

## Targeted Drug Delivery to Solid Tumors by Thermally Responsive Polypeptides

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This talk will describe thermal targeting of cancer therapeutics to solid tumors by two different classes of thermally responsive recombinant elastin-like polypeptides (ELPs) that exhibit a lower critical solution temperature transition slightly above 37 °C. The first generation of ELPs that we have designed as thermally triggered molecular actuators for drug delivery are pseudorandom copolymers of the VPGXG repeat where the mole fraction of X and the polymer chain length were precisely specified so the polypeptide would undergo its phase transition between 37 and 42 °C. In vivo fluorescence videomicroscopy of human tumors implanted in nude mice demonstrated that the phase transition of this thermally responsive ELP occurs in heated tumors resulting in the formation of micron-size aggregates of the thermally responsive ELP within the heated tumor. The phase transition results in a ~two-fold increase in tumor localization compared to the same polypeptide without hyperthermia even for heating periods as short as one hour. We have observed that thermally cycling the tumor can further increase the uptake of the ELP within the tumor by five-fold compared to the same polypeptide without hyperthermia. Doxorubicin was conjugated to this first generation ELP carrier via an acid labile hydrazone bond to enable release of the drug in the acidic environment of lysosomes. The ELP-doxorubicin conjugate was endocytosed by squamous cell carcinoma cells and trafficked into lysosomes, as observed by the colocalization of the doxorubicin with a lysosome-specific dye by confocal fluorescence microscopy. The ELP-doxorubicin conjugate and free drug exhibited equivalent cytotoxicity in cell culture. These results suggest that thermal targeting of a soluble macromolecular carrier may be useful for the delivery of cancer therapeutics.

A second generation of diblock ELPs will also be described that function as temperature triggered polymer amphiphiles. Two classes of ELP amphiphiles have been synthesized: the first class form monodisperse, ~60 nm diameter micelles in the range of 37-42 °C, a range approved for clinical hyperthermia of solid tumors, which will allow the multivalent presentation of tumor specific ligands only in tumors, thereby enhancing their accumulation in tumors. The second class of diblock ELPs are designed to undergo their

monomer to micelle transition at room temperature to enable thermally triggered loading of drugs or imaging agents into the core of the micelle, followed by release of their contents upon undergoing their micelle- aggregate transition in heated tumors.