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DRUG DISCOVERY & DEVELOPMENT

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In Vivo Imaging Technologies in Drug Research

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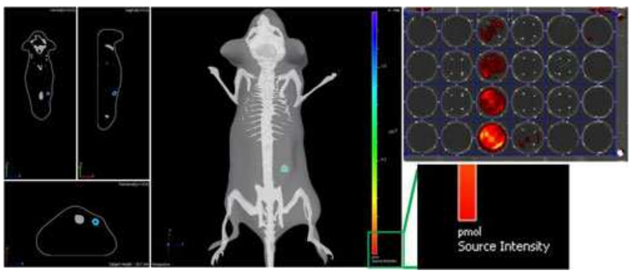


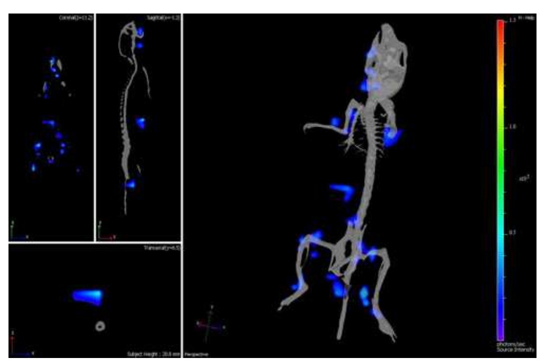
Measurement of fluorescent dye concentration in a 3D tumor model.

In vivo imaging technologies provide insight into all stages of the drug development process from target identification to the optimization of clinical trials. By looking at disease processes and monitoring therapeutic effects in the living animal, researchers are able to unravel the complex biological events in real time and repeatedly image the same animals in a longitudinal study, providing a high level of statistical significance while sacrificing fewer animals. Drug developers are using optical imaging modalities throughout the development pipeline to reduce costs, increase efficiency, and obtain deeper insight into the mode of action.

Optical imaging technology

The equipment for optical imaging includes an ultra-sensitive large-format camera to detect low light emissions, a low f-number lens, and high efficiency filters to maximize the available signal. A temperature-controlled stage with anesthesia manifolds minimizes animal disturbance during the imaging process.

Ideally, a back-thinned CCD cooled to -90°C is used to reduce the background and provide maximum signal to noise. For quantitative measurements, a calibrated system is necessary for a longitudinal study when the software must correct for aperture and exposure time to establish absolute units. Tomographic methods are used to localize the signal in three dimensions and provide reconstructions that can be co-registered with CT, MRI, or other imaging techniques.


Bioluminescent cells tracking to lymph nodes in a leukemia model.

An optical imaging system should capture fluorescent or bioluminescent signals in 2D or 3D and may combine other features such as X-ray or kinetic data capture for dynamic imaging.

At its best, optical imaging uses a combination of fluorescent and bioluminescent reporters to provide sensitive and quantitative monitoring of disease progression and therapeutic response. The results are achieved non-invasively, in real time, and multiple animals can be imaged at once without exposing them to harmful radiation.

Bioluminescence imaging of lung metastases. (All images: Caliper Life Sciences)

Fluorescence is used to visualize cells, to analyze compound biodistribution, and to tag a variety of specific probes. With spectral unmixing, multiple fluorescent signals can be resolved and quantified in a single animal. Bioluminescent labels are used to track active cells or monitor gene expression. Bioluminescence can be extremely sensitive for cell detection. Used to track the progress of infectious agents it can reveal reservoirs of residual disease and it show tumor metastases at the earliest stage of development in lymph nodes or bones.

Examples in Drug Development

Optical imaging is used in all therapeutic areas, and can be applied at multiple steps in the development process. **Cubist** used optical imaging to demonstrate bactericidal activity in a peritonitis model during the development of Daptomycin. **Pfizer** used imaging in the development of Sutent to demonstrate anti-tumor activity and explored a variety of orthotopic and sub-cutaneous tumor models. For **Novartis**, optical imaging provided the tools to explore an ovarian cancer model for AEE-788 and multiple myeloma for CHIR51. And **Abbott** recently published information on ABT-888, a new cancer drug going into clinical trials, in which the optical data co-registered with X-ray.

Optical imaging can provide mechanistic insight into the mode of action to inform decision making in drug development. Co-registering optical data with traditional imaging modalities like CT provides the final translational step to the clinic. Whole animal imaging using optical reporters is gaining acceptance in all therapeutic areas as new reporters and imaging probes add to the repertoire of assays.

References

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