TECHNICAL NOTE

Pre-clinical *in vivo* Imaging

Fluorescence Molecular Tomography (FMT) Imaging Techniques

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Abstract

Recent advances in optical technology have taken fluorescent imaging beyond the standard two-dimensional (2D) epifluorescence imaging into the realm of three-dimensional (3D) fluorescence molecular tomographic (FMT®) imaging for improved localization and quantification in deep tissue. This requires the transillumination of animals (*i.e.* the passing of light through the animals) rather than the standard surface illumination used for epifluorescence assessment. This advance brought by fluorescence tomography is accompanied by the need for extra care in performing proper imaging. Experimental animals must be prepared for transillumination imaging by hair removal, must be properly injected with imaging agents for optimal delivery to imaging sites and minimization of artifacts, and scans must be set up and acquired under optimal conditions and settings. This technical note provides both the in depth details on performing proper imaging as well as data examples to illustrate the ramifications of suboptimal experimental procedures. Performed properly, the pairing of powerful, deep tissue FMT imaging with appropriate near infrared (NIR) imaging agents allows the detection and quantification of important biological processes, such as cellular protease activity, vascular leak, and receptor upregulation, by accurately reconstructing the *in vivo* distribution of systemically-injected NIR imaging agents. The ability to use fluorescent imaging agents that detect and quantify a variety of biological activities is already expanding the horizons of pre-clinical research and drug development.

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Materials and Methods

Fluorescent Agents

Three different fluorescent agents (AngioSense 680 EX, AngioSense 750 EX, and ProSense 750 FAST) were used to image tumors under different experimental conditions. The imaging dose for these agents was as recommended in the product insert (2 nmol/25 g mouse).

Table 1. **Basic properties of two different PerkinElmer fluorescent tumor imaging agents.**

	AngioSense 680/750 EX	ProSense 750 FAST
Agent Type	Untargeted vascular agent	Pan-cathepsin activatable agent
Molecular Weight or Size	~70,000 g/mol	~22,500 g/mol
Ex/Em	670/690 nm 750/770 nm	750/770 nm
Blood Half-life	5 h	5 h
Tissue Half-life	96 h	96 h

Agent Summary. Characteristics of the agents (MW/size, excitation/emission [Ex/Em], and blood/tissue pharmacokinetics) were determined in multiple independent studies. Blood half-lives were measured by blood collection from mice at different times post-intravenous injection. Blood samples were measured for fluorescence levels in a fluorescence microplate reader. Tissue half-lives were determined by time course FMT 4000 imaging of tumors.

4T1 Tumor Model

Six to eight week-old female *nu/nu* and BALB/c mice were purchased from Charles River Laboratories (Wilmington, MA) and maintained in a pathogen-free animal facility with water and low-fluorescence mouse chow (Harlan Tekland, Madison, WI). Handling of mice and experimental procedures were in accordance with PerkinElmer IACUC guidelines and approved veterinarian requirements for animal care and use. To induce tumor growth, mice were injected in either the upper mammary fat pads, or different subcutaneous sites, with $5x10^5$ 4T1 mouse breast adenocarcinoma cells/site (ATCC, Manassas, VA), yielding tumor masses within 5-7 days (see Figure 1).

This model, with positioning of tumors either on upper mammary fat pads, central torso, or on the flank, provided a tool to assess the effects of depilation (BALB/c), scan field size, proper intravenous injections, and tumor/animal positioning on qualitative and quantitative aspects of tomographic fluorescence imaging.

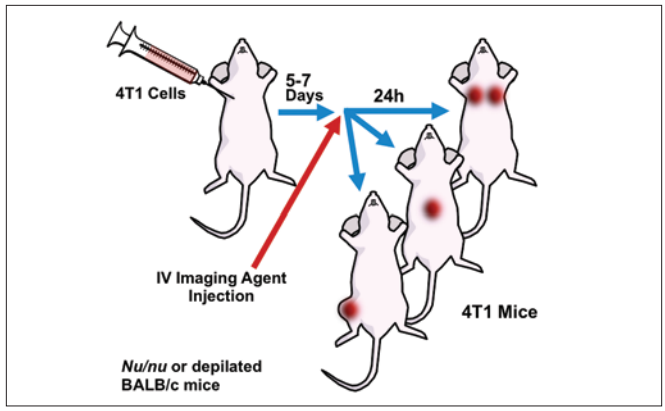

Figure 1. 4T1 Orthotopic breast cancer model.

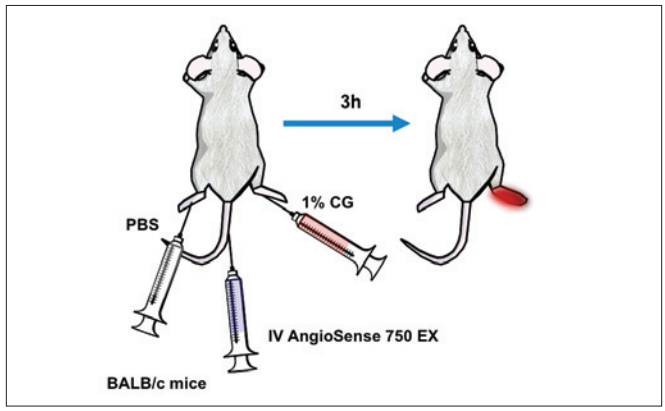

Figure 2. Carrageenan paw edema.

