Advances and Challenges in the Development and Translation of Molecularly Engineered Nanomaterials for Clinical Applications

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Advances in molecularly engineered nanomedicines for targeted detection and treatment are fueling a paradigm shift in our ability to precisely target a variety of diseases and safely deliver drugs for achieving efficacious outcomes, particularly when coupled with image-directed approaches. Towards this end, agents designed as multimodal imaging probes can help navigate technical hurdles accompanying this process, serving as companion diagnostic tools for facilitating product translation, monitoring treatment responses, and guiding stratification of patients to specific treatment arms. Key determinants needed to successfully achieve these deliverables often rely on the development of particle probes with favorable PK, clearance, and the ability to maximize accumulation of diagnostic/therapeutic payloads and responses at disease sites using quantitative imaging approaches. Critical to this effort is the ability to flexibly adapt formulations of clinically promising nanomedicines as a means of improving their physicochemical, imaging, biological, and/or therapeutic performance and establishing suitable translational/clinical endpoints. Issues relating to solubility, stability, transport, barrier penetration, time-dependent changes in drug uptake, and intratumoral distributions are important considerations. These properties are generally challenging to quantitate in the context of drug delivery applications due to the complexity of the biological systems involved and an inability to generally monitor this process non-invasively in the absence of drug labeling. The future success of nanomedicine will also, in part, rest upon implementing more effective clinical trial designs that consider these foregoing issues. Designing novel treatment strategies for image-directed drug delivery will also have far-reaching implications in clinical settings for individualizing cancer care.

As an example, Memorial Sloan Kettering (MSK) and Cornell University-Ithaca have translated an ultrasmall (<8 nm), targeted, and deep red/NIR dye-encapsulated core-shell silica nanoparticle platform, Cornell prime dots (or C' dots), to the clinic for both image-guided surgical and theranostic applications in multiple tumor types, in conjunction with a start-up company, Elucida Oncology Inc. These platforms significantly improve upon key biological and safety features that may hinder translation of larger-size platforms. Importantly, the ability to tune and precisely control C' dot physicochemical properties has been crucial for not only maintaining its sub-8-nm size, despite surface adaptation with an array of multiple targeting moieties, therapies, and radiolabels, but for achieving favorably biological properties and reproducible batch-to-batch performance. By leveraging the beneficial properties of this multifunctional platform, we have been able to achieve highly sensitive and specific disease detection, as well as improve therapeutic index in clinically relevant models.