Preclinical Imaging Services

Of the 160 exhibitors in Baltimore, 12 mentioned “preclinical imaging” and/or “small animal instrumentation” as important components of their business service descriptions. Some of these companies (inviiCRO [Boston, MA], IsoTherapeutics Group [Angleton, TX], MPI Research [Mattawan, MI]) can be seen as CROs (an abbreviation that flexibly covers either clinical or contract research organizations) that conduct animal imaging and analysis using mostly established imaging techniques to evaluate new radiotracers or therapy candidates. Their research quantitatively measures target uptakes, background clearances, and standardized uptake values in rodents and nonhuman primates in a quest for the next generation of drugs. More advanced studies by these CROs can also evaluate potential therapies by comparing diseased animal controls with groups receiving therapy agents. Promising results in these animal studies can transition into human studies that lead to new advances in clinical care.

This preclinical arena has seen recent activity in mergers and establishment of new companies. Last year, PerkinElmer, Inc. (Waltham, MA) and Sofie BioSciences (Culver City, CA) entered a partnership in which PerkinElmer will commercialize and sell preclinical small animal imaging scanners. Since its incorporation in 2008, Sofie BioSciences has combined new PET imaging agents with imaging and synthesis systems to provide researchers and physicians with tools to investigate the biology of disease. PerkinElmer is a global company and has reported annual revenue of more than $2 billion. This company has about 7,600 employees in more than 150 countries and is a component of the S&P 500 Index. Their venture into small animal imaging shows that this sector is attracting investment interest and has a strong business future.

Cubresa Inc. (Winnipeg, Canada) markets SPECT and PET scanners that can be integrated into existing preclinical CT and MR systems. Their MR-compatible small animal PET insert can be used for simultaneous PET and MR imaging in existing MR scanners. They emphasize the challenges of sequential imaging in meaningful analysis of functional data in animal studies. Cubresa is targeting researchers at hospitals, universities, and pharmaceutical companies to use their instrumentation for drug discovery, understanding diseases, and investigating new potential therapies.

Sedecal (Algete, Spain) offers integrated PET/CT and PET/MR scanners. It is interesting to note that their 1.5T/3T MR scanner operates cryogen-free.

Mediso Medical Imaging Systems (Budapest, Hungary) offers a combination of dedicated animal imaging scanners as well as multiple-headed clinical cameras for use in hospital-based nuclear medicine departments.

New Modality Development for Small Animal Imaging

Another subgroup of these 12 companies develops new imaging methods as part of services to radiopharmaceutical companies and potentially to instrumentation manufacturers. They develop and test new instrumentation and modalities in a preclinical environment, with the hope that these may prove to be applicable in human studies. TriFoil Imaging (Chatsworth, CA) is in its second year of operation and is a merger of companies with 10 years of SPECT clinical instrumentation (Bioscan, Inc. [Washington, DC]) and 15 years of solid-state digital detector development (Gamma Medica-Ideas, Inc. [Northridge, CA]). TriFoil has incorporated the recent commercial availability of digital cadmium-zinc-telluride (CZT), avalanche photon diode (APD), and digital single-photon detector arrays to develop a new generation of multimodality preclinical nuclear, optical, and CT imaging equipment. At their SNMMI booth the company highlighted the direct detection of radio-pharmaceuticals with CZT and APD detectors and the use of silicon photon-array detectors for optical tomography in small benchtop designs. The interesting development here is that PET, SPECT, or tomographic fluorescence (FLECT) imaging could be combined with CT into their instrument form factor (Fig. 1) in the InSyTe series. Among the functional imaging modalities, FLECT is the newest development and is a first true 3D tomographic optical system using a rotating gantry and laser combination, allowing for
optical quantitation. Figure 1 shows a fluorescent dye highlighting the location of a lung carcinoma and a radiotracer targeting the surface of carcinoma cells in the same animal. The reported depth of penetration and signal detection for the instrumentation is 20–30 mm, so that deep-seated structures can be reconstructed by acquiring projection data encircling the subject. Fluorescence imaging is widely used in the basic research community, but the potential of clinical translation has been limited, in part because most fluorescent imaging is 2D. Clinical fluorescent imaging is almost entirely intraoperative, because most detection systems and fluorescent probes will not work in the attenuating/absorptive volume of the human body. By developing methods to visualize deep tissue, fluorescence could open a new door for optical imaging in clinical research.