Carrageenan Paw Edema Model

To induce paw inflammation, BALB/c mice were injected in the right hind footpad with 30 µL of a 1% carrageenan (CG) solution prepared in PBS. The left hind footpad was injected with 30 µL PBS and served as an negative internal control. Intravenous injection of 2 nmoles/mouse of a NIR vascular imaging agent (AngioSense™ 750 EX) provided a quantitative biological imaging readout of vascular leak into the affected paw at 3h.

Brain Fluorescence Model

Nu/nu mice were anesthetized using inhaled isoflurane and injected intravenously with AngioSense 750 EX to provide circulating background fluorescence. At 24h after injection, mice were sacrificed by CO_2 inhalation and ~40 pmol of AngioSense 750 EX was injected intracerebrally into the right hemisphere of the brain to provide a discrete, small region of brain fluorescence.

In Vivo FMT 4000 tomographic imaging and analysis

For studies examining the effect of hair on tumor imaging, tumor-bearing mice were anesthetized using an intraperitoneal injection of ketamine (100 mg/kg) and xylazine (20 mg/kg) and depilated prior to imaging. Nair lotion (Church & Dwight Co., Inc., Princeton, NJ) was applied thickly on skin over the upper torso (front, back, and sides) of each mouse, rinsed off with warm water, and re-applied until all fur had been removed. Mice were then imaged using the FMT 4000™ fluorescence tomography *in vivo* imaging system (PerkinElmer, Waltham, MA), which collected both 2D surface fluorescence reflectance images (FRI) as well as 3D fluorescence molecular tomographic (FMT) imaging datasets. Nu/nu and SKH-1E mice required no depilation.

FMT Reconstruction and Analysis

The collected fluorescence data was reconstructed by FMT 4000 system software (TrueQuant v3.0, PerkinElmer, Waltham, MA) for the quantification of three-dimensional fluorescence signal within the tumors and lungs. Three-dimensional regions of interest (ROI) were drawn encompassing the relevant biology.

Introduction and Results

Optimal FMT imaging of living animals requires special care in preparing animals and in performing the experimental procedures. This is especially important because errors in experimental design, such as hair removal, agent injection, and size and position of tomographic scan fields, can have tremendous impact on the quality and quantification of fluorescence signal. In some instances, neglecting some of these important considerations can mean the difference between successful, interpretable imaging and false negative results. To best illustrate the issues that most affect the accuracy of near infrared (NIR) tomographic imaging, a series of studies and illustrations were designed to address common mistakes in depilation, considerations in animal/imaging site positioning, the range of effective scan field sizes, the impact of suboptimal injections, and specific approaches for paw and brain imaging.

An orthotopic 4T1 breast tumor xenograft model (in *nu/nu* or BALB/c mice) was imaged using either vascular agents or cathepsin-activatable agents to assess both image quality and tumor fluorescence quantification (in pmol) under various imaging conditions. Brain imaging was addressed in a direct brain injection study to provide a single discrete site of fluorescence of known concentration, and paw imaging was explored using a well characterized paw inflammation model, carrageenan paw edema.

Proper Depilation

Animal hair is highly effective at blocking, absorbing, and scattering light during optical imaging. Even light within the NIR spectrum, which typically shows minimal scattering and absorbance in tissue, is significantly absorbed and scattered by hair. This is of particular concern for fluorescence molecular tomography, which utilizes a transilluminating light source that passes through both sides of the animal (*i.e.* two regions of hair-covered skin). Nude mice, or immunocompetent hairless SKH1-E mice, do not require depilation, however conventional strains of haired mice, like BALB/c or C57BL/6, require depilation (Figure 3).

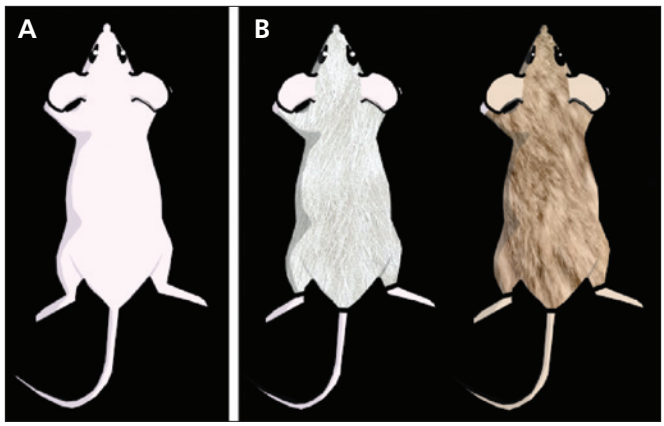

Figure 3. A) Depilation not required: nu/nu mice; SKH1-E (immunocompetent hairless); B) Depilation required: normal, haired mouse strains (BALB/c, C57BL/6 etc.)

To explore the impact of depilation on *in vivo* imaging, BALB/c mice bearing established orthotopic, syngeneic 4T1 breast cancer tumors were injected IV with AngioSense 680 EX and imaged without depilation, with partial depilation (only ventral), and with full depilation (ventral and dorsal). Both 2D (epifluorescence) and 3D (tomographic) images were acquired using the FMT 4000 as described in the Methods section. The biggest impact seen in imaging non-depilated mice is the incorrect localization of fluorescence, both in 2D and 3D. Regions in which hair is thinning or parted allow a disproportional amount of the fluorescence to show, thus affecting both epifluorescence and tomography results (Figure 4A). This leads to significant variability in imaging and at times prevents low level signals from being seen at all. Either partial depilation (*i.e.* ventral depilation only) or complete depilation generated comparable results, however qualitative differences were seen with regard to tomographic imaging, favoring complete depilation. Dorsal only depilation (not shown) gives the same results as non-depilation, supporting the absolute need for depilation on the side of the animal facing the camera.

