Cancer imaging using MARS spectral CT:
New methods for detection

MARS scanners generate multi-energy images with high spatial resolution and low noise. MARS imaging simultaneously identifies and quantifies various components of soft tissues, bones, cartilage as well as exogenously administered contrast agents, nanoparticles and pharmaceuticals in a single scan. This ability to detect contrast agents and intrinsic markers simultaneously has enabled research into new methods of cancer and tumor detection.

MARS spectral CT is a new tool that allows researchers to accurately identify and quantify high-Z materials (Figure 1) while retaining information about the biological context of the specimen.

Detecting cancerous tumors by imaging can be difficult due to low contrast differences between normal tissue and cancerous material. Traditional imaging modalities struggle to identify tumors until they are large. Once a lesion has been identified, a biopsy may still be required to determine whether the lesion is cancerous or benign.

MARS spectral CT offers new non-invasive methods for detecting tumors. Through improved detection of low contrast materials and quantification of targeted nanoparticles [1], detecting and characterizing early stage tumors may be possible [2].

There are a number of approaches that are capable of improving tumor detection including taking advantage of neovascularization, cancer cell surface markers and co-incident markers such as microcalcifications.
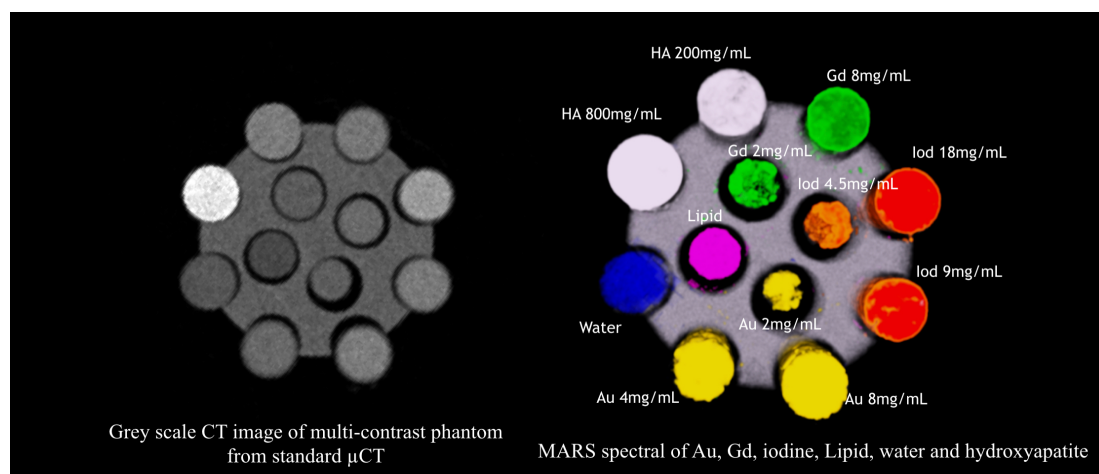

Grey scale CT image of multi-contrast phantom from standard μCT

MARS spectral of Au, Gd, iodine, Lipid, water and hydroxyapatite

Figure 1 Quantitative imaging using spectral CT. Left, standard greyscale CT image; right, MARS image with separate colors for each material and color intensity representing concentration.

Targeting neovascularization via nanoparticle detection

Using small nanoparticles it is possible to find angiogenesis (or new vessel formation) in tumors. This is due to the fact the newly formed vessels will leak, leading to a build up of nanoparticles within the tumor, known as the enhanced permeability and retention effect.