The use of TriFoil’s digital detectors also makes it possible to dock PET systems directly in front of a magnet as strong as 7 T. Their PET system has been successfully integrated with 3T liquid cryogen-free and self-shielded MR systems, so that inline PET/MR imaging can be used in standard preclinical laboratory facilities. Although the current combined scanners in hospital imaging departments effectively combine PET or SPECT (molecular imaging) with CT or MR (anatomic scans), the TriFoil poses the interesting question as to whether molecular imaging modalities (PET, SPECT, and FLECT) could someday be combined for patient-based clinical use.

iThera Medical (Munich, Germany) combines the concept of optical contrast with ultrasound detection. In their Multispectral Optoacoustic Tomography (MSOT) systems, pulsed light of multiple wavelengths illuminates the tissue of interest. In response to photon energy absorption by tissue, acoustic responses are generated via the photoacoustic effect and are then detected with acoustic (ultrasound) detectors. By modeling photon and acoustic propagation in tissues and using inversion methods, images can be generated and spectrally unmix to yield the biodistribution of reporter molecules and tissue biomarkers. Light of different wavelengths is selected to target the absorption transient of specific chromophores or fluorochromes as selected for spectral differentiation. In short, MSOT excites biomolecules with a laser and measures the sound emitted by these excitations (using ultrasound probes).

MSOT brings a new spectrum of functional information into molecular imaging. Figure 2 shows the same coronal slice of a mouse using 3 techniques. An MSOT scan with no contrast (top) shows hemoglobin (oxygenation), with blood vessels indicated by arrows. The bottom image shows the same slice after injection with indocyanine green (ICG), an already U.S. Food and Drug Administration (FDA)–approved contrast agent for assessing cardiac output, hepatic function, hepatic blood flow, and ophthalmic angiography. Because this injected dye can be imaged repeatedly using MSOT, an uptake and clearance curve can be quantitated as the dye passes through the vasculature. The MSOT EIP (Experimental Imaging Platform) is now available (Fig. 2).

European clinical trials have already been conducted using this device for various indications, including peripheral vascular disease and breast cancer, and for applications including ICG lymphography for sentinel lymph node (SLN) detection and nodal assessment. In a recent clinical trial involving melanoma patients, SLNs could be detected in concordance with standard lymphoscintigraphy by injecting ICG and then spectrally unmixing. Melanin itself can be spectrally unmixed using MSOT, thereby providing

FIGURE 1. Top: TriFoil’s benchtop combined scanner. Bottom: Lung carcinoma (A5 49 luc cells) imaged with (left) FLECT/CT (RGD-Cy5.5 probe) and (right) SPECT/CT (RGD 99mTc radiotracer). Courtesy of Drs. S. Pesnel, M. Vandamme, and A. LePape, CNRS, Orleans, France.

FIGURE 2. Left: MSOT image (top) shows superior sagittal sinus, posterior cerebral artery, and temporal artery (arrows) imaged in a rodent brain without injected dye; (center) a similar cryosection coronal slice; and (bottom) MSOT image with ICG dye (green) in the same rodent brain slice. Right: iThera’s MSOT Experimental Imaging Platform in use. Courtesy of iThera Medical.
an indication of lymph node metastases. The company plans for Conformité Européenne Marking and FDA approval in 2016. The depth to which MSOT can image in tissue is 3–5 cm, depending on tissue type, so iThera Medical is concurrently investigating the use of this technique for a variety of diagnostic and intraoperative applications.