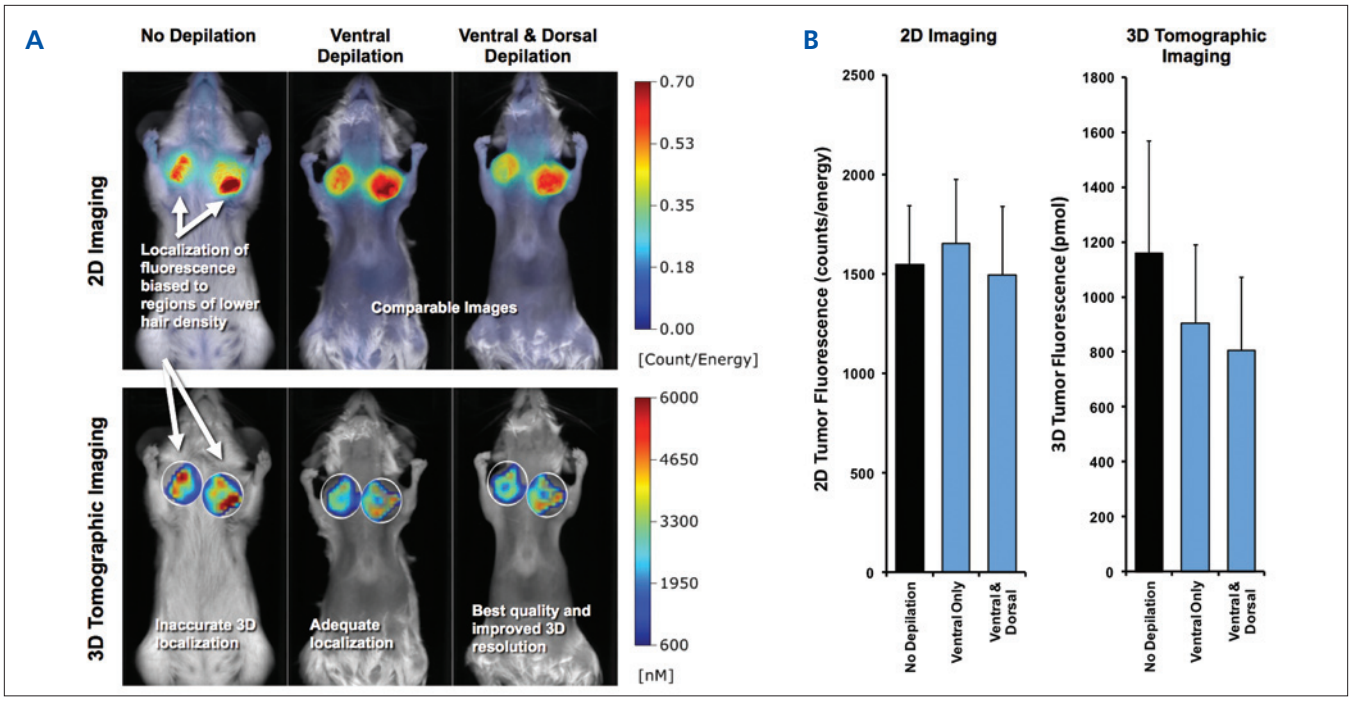

Figure 4. **Effect of depilation on fluorescence imaging.** A representative mouse bearing two established 4T1 tumors implanted superficially in the mammary fat pad was imaged at different states of depilation by both 2D and 3D imaging (A) to show depilation effects on fluorescence localization. Quantitative results (B) show modest differences with depilation.

This suggests that the effect of light scattering at the point of light entry is somewhat less than the effect of light scattering on the side toward the camera. Minimal effects were seen on signal quantification in this particular dataset by either 2D or 3D imaging (Figure 4B); although there was a trend for non-depilated animals to show both improper 3D localization and higher quantification.

Although the differences are not dramatic, partial depilation generates abnormal 3D reconstructions and variability in results that is best avoided, so full depilation is the recommendation. Naturally, the impact of not removing the fur prior to imaging is much greater when imaging dark-haired mice (not shown).

Proper Injection and Injection Route

The imaging agent route of injection is an extremely important consideration when imaging fluorescence. In general, NIR imaging agents are designed for intravenous injection and are not optimized for injections by any other routes (*e.g.* intraperitoneal, intramuscular, subcutaneous). In particular, large molecular weight imaging agents do not distribute out of the peritoneal space effectively following injection and generally require direct delivery to the vasculature.