Mice which had subcutaneously implanted Lewis lung cancer tumors (~75 mm^3) were tail-vein injected with 200 µL of 15 nm Aurovist gold nanoparticles at 100 mg/mL. After 24 hours, mice were euthanized and MARS scanning was conducted using the energy thresholds set at 28-47, 48-67, 68-80 and 81-120 keV [3]. The MARS scanner generates a series of images for each energy threshold on which a material decomposition (MD) is performed. These can then be viewed in either 3D (Figure 2) or as more traditional axial, sagittal and coronal slices (Figure 3). Both the 3D MARS image and the 2D slice views clearly show gold nanoparticle uptake in the implanted tumor as well as retention in the kidneys.
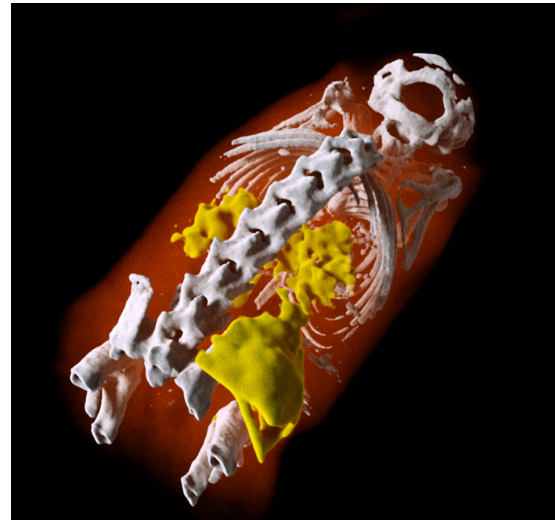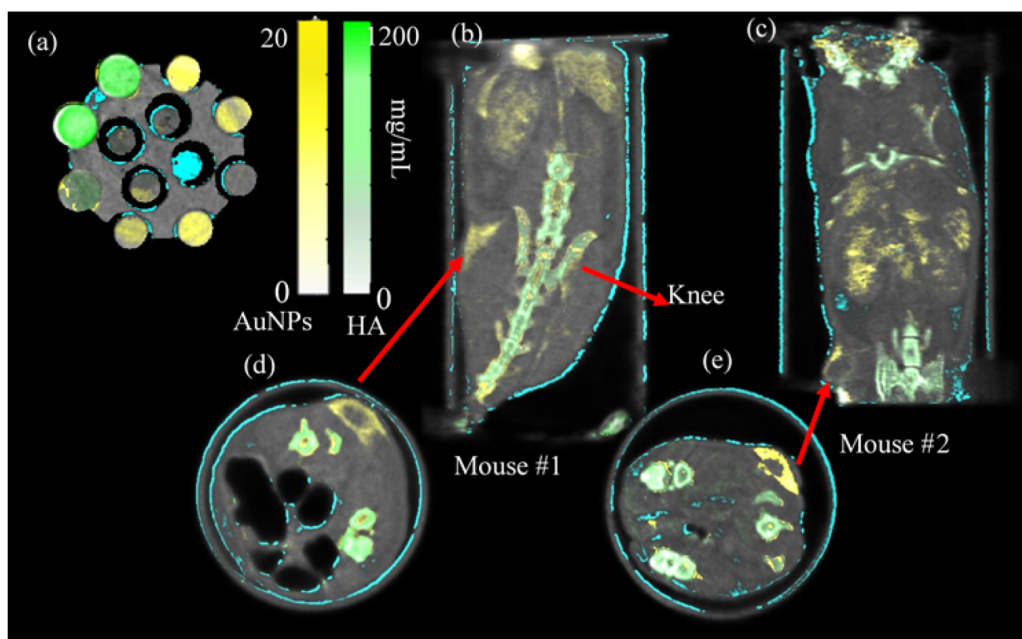

Figure 2 **3D MARS image of a tumor in a mouse**

This technique successfully identified the tumor using gold nanoparticle uptake via tumor neovascularization.

AuNPs (yellow), HA (green), Lipid (cyan) and water (gray)

Figure 3 **Mice with a tumor implanted in the flank, showing a high density of gold nanoparticles (AuNPs). Color intensity is related to the concentration.**

Using targeted nanoparticles to identify tumor phenotype

Tumor phenotype is important for determining treatment approach. The HER2 status of breast cancer tumors is a common target. Monoclonal antibodies are incorporated into pharmaceuticals to target surface proteins to direct treatment. The binding of the antibody to the target cell triggers an immune response or prevents cell growth. By attaching a high-Z nanoparticles to the antibody, specific cell binding can be measured using spectral CT. This has uses for investigating drug uptake as well as tumor heterogeneity.

Researchers have successfully identified HER2 positive breast cancer cells (SKBR3 cells) using MARS spectral imaging of targeted nanoparticles (Figure 4). The binding of gold nanoparticle complexed-Herceptin, a common HER2 targeted drug,was measured. To show the specificity of the functionalized gold nanoparticle binding, gold nanoparticle complexed - Rituximab, an antibody targeted to CD20 was used as a control SKBR3 cells have low levels of CD20. A cross-over study using Raji cells, which have high levels of CD20 and low levels of HER2 was also conducted (Figure 5) [3]. In addition, this type of study with functionalized gold nanoparticles has also been successfully conducted using ovarian cancer cell lines.