Transition to Use in Humans

In addition to drug discovery, one of the goals of small animal imaging is transitioning improved scanning methods for use in humans. MILabs (Utrecht, The Netherlands) has done exactly that with their announcement of G-SPECT at this year’s SNMMI meeting. Since 2006, when MILabs emerged from the University Medical Centre in Utrecht, they have supplied state-of-the-art small animal imaging cameras worldwide. The top panel of Figure 3 shows their newest VECTro4CT system, which integrates ultra-high-resolution small animal PET (single-photon, 0.75-mm resolution), SPECT (0.25-mm resolution), and X-ray CT imaging. The cylindrical collimators can be inserted into the imaging bore, and each cylindrical insert (containing multiple pinhole apertures) is engineered to accommodate mouse-, rat-, or rabbit-sized animals. By expanding the gantry size and re-engineering the collimator pinhole insert, MILabs has built a unit capable of imaging a human head. Figure 3 shows the image of a Derenzo phantom (filled with $^{99m}$Tc) acquired on this G-SPECT camera. The spatial resolution (2.5 mm) is quite impressive, with a sensitivity capable of reconstructing a point source that moves to a new position every 1 second (as shown in a dynamic sequence displayed at the MILabs booth). Such camera performance raises new questions as to which clinically important details might be visualized using this approach and currently available FDA-approved perfusion agents, such as those for dopamine transporter imaging in Parkinson disease. Here is a clear example of a camera originally designed for animal imaging that is making the transition to clinical human applications.

Many of the smaller companies found around the periphery of the central larger booths in the SNMMI Exhibitors’ Hall offer interesting new ideas and innovative developments. Brain Biosciences, Inc. (Rockville, MD) showed an annular PET scanner using $2 \times 2 \times 13$-mm lutetium-yttrium oxyorthosilicate crystals comprising 15,210 detector elements coupled to photomultiplier tubes. The scanner gantry itself measures $54 \times 33 \times 53$ cm, and similar-sized electronics and acquisition computers (1.5 meters away from the gantry) make for a flexible, configurable installation. The nominal axial and transverse spatial resolution of 2 mm is well within acceptable camera performance specifications. What makes this scanner highly interesting is that with a 22-cm field of view diameter and 22.5-cm axial field of view, it easily accommodates a human adult head (Fig. 4). Image resolution in a Hoffman 3D phantom is quite acceptable for clinical applications. As seen in...
the Brain Biosciences booth, the white annular unit fully contains the PET camera components. This design makes us rethink what a PET scanner looks like, how it can be incorporated into clinical practice, and the ease with which it can be moved between imaging sites for shared use. The company reports that it is currently pursuing FDA-approval and is working out the logistics of leasing and/or sharing use of such scanners.

**Conclusion**

This year at SNMMI, the Exhibitors’ Hall showed new imaging technologies already being used commercially for small animal imaging. Many of the companies using these techniques (not yet approved for human use) demonstrate the potential of these new methods that may well be clinically implemented in the near future.

These companies came from an international arena, and their exhibits emphasized 3 central aspects of the SNMMI Exhibitors’ Hall, which each year: (1) brings developments and services from a well-developed worldwide network of companies; (2) provides a view into the future of potential new diagnostic modalities; and (3) confirms that our newly adapted “and Molecular Imaging” added to “Society of Nuclear Medicine” has created an opportunity for new ideas to come into the field. A few of the 12 companies interviewed mentioned that only after “MI” was added to the SNMMI name did they feel the time was right to come and present their results and new technologies. Our evolution continues, from the early use of Geiger counters to rectilinear scanners to PET rings and multihead SPECT cameras to combined PET/MR and SPECT/MR cameras. The preclinical arena, with developments contributed by small and midsized companies, points the way to the future. We look forward to seeing more in 2016 in San Diego.
From the Exhibitors' Hall: SNMMI Annual Meeting 2015

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