To explore the impact of route of injection and quality of injection on imaging quality and quantification, *nu/nu* mice bearing established orthotopic 4T1 breast cancer tumors were co-injected with the vascular agents AngioSense 680 EX and AngioSense 750 EX. AngioSense 680 EX served as the optimal control via IV injection, and AngioSense 750 EX was either co-injected under optimal conditions, given as a "bad IV" (*i.e.* partial IV/partial SC injection), or administered IP. All 750 nm results were normalized to 680 nm (proper injection control) results for optimal comparison. FMT quantification of tumor, abdominal, and tail fluorescence

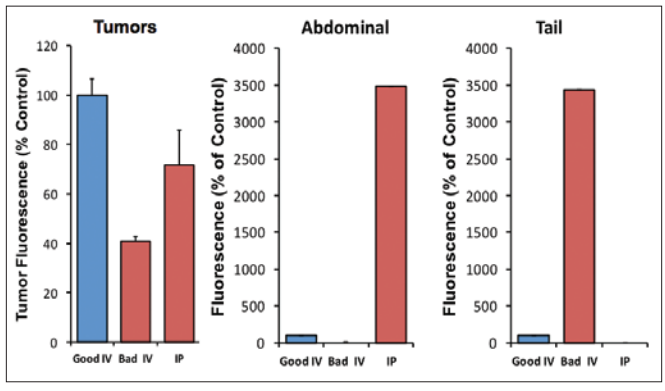

Figure 5. **Quantitation of NIR agent with variation of injections.** The mice from Figure 4 were quantitatively assessed by TrueQuant™ software for the amount of epifluorescence in tumors, the abdomen, and the tail. Data is represented as % of the "good IV" control.

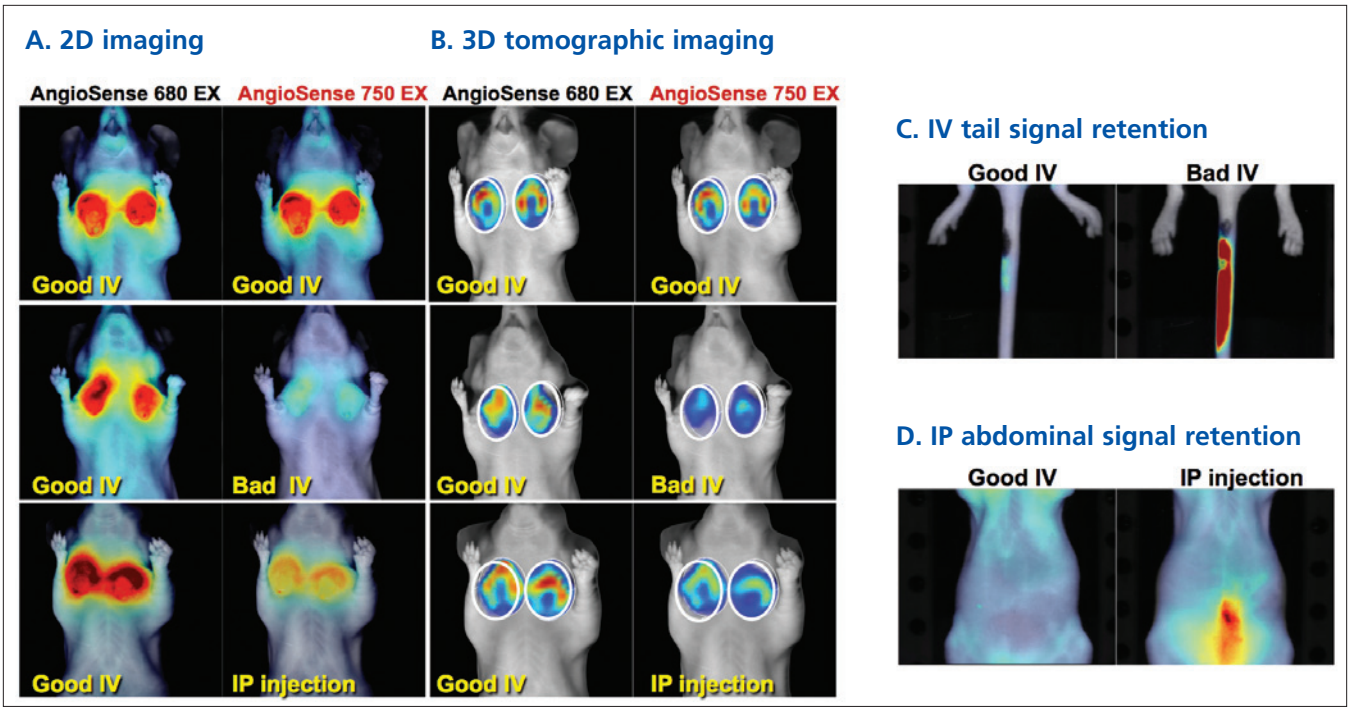

Figure 6. **Effect of proper NIR agent injection on tumor imaging.** Three representative *nu/nu* mice bearing two established 4T1 tumors implanted superficially in the upper mammary fat pads were injected with AngioSense 680 EX & AngioSense 750 EX under different injection conditions. Mice were by both 2D (A) and 3D (B) imaging to show injection effects on fluorescence localization to tumors. (C) Proper intravenous injection shows little retention of signal in the site of tail vein injection, whereas poorly performed IV injection (*i.e.* mostly subcutaneous delivery) shows high fluorescence retention in the tail. (D) IP injection leads to signal retention within the abdominal region.

(Figure 5) shows ~25-50% signal decrease in tumors upon IP or bad IV injection, respectively. If IV injection quality is a significant experimental variable, then the accuracy of measurements could vary considerably from mouse to mouse, perhaps limiting the ability to generate statistically meaningful results. IP injection, although it worked reasonably well for AngioSense 750 EX, is not recommended and shows lower, more variable signal than a properly performed IV injection.