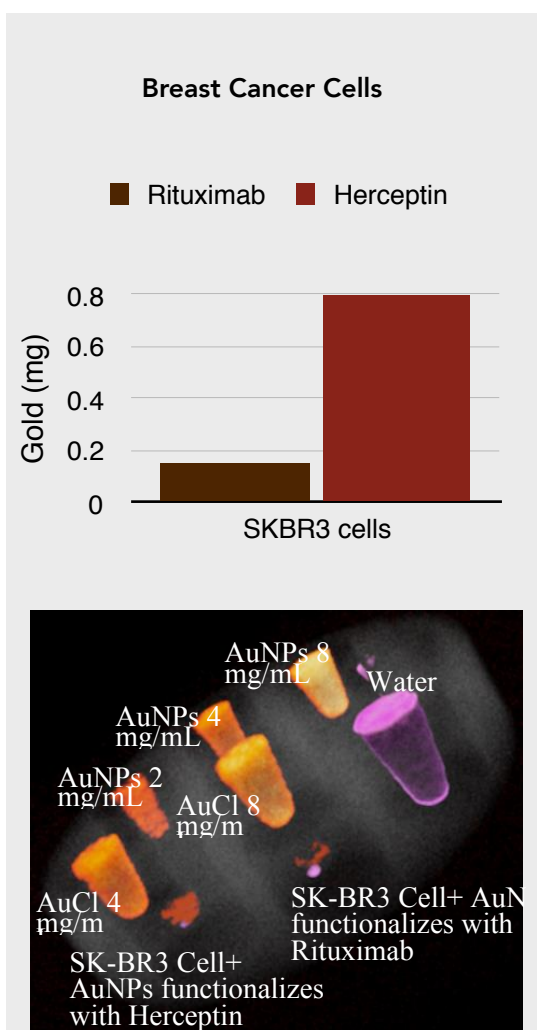Both cell phenotype and targeted drug delivery can be measured using spectral CT.

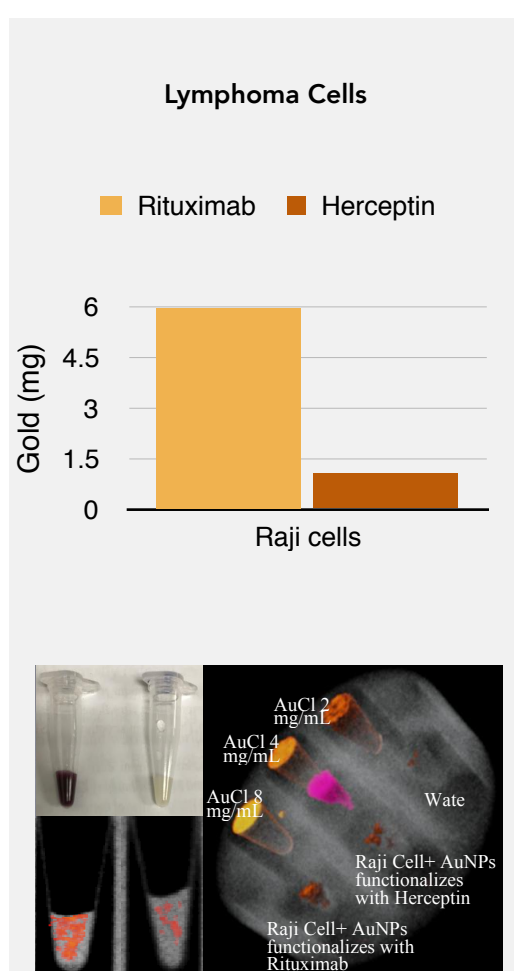**Figure 4** Surface binding of targeted nanoparticle, Herceptin, vs control, Rituximab.

Figure 5 Surface binding of targeted nanoparticle, Rituximab, vs control, Herceptin.

