Theranostic Metal-based Systems Modulate Nuclear EGFR Activity

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Nucleus-translocated Epidermal Growth Factor Receptor (npEGFR) defines an emerging marker of resistance to targeted cancer therapies. We are introducing a novel system of anti-EGFR targeted molecular imaging agents for the management of malignancies overexpressing the npEGFR with prototype metal based functionalized compounds engaging cutting edge synthetic and coordination approaches. Despite efforts to achieve bimodal imaging using a combination of d block transition metal (optical) and f-block lanthanide metal (magnetic) in a unimolecular organic framework, possessing anti-EGFR therapeutic potential, with optimized in vivo stability, targeting efficacy and desirable pharmacokinetics for clinical translation remains a major challenge. A series of hetero-bimetallic complexes containing (i) luminescent ruthenium polypyridyl complex having a carboxylic arm and (ii) functionalized cyclen (1,4,7,10-tetraazacyclododecane) based lanthanide chelators containing anilinoquinazolines pharmacophore and ethylenic linker to bridge ruthenium polypyridyl complex, have been synthesized and spectroscopically characterized. Sensing and therapeutic attributes are explored against those of citric acid functionalized, silica-coated, magnetite, rhodamine nanoparticles (rNPs) end-functionalized with NH2 or COOH and grafted with the same TKI.

Vibrating sample magnetometry and relaxometry confirmed appreciable magnetic properties and suitability for MR Imaging while reversible saturation of magnetization enabled applications for magnetically guided therapies. Live CRC cell lines with differential expression of EGFR were assessed for inducible spatial expression of pEGFR and temporo-spatial trafficking of NPs or Ru-Gd complexes under confocal microscopy. Zeta-potential dependence of nuclear delivery was documented. Proapoptotic efficacies of (i) hetero–bimetallic complexes and (ii) irreversible TKI were assessed against clinical controls. In vivo biodistribution and pharmacokinetics disclose whether TKI-Ru-Gd complexes can serve as theranostic solutions for better bioavailability and reduced long-term toxicity.

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