Figure 6 (upper row) shows that both vascular agents provide comparable IV intratumoral distribution and tumor definition, both by 2D and 3D imaging. When AngioSense 750 EX was administered in a manner to mimic a "bad IV", the quality of tumor imaging and the absolute intensity of fluorescence was compromised relative to properly administered AngioSense 680 EX (middle row). Similarly, IP injection yielded somewhat lower delivery of AngioSense 750 EX to the tumor sites as compared to proper IV injection (lower row). Figures 6C and 6D further indicate the impact of injection site signal on imaging with bad IV injections showing subcutaneous accumulation in the tail and IP injections to abdominal signal retention (quantified in Figure 5). The IP approach also precludes imaging in the lower torso of the mouse due to excessive residual abdominal signal.

Lower molecular weight imaging agents (*i.e.* <5000 kDa), and even some larger agents, may be quite effective for imaging via IP injection. However, the researcher should expect that, because of changes in blood pharmacokinetics relative to IV injection, the optimal timepoints for imaging may change relative to IV administration. IP injection may yield lower peak circulation levels, yet more prolonged net exposure.

Proper FMT Scan Size

Appropriate placement and sizing of tomographic scan fields (see Figure 7) are important components to successful tomographic imaging and quantification. Proper depth localization requires that some of the laser source points be positioned distal to the biological site being imaged. Nearby laser positions will less efficiently excite fluorophores at the biological site due to the increased distance, whereas proximal laser positions will excite fluorophores maximally. Imaging across the entire scan field, an array of multiple proximal and nearby laser positions, provides sufficient diversity of fluorescent patterns such that accurate size and position of the imaged biology can be determined and represented in 3D.

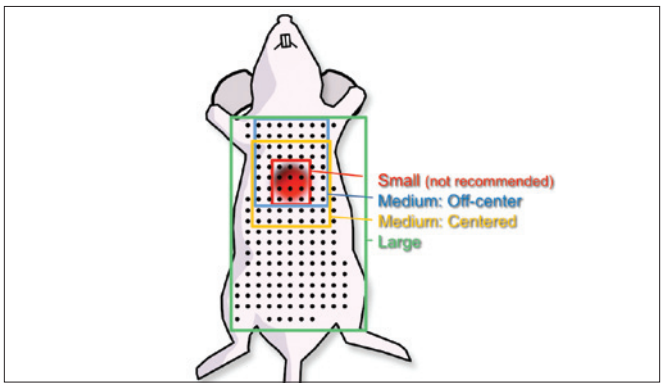

Figure 7. Scan field placement and size.

The images shown in Figure 8 illustrate the impact of scan field size and position (Figure 8A) on tumor image quality (Figure 8B). A scan field that is undersized (*i.e.* only placing laser source points directly in the tumor region) yields a poorly reconstructed tumor by tomography that often does not co-localize well to the obvious position of the superficial tumor. It is recommended that scan fields be sized appropriately to allow at least 1-2 rows of laser source points to surround the biological site, however the FMT reconstruction can work reasonably well even under conditions in which the site of biological signal is near the edge of the scan field (Figure 8B). The medium optimal field, or larger, provides the ideal conditions for generating consistent quantitative data and high quality tomographic images. The obvious benefit of the larger scan field is the ability to detect and quantify other sites of fluorescence, as seen with bladder detection in the "large field" tomographic image. All three scan field approaches incorporating nearby points, however, yield good quality reconstructions and quantification of tumor fluorescence with only a 10% coefficient of variance in their pmol values. This offers maximal flexibility for imaging complex, multiple sites of fluorescence with minimal impact of site position.

Whereas the 2D epifluorescence images of this superficial tumor (acquired by a different imaging process and different light source) are very consistent upon repeated imaging (Figure 8C), it is important to note that detection of deep tissue tumors would be more problematic and challenging with regard to accurate quantification. This is illustrated by the ~2X under-representation of signal within the bladder as measured by epifluorescence as compared to what is measured by tomography.

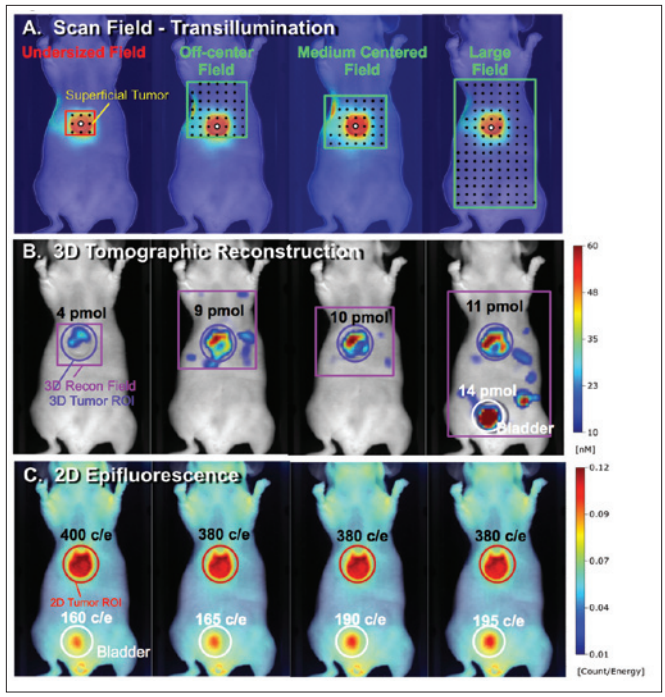

Figure 8. **Effect of proper scan field size on imaging quality.** A representative nu/nu mouse bearing a single established subcutaneous 4T1 tumor implanted over the upper abdominal region was injected IV with ProSense 750 FAST and imaged 24h later. The same mouse was imaged using 4 different scan fields to assess the effects of different scanning approaches on tomographic reconstruction quality. (A) Representation of scan field sizes and laser positions, with transillumination fluorescence represented from a single laser position behind the center of the tumor, indicated by the white dot. (B) Tomographic 3D fluorescence datasets with reconstruction field and ROIs placed for quantification. (C) Reference 2D epifluorescence images collected in parallel prior to each tomographic image acquisition to confirm consistency of superficial fluorescence.