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Future of spectral CT imaging for cancer detection

Spectral imaging is already improving health outcomes for patients through increased contrast and differentiation of intrinsic materials (Figure 6) in addition to iodine mapping. Clinically, spectral CT has been found to provide added value for the diagnosis of ovarian cancer [4], used to assess neovascularization in gastric adeno-carcinoma [5], and measure tumors in pancreatic cancer patients [6]. However, spectral CT also has the ability to go beyond just improvements to traditional detection methods to new areas.

Spectral CT has the potential to advance functional imaging and direct measurement of biomarkers. Functional imaging, particularly through the use of multiple contrast agents (Figure 7), provides a level of detail beyond the traditional measurements of tumor size and location. Being able to monitor changes in blood flow and cellularity will help to detect physiological changes in the tumor itself. Direct measurement of biomarkers delivers another method to monitor tumor progression, which could reduce reliance on serum markers. Tools such as these will help clinicians to adopt personalized treatment approaches and enable earlier detection of cancer [7].

Summary

Preliminary results from *in vitro* and *in vivo* experiments showcase some of the ways spectral CT may improve tumor detection for patients in the future. Non-invasive quantitative imaging allows researchers to measure early signs of cancer in animal models, detect targeted cells based using functionalized gold nanoparticles and identify tumors through nanoparticle retention due to neovascularization. The spectral CT modality offers researchers new methods to investigate drug delivery, treatment progress, and tumor microenvironment.
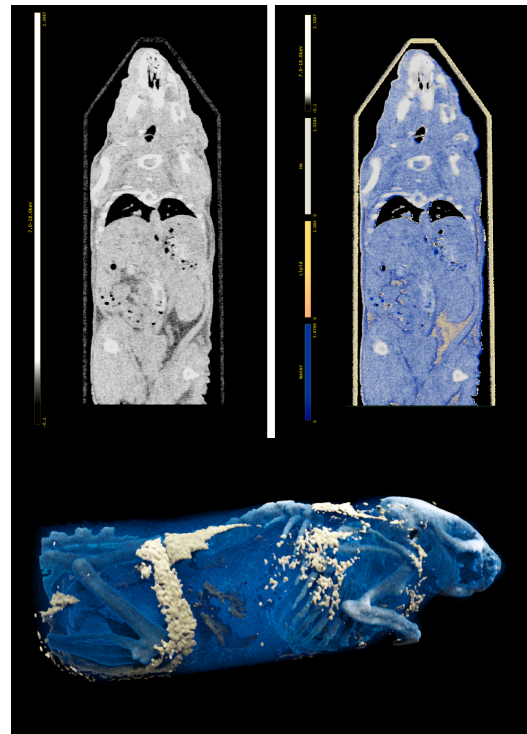
Figure 6 Intrinsic imaging. Top left, energy image; top right, MD image; bottom, 3D render of MD image.
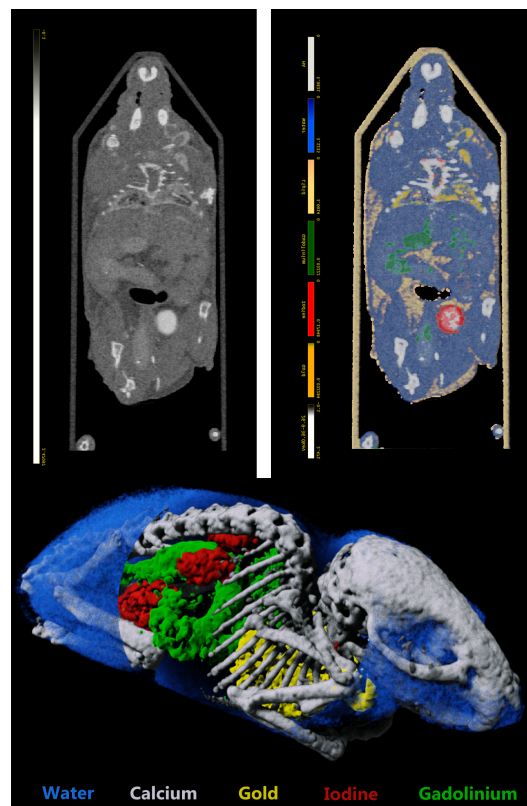

Figure 7 Multicontrast imaging. Top left, energy image; top right, MD image; bottom, 3D render of MD image.

References

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