AbstractID: 14526 Title: Next Generation of Imaging Platforms: Clinical Validation of Nanomedicine

In the 1990's, successful targeting of a particle to a biochemical epitope was a considered a quest for the "holy grail" by many scientists, but today such agents are in or poised to enter clinical trials. In some respect simply achieving an IND and beginning phase I clinical trials has been the primary goal, but as is always the case, such milestones fall quickly only to be replaced by new, more ambitious targets. Beyond the significant issues of probe safety and bioelimination, the clinical validation of nanomedicine agents presents challenges that must be assessed in both animals and patients.

One fundamental issue, ignored by many labs, is proof that the nanoparticle construct with its homing ligands, imaging moieties, and possible drug cargo remain intact in circulatory transit to the target. Many agents, stable in vitro, rapidly disintegrate in vivo. Phase I safety studies must include pharmacokinetic studies in which the clearance rate of each key component is tracked over time to demonstrate parallel clearance profiles. While some elements of the particle may be easy to follow in whole blood, the bioanalytical challenges become substantial for low-level components, such as the homing ligands, which may be present only at pico-molar concentration in blood.

The issue of appropriate targeting to the tissue of interest is a prime concern. Prior to clinical trials, extensive characterization of homing ligand binding affinity and specificity must be performed in both buffer and blood matrices to assess interactions with blood constituents. However, even low affinity binding measured in vitro can markedly impair targeting in vivo when the relative concentration of the interfering substance is in millimolar concentrations and the tissue biomarker expression is at a nano- or pico-molar level. While fouling of the homing mechanism can sometimes be overcome by increased dosage, the potential for redirection to off-target sites must be evaluated as a potential for false positive readings. The time dependent accumulation of probes at the target tissue in conjunction with diminishing blood levels represents a key element in the validation of any probe, and in this regard, noninvasive imaging can play a substantial role. The pharmacokinetics of nanoparticles is different from traditional small molecule probes, and new compartmental modeling tools designed for nanotechnology and based on imaging, e.g., NanoPK, may serve an important role in the validation of targeting. Additionally, the removal of target tissue may be required to corroborate homing efficacy of nanoparticles and this issue may greatly influence the early indications selected for development in order to facilitate tissue accessibility for pathological correlation.

A significant challenge for molecular imaging is the reproducible quantification of targeted signal. Although detection of a target versus normal control has often been considered adequate in preclinical animal model publications, the viability of molecular imaging as a clinical management tool will be dependent on interrogating a quantifiable signal and correlating it with a pathological status, minimally to establish categories of mild moderate or severe disease. Whether after treatment or expectant observation, molecular imaging must enable a patient to be restudied and the biochemical change measured accurately for comparison with prior results. The ability to achieve reproducible, quantitative molecular imaging will be an important milestone that requires improved control of the variability inherent in imaging techniques today.

Ultimately, validated agents administered under controlled protocols will produce quantifiable personalized characterizations of cancer. These new data will lead to the development of clinical guidelines reflecting an evidence based medicine approach to nanomedicine. Although very challenging, the greatest contribution of nanomedicine will come from the early diagnosis and treatment of disease, likely suggested by future advanced genomic based screening tools employed in physician offices or even at home. For reliable clinical management of these nascent pathologies in asymptomatic patients, molecular imaging must become a robust technology with functional evidence based guidelines for use.

AbstractID: 14526 Title: Next Generation of Imaging Platforms: Clinical Validation of Nanomedicine

Questions: Clinical validation of nanoparticles is multifaceted and starts with validated chemistry. True

The retained integrity of nanoparticle constructs in circulation can be demonstrated by following the parallel pharmacokinetics of the different components. True

Robust quantification of imaging and reproducibility over time will be needed for noninvasive management of nascent cancer therapy. True