Effect of Tumor/Animal Positioning

Appropriate positioning of the animal can also affect the quality of both 2D and 3D imaging when the biological site is not centralized on the animal's body. This is because the same tumor, in a different orientation, may often present both a smaller visible surface area as well as a different tissue depth. For 2D imaging, this can have a dramatic effect on quantification as this type of imaging is highly dependent on signal depth. However, the quality of 3D imaging can also be affected by animal positioning when the site of biology to be imaged is on the edge of the animal. In the extreme example of a flank tumor that protrudes laterally from the animal, there may be an air gap beneath the tumor, precluding optimal laser transillumination. As long as this is not the case, optimal 3D imaging can be achieved if care is taken to properly size and position the scan field. The TrueQuant reconstruction algorithm does not absolutely require multiple laser source points directly through the biological site. However, it is still essential to have enough nearby laser source points placed for optimal image acquisition. The best, and recommended, approach is to reposition the animal to place the biological site more centrally within the imaging field of view or to implant tumors in a slightly more dorsal position. This allows optimal placement of laser source points on all sides of the biological for the highest quality 3D reconstruction.

To illustrate the issues of proper imaging of biological sites that are positioned either laterally or centrally on the mouse's body, we implanted a single 4T1 tumor subcutaneously on the flank of a nude mouse. We positioned the mouse either prone (tumor protruding laterally to the left) or on its side (tumor centralized in the imaging field of view). Figure 9A illustrates the scan field sizes and positions examined, and it is clear that, as in Figure 8) a small scan field that does not provide a row of laser positions surrounding this laterally-placed tumor yields a poor reconstruction and low tumor quantification in pmol. In contrast, more accurate reconstruction can be generated when the mouse is repositioned to centralize the tumor and a fully encompassing scan field is placed (Figure 9B). The lateral positioning can work reasonably well if the scan field is enlarged to include additional laser source positions above/right and below/right relative to the tumor mass. This approach achieves an improved 3D tumor reconstruction as well as quantification (Figure 9D) similar to that of the centralized imaging. However, the data will suffer somewhat with regard to accurate depth localization without appropriate encircling laser positioning as defined in Figures 7 and 8.

It is interesting to note the impact of tumor position on 2D epifluorescence imaging (Figure 9C); the laterally placed tumor consistently shows half of the signal evident in the centralized tumor image. There is no imaging solution that can improve 2D epifluorescence quantification in comparing such significant changes in position.

