Cooperative Nanomaterial System to Sensitize, Target, and Treat Tumors

Ji-Ho Park[1], Geoffrey von Maltzahn[2], Erkki Ruoslahti[3], Sangeeta N. Bhatia[2], and Michael J. Sailor[4]
[1]Department of Bio and Brain Engineering, Korea Advanced Institute of Science and Technology, Daejeon 305-701, Republic of Korea, [2]Harvard-MIT Division of Health Sciences and Technology, Massachusetts Institute of Technology, Cambridge, MA 02139, USA, [3]Vascular Mapping Center, Stanford-Burnham Medical Research Institute at UCSB, University of California, Santa Barbara, Santa Barbara, CA 93106, USA and [4]Department of Chemistry and Biochemistry, University of California, San Diego, La Jolla, CA 92093, USA

Statement of Purpose: A significant barrier to the clinical translation of systemically administered therapeutic nanoparticles is their tendency to be removed from circulation by the mononuclear phagocyte system. The addition of a targeting ligand that selectively interacts with cancer cells can improve the therapeutic efficacy of nanomaterials, although these systems have met with only limited success. Current approaches to nanoparticle targeting lack mechanisms of communication and amplification through which specific targeting events could assist the targeting of materials still in circulation. By contrast, natural systems frequently improve the efficiency of targeting through communication and cooperation between multiple components in a system. Here, inspired by such biological systems, we built a 'nanosystem' comprised of two distinct nanoparticle populations that communicate and cooperate each other *in vivo* to amplify drug or imaging payload delivery.

Methods: PEGylated gold nanorods (NRs) were prepared with a peak plasmon resonance at 800 nm. LyP1-conjugated iron oxide nanoworms (LyP1NWs) or doxorubicin liposomes (LyP1LPs) were prepared by attaching LyP-1 (Cys-Gly-Asn-Lys-Arg-Thr-Arg-Gly-Cys) peptides with an extra cysteine to maleimide-terminated NWs or LPs in PBS, respectively. Mice bearing bilateral MDA-MB-435 human carcinoma tumors were intravenously injected with NRs (10 mgAu/kg). At 72 h postinjection of NRs, control LPs, or LyP1LPs (3 mgDOX/kg) were systemically administered and the tumor in one flank was irradiated with NIR-light (□0.75 W/cm^2 and 810 nm) for 30 min, maintaining an average tumor surface temperature at ~45 °C under infrared thermographic observation. For targeting studies, at 24 h postinjection of liposomes, doxorubicin fluorescence in the homogenized tumors was analyzed. For therapeutic studies, tumor volume and mouse mass was measured every 3 day after the single treatment for a period of 3–4 weeks by an investigator blinded to the treatments administered.

Results: We construct a cooperative nanosystem consisting of two discrete nanomaterials (Figure 1). The first component is gold nanorod "activators" that populate the porous tumor vessels and act as photothermal antennas to specify tumor heating via remote near-infrared laser irradiation. We find that local tumor heating accelerates the recruitment of the second component: a targeted nanoparticle consisting of either magnetic nanoworms or doxorubicin loaded liposomes. The targeting species employed in this work is a cyclic nine-amino acid peptide LyP-1 that binds to the stress-related protein, p32, which we find to be upregulated on the surface of tumor-associated cells upon thermal treatment. Mice containing xenografted MDA-MB-435 tumors that are treated with the combined NR/LyP-1LP therapeutic system display significant reductions in tumor volume compared with individual nanoparticles or untargeted cooperative system.

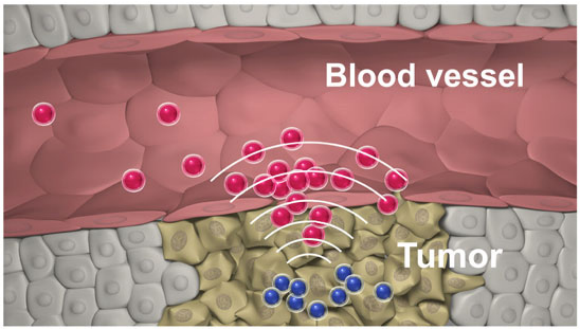

Figure 1. Generic architecture for a bio-inspired nanosystem for amplified tumor targeting

Conclusions: This study demonstrates that the appropriate combination of nanomaterials currently under investigation in cancer therapy can significantly enhance therapeutic efficacy relative to the individual components. Site-specific photothermal heating of NRs can engineer the local tumor microenvironment to enhance the accumulation of therapeutic targeted liposomes, which increases the overall hyperthermal and chemotherapeutic tumor-destroying effects. This cooperative nanosystem holds clinical relevance because gold salts (for rheumatoid arthritis therapies) and doxorubicin-containing liposomes (Doxil®) have been approved for clinical use, and local hyperthemia is a well-established means of destroying diseased tissues in the human body. Although the liposomes in this study are similar to Doxil®, it should be pointed out that the gold nanorod and iron-oxide nanoworm formulations used in the study are somewhat distinct from clinically approved gold or iron oxide materials. Because they are quite bioinert, much work needs to be done to investigate the long-term fate and biosafety of systemically administered gold nanorods in the human body. Cooperative, synergistic therapies using dual or multiple nanomaterials could significantly reduce the required dose of anticancer drugs, mitigating toxic side effects, and more effectively eradiating drug-resistant cancers.