Despite recent advances in imaging probe development for biomedicine, the translation of targeted diagnostic platforms remains challenging. Nanomaterials platforms currently under evaluation in oncology clinical trials are largely non-targeted drug delivery vehicles or devices to thermally treat tissue; these are not typically surface modified for direct detection by clinical imaging tools. New tumor-selective platforms need to satisfy critical safety benchmarks, in addition to assaying targeted interactions with the microenvironment and their effects on biological systems. Coupled with metabolic imaging and analysis tools, such as PET, complete and quantitatively accurate data sets for whole body distributions, targeting kinetics, and clearance profiles of new diagnostic platforms undergoing preclinical testing or transitioning into early-phase clinical trials can be acquired.

We applied these methods to a novel class of ultrasmall, fluorescent core-shell silica nanoparticles, Cornell dots (C dots). Such fluorescent particle probes offer enormous scientific and technological promise as labels and photon sources for a range of biotechnological and nanomedicine applications. Many applications require size-controlled, monodisperse, bright nanoparticles that can be specifically conjugated to biological macromolecules and targeted to specific environments. As an alternative to single molecule fluorophores and probes with unresolved toxicity issues, C dots hold particular promise as they are biocompatible and water soluble, and silica chemistry is well-established and extremely versatile. The silica matrix is coated with polyethylene glycol chains to neutralize surface charge, effectively reducing immune system recognition and uptake by the reticuloendothelial system. Its further surface functionalization with targeting moieties and long-lived radionuclides has resulted in a selective, multimodal (PET-optical) platform for extended cancer detection/imaging, staging, and targeted therapeutics. The efficient renal clearance of this particle coupled with its tumor-selective accumulation in human melanoma models provides an ideal cancer diagnostic probe. First-in-human clinical trials have been completed in metastatic melanoma patients using this inorganic particle as a drug following FDA investigational new drug application (IND) approval.

We have additionally investigated the use of this rapidly-cleared dual-modality C dot platform, along with intraoperative hand-held optical-PET imaging devices, for sentinel lymph node (SLN) mapping in a spontaneous melanoma miniswine model. Injected locally about the tumor site, this rapidly-cleared dual-modality C dot platform has enabled real-time optical imaging of lymphatic drainage patterns, thereby improving visualization of the surgical field and simplifying SLN mapping procedures for surgeons. Superior detection sensitivity and discrimination of metastatic tumor burden within PET-positive neck nodes has also been observed in these proof-of-concept studies, as compared with standard-of-care tracers for cancer staging. In surgical settings, the possibility of visualizing nodal disease spread and tumor extent in relation to critical structures has important implications for disease staging, prognosis, and treatment planning.

Advances in nanotechnology, in conjunction with image-directed approaches, have also fueled a paradigm shift in targeting and safely delivering drugs. Nanocarrier size, architecture, and chemical composition can be fine-tuned to achieve properties optimal for loading and controlled release of therapeutic agents, patient safety/compliance, modulating kinetic profiles, and
reducing unwanted side effects. By combining therapeutic particle tracer preparations with bioimaging approaches, drug delivery, lesion localization, and the extraction key tumor biologic properties can be achieved and used to individualize treatment planning protocols. Along with knowledge of drug-specific activity, injected drug dose, uptake kinetics, and measured IC\textsubscript{50} values, drug dosing regimens needed to achieve therapeutic efficacy may be estimated.

The ability to flexibly adapt the formulation of clinically-promising drugs to improve their physicochemical and/or biological properties, in combination with metabolic imaging tools, will be crucial to quantify and establish suitable clinical trial endpoints. At present, prescribed drug dosing regimens for treating tumors are based on patient body surface area or weight considerations rather than on the metabolic/functional characteristics of individual tumors, as established by quantitative imaging approaches, such as PET. Issues relating to solubility, transport, barrier penetration, time-dependent changes in drug uptake, and intratumoral distribution are additional considerations. These properties are often not generally evaluated in the context of drug delivery due to the complexity of the biological systems involved and the inability to serially monitor this process non-invasively in the absence of drug labeling. The future success of molecular medicine will, in part, rest upon our ability to offer improved clinical trial designs addressing these foregoing issues. In conclusion, the adoption of such an approach for image-directed drug delivery in clinical settings will have far-reaching implications for personalizing cancer care in terms of treatment planning, stratification to appropriate trial arms, and response monitoring.