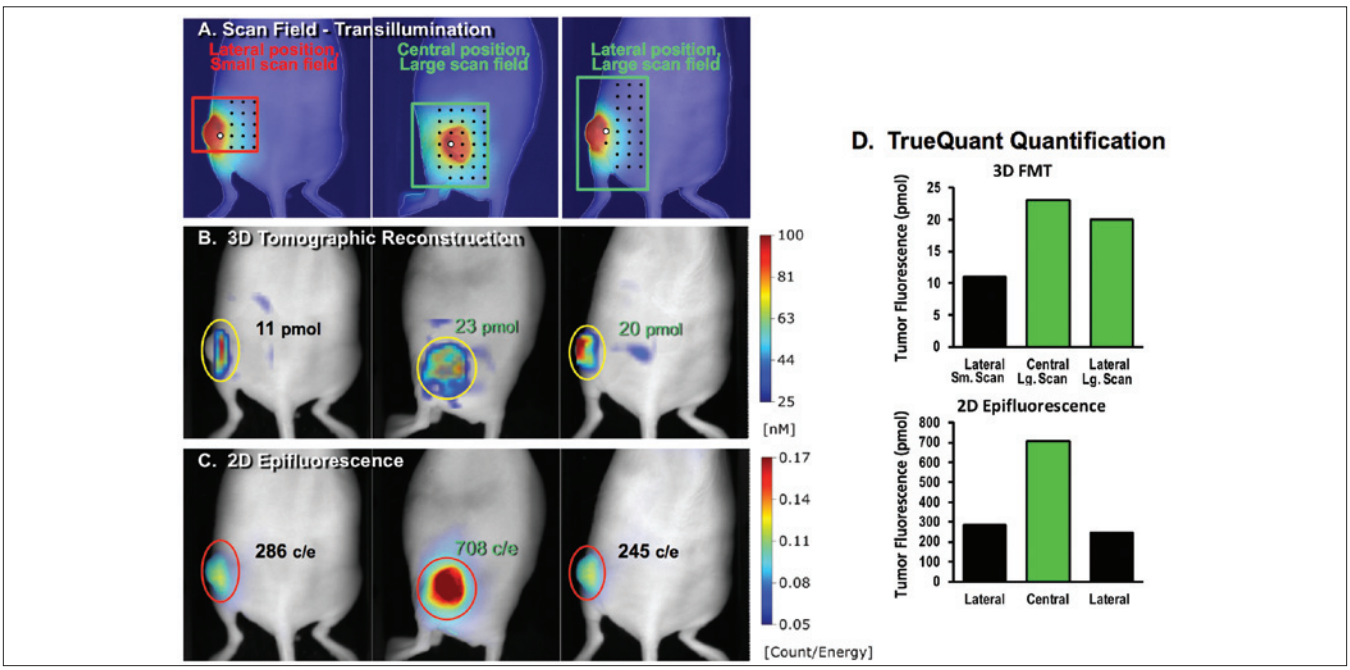

Figure 9. **Effect of tumor/animal positioning on imaging quality.** A representative nu/nu mouse bearing a single established subcutaneous 4T1 tumor implanted on the left flank was injected with ProSense 750 FAST and imaged 24h later. The same mouse was imaged using 2 different animal positions that placed the tumor either laterally or centrally within the imaging field of view. (A) Representation of scan field sizes and laser positions, with transillumination fluorescence represented from a single laser position behind the center of the tumor, indicated by the white dot. (B) Tomographic 3D fluorescence datasets with reconstruction field and ROIs placed for quantification. (C) Reference 2D epifluorescence images collected in parallel prior to each tomographic image acquisition to confirm consistency of superficial fluorescence. (D) Quantification of 3D (upper) and 2D (lower) imaging data by TrueQuant software.

Optimal Paw Imaging Technique

As FMT utilizes transillumination of tissue, it is important to position the laser at each source point with tissue between it and the camera. Without the intervening tissue, the laser would directly project to the camera, providing useless data and potential harm to the camera. To avoid this issue, the FMT 4000 identifies the boundaries of the animal and places each laser source point a minimum of 3 mm from the boundary. This means that the system will generally not place laser source points in any tissues less than 6 mm in width (*e.g.* in paws or tail).

To image biological changes in the paws of mice, it is necessary to modify the imaging procedure to facilitate the transillumination of narrow parts of the anatomy by using a tissue imaging block (a thick resin material that mimics the NIR scattering and absorbance of normal tissues) beneath these regions (Figure 10). Without the block, as can be seen in Figure 11A (left panel), even a large scan field drawn around the lower abdomen and legs is unable to place source points within the paw regions. An imaging block can be placed beneath the lower torso and legs/paws of the animal to allow a full scan field across the legs and paws. A sloped region on one end of the block (placed under the abdomen) minimizes discomfort of the animals, and the paws are positioned on the flat upper surface. The use of clear double-sided sticky tape (placed between the paw and the block) allows the paws to be fully stretched out onto the flat surface and away from the abdomen (right panel). This also facilitates better centralization of the paws as compared to using the block without tape (middle panel).

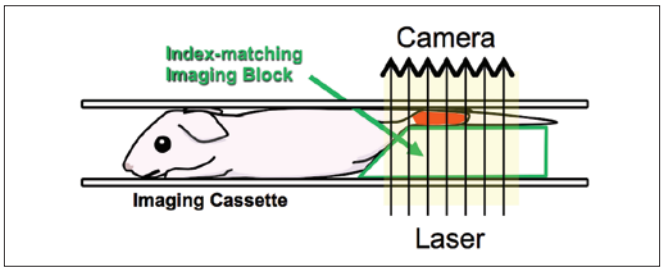

Figure 10. Paw tomography using imaging block.

Figure 11B (left panel) shows the truncated reconstruction field generated when the imaging block is not used, capturing only the ankle region of the paws. In contrast, use of the imaging block allows the generation of a large reconstruction field that fully captures both paws (middle and right panels). The taped paws (right panel) show better positioning and there is less risk of imaging artifacts because of the good contact of the paws to the flat surface of the block. Nevertheless, the quantification is similar with and without tape.

For 2D epifluorescence imaging (Figure 11C) there is a modest effect of the imaging block on paw fluorescence, with slightly lower signal seen in the absence of the imaging block. The overall results are very similar, however, with and without the block, and has been found to be consistent within each approach.

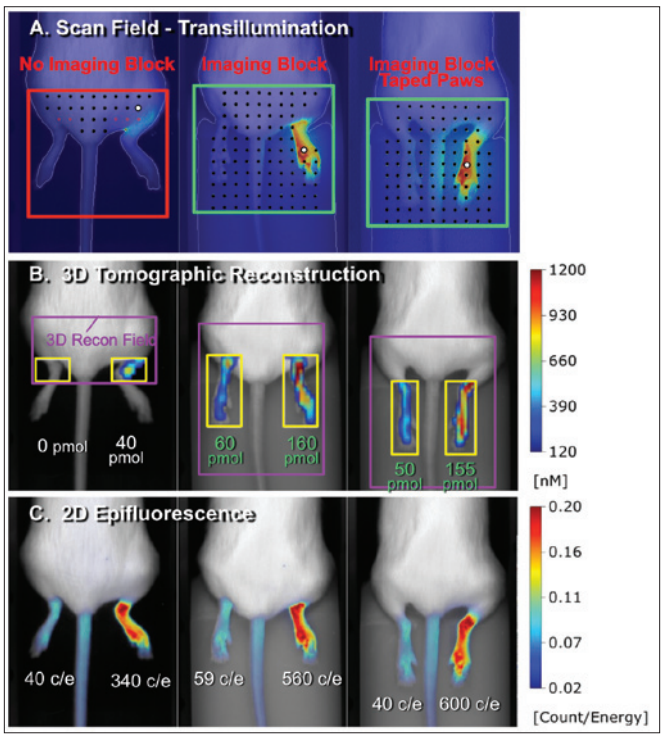

Figure 11. **Imaging paw inflammation.** A representative BALB/c mouse was injected in the right paw with 1% carrageenan and in the left paw with PBS. Immediately thereafter, the mouse was injected intravenously with AngioSense 680 EX to assess the vascular leak at 3h associated with the induced edema response. The same mouse was imaged dorsally using 3 different approaches; (1) imaged without any special consideration for the small anatomy to be examined, (2) imaged with the paws elevated on an index-matching imaging block, and (3) imaged with the paws elevated on an index-matching imaging block and paws taped in place to extend the legs/paws away from the lower torso. (A) Representation of scan field sizes and laser positions, with transillumination fluorescence represented from a single laser position, indicated by the white dot. Red dots indicate source points omitted during the scan because of excessive light transmission. (B) Tomographic 3D fluorescence datasets with reconstruction field and ROIs placed for quantification. (C) Reference 2D epifluorescence images collected in parallel prior to each tomographic image acquisition to confirm the consistency of superficial fluorescence.

Brain Imaging

Head/brain imaging by FMT faces no restrictions with regard to the ability to effectively transilluminate the skull. Reasonable images can be acquired under a variety of experimental settings, however scan field "pitch" (the density of laser source points per scan field) can have some impact due to the small anatomy being imaged. Scan field should be sized to the skull rather than to the entire head/ears, as the thin ear tissue is too thin and will not be image-able by transillumination (Figure 12A). Either the standard scan pitch or fine pitch will both work well in yielding good 3D images as well as accurate quantification, whereas the coarse scan will underestimate the amount of signal in the brain (Figure 12B).

Because of the small size of the brain region, fine scanning is generally recommended in order to provide more laser sources through the specific site within the brain tissue. For more diffuse brain signal (as in brain inflammation), the reconstruction will show broad areas of signal through the head, generally localized to the brain. Discrete hot spots of inflammation within broad inflammation in the brain may be difficult to discriminate and localize due to the inability to provide laser positions outside the brain during imaging, however the quantification of total brain signal will agree well with ex vivo validation.

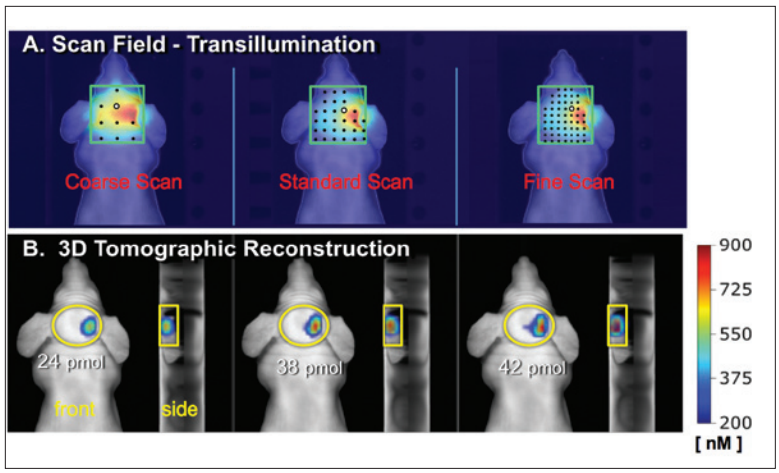

Figure 12. **Imaging Brain Fluorescence.** A representative nu/nu mouse with systemic levels of AngioSense 750 EX was killed and injected in the right hemisphere of the brain with ~40 pmol of AngioSense 750 EX. The same mouse was imaged dorsally using 3 different laser source point densities; (1) course scan field (5 mm spacing for laser source points), (2) medium scan field (3 mm spacing for laser source points), and (3) fine scan field (2 mm spacing for laser source points). (A) Representation of scan field sizes and laser positions, with transillumination fluorescence represented from a single laser position, indicated by the white dot. (B) Tomographic 3D fluorescence datasets with reconstruction field and ROIs placed for quantification.

Conclusions

Optimal FMT imaging of living animals generates complex 3D images of fluorescence utilizing specific NIR imaging agents designed to detect and quantify in situ biology. The ability to detect and localize fluorescence in 3D is an essential component to accurate quantification, providing a distinct advantage to standard 2D epifluorescence imaging (which is dominated by superficial signal and subject to depth-dependent variability). This accurate localization of fluorescent signal is absolutely dependent on the use of careful imaging procedures that effectively allow the delivery of light through tissue in a matrix pattern that captures both proximal and distal sites with respect to the biological site of interest. Proper hair removal is one of the critical steps for fluorescent tomography in order to provide an unobstructed surface for light penetration. Hair must be removed on the front, back, and sides of the appropriate region on the mouse and the approriate site for imaging should be centered in the imaging window if possible. Agents must be injected properly (according to instructions), and the scan field must be appropriately sized around the site of interest to provide sufficient proximal and distal views for determining signal localization and quantification in 3D. Smaller anatomical sites such as paws, which present a challenge for optical tomography, can be imaged by placing them on an imaging block that mimics the density of normal tissue. This provides a robust means for transilluminating the paws and generating quantitative data.

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Paw Imaging

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Brain Imaging

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