431b Engineered Lipid-Based 'Polysomes' for Targeted Multimodal Therapy of Disseminated Metastatic Cancer

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Disseminated metastatic cancer is rarely cured by current treatment options. *In vitro* studies, however, demonstrate synergistic killing of cancer cells when combinations of therapeutic agents are used simultