



Introduction to Technological and Multimodal Advances in Preclinical PET Imaging

Introduction

Preclinical PET imaging provides valuable insights into neurology, cardiology and metabolic disease and offers options for *in vivo* visualization of disease processes over time. Developments in instrumentation and reporters have resulted in imaging systems with increased potential for basic research, as well as for translational and clinical applications. In addition, more sophisticated models are now available to address a range of research and therapeutic questions.

Preclinical PET imaging produces quantitative, spatially and temporally indexed information on normal and diseased tissues. Importantly, because of the non-invasive nature of the technique, imaging allows longitudinal (serial) study of animal models of human disease. This allows monitoring of disease from inception to progression, as well as of treatment options over a period of time. Each animal acts as its own control, reducing biovariability. Not only does this minimize the number of experimental animals required, it also gives results in real time, reducing the need for expensive and labor intensive histology. Moreover, in contrast to cell or tissue culture based experiments, studies in intact animals incorporate the interacting physiological factors present in a complex living system.

Evolution of Preclinical PET Imaging

Each of the common preclinical modalities (i.e. PET, SPECT, Optical, CT, and MR) offer distinct advantages, but arguably PET imaging is at the forefront of the revolution in functional imaging with direct potential for clinical translation. This is, in

part, due to its ability to evaluate and quantify changes in drug biodistribution and pharmacokinetics, amongst others, which aid the assessment of drug efficacy^[1]. The depth of imaging available by PET is another key strength of this technique, together with excellent temporal resolution^[2]. In addition to these benefits, PET imaging is extremely sensitive to molecular details. PET imaging systems are becoming increasingly advanced and affordable, and multimodal imaging systems are now commonly found in large research laboratories, with functional modalities frequently combined with anatomical modalities for context.

Initially using clinical-scale instrumentation, imaging provided a non-invasive means of assaying biological structure and function *in vivo*. The development of dedicated small animal imaging systems followed and, more recently, techniques in molecular imaging have been established to allow imaging modalities to be combined into multi-modal methods. Among these, the combination of positron emission tomography (PET) and computed tomography (CT) is a successful imaging strategy and has become an important tool in clinical practice. Technological approaches that combine magnetic resonance imaging (MRI), optical modalities, and PET have now been introduced. PET/MRI and the resulting combination of molecular, morphological and functional information will pave the way for a better understanding of physiological and disease mechanisms in the preclinical setting.

However, PET imaging is not without limitations, even with these advanced systems. Many available systems lack good spatial resolution^[3]. Small anatomical structures cannot be distinguished or accurately analyzed with low resolution PET.

Additionally, PET imaging lacks anatomical context.

Technological advances have emerged to tackle these limitations, bringing significant improvements to the resolution issues faced by researchers. Using instruments that utilize innovative crystal technology and high sensitivity detectors, researchers can now obtain complete Full Field of View Accuracy (FFVA), which offers precise, homogenous sub-millimeter volumetric PET resolution in all three axes across the whole field of view. The latest breakthrough in PET detector technology enables rings to be located in-line with either MRI or CT, a design which also supports integrated PET and MR imaging. Advanced depth-of-interaction (DOI) detection enables precise 3D localization of events without the constraint of having to work with conventional crystals configured in discrete layers. The result is the generation of an area of optimum resolution up to 10 times larger than conventional systems, providing unprecedented clarity.

cryogen-free magnet, and incorporate functions such as diffusion weighted imaging (DWI) that can be included into preclinical studies. These technology combinations are being applied in a number of clinical areas including oncology, neurology, cardiology and metabolic disease. In addition to cross-platform methodologies, integrated PET/MR solutions are employed to streamline workflows.

Conclusion

There are considerable benefits of preclinical PET imaging – aiding researchers as they seek to translate their work from *in vivo* models into the clinical situation. The sub-millimeter spatial resolution now available is a key improvement, which will allow researchers to produce much higher quality images



Figure 1. Integrated preclinical PET imaging systems employing sub-millimeter resolution and Full Field of View Accuracy. A) Bruker Albira Si PET/SPECT/CT system. B) Bruker PET/MR 3T system.

This new technology has been successfully implemented into a tri-modal PET/SPECT/CT imaging system, and a bi-modal PET/MR system (Figure 1). Moreover, there is now the ability to transport a sedated subject to another instrument for further functional and/or anatomical study, for example to an MR, microCT, or Optical system. The use of multimodal animal beds removes any requirement to disturb the animal during study. This accurate positioning facilitates the layering of the three images to provide better understanding of the molecular mechanism or interaction of interest, with a correct anatomical reference. A further layer of imaging can therefore be added to the molecular visualizations achieved, with intelligent software ensuring precise automatic co-registration of images.

There is growing interest in combining PET imaging with MRI in this manner, as MRI provides superior soft tissue contrast, one of the key challenges for PET imaging. MRI techniques have also advanced with developments including a new 3T

for analysis. This is particularly valuable for scientists looking at small anatomical features.

In addition, the introduction of a multimodal animal platform allows for considerably better image co-registration when using cross-platform imaging protocols. This again, adds significantly to the quality of data now available. There are further benefits in cross-platform imaging; it maximizes access to equipment, and has the potential to minimize down-time for maintenance. But perhaps most importantly – given that all-modality imaging systems are not currently available – is how the developments described here, that allow full integration of all modality combinations, are advancing the state of the art and bringing more powerful data to the research community.

References

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