors for which these imaging modalities are such effective tools.

### **Are clinical oncologists becoming more skilled at reading images?**

Yes, they are. Most people are still not familiar with dynamic contrast MRI or with using PET scanning to study blood flow. However, PET scanning for measuring metabolism is becoming a major technique and is being used for diagnosis in many different disease settings, including lung cancer and

head and neck cancer. Most cancer centers now have PET scanners. While most centers do not have a cyclotron beneath the building where radioactive isotopes can be generated, precluding use of  $^{15}\text{O}$ , for example, there are techniques using more long-lived tracers that can be produced off site and shipped to the center overnight. It's likely that imaging will become more commonplace over the next few years.

### **In what other settings is imaging being explored?**

One of the major questions right now with imaging is whether it can be used to guide treatment, to help determine which patients should receive which drugs. Everything spoken about above pertains to imaging as a research tool. But can it be used as a diagnostic tool or to help select the most appropriate treatment approach? This will be the next big step for imaging.

### **Suggested Reading**

Davis DW, McConkey DJ, Abbruzzese JL, Herbst RS. Surrogate markers in antiangiogenic clinical trials. *Br J Cancer*. 2003;89:8-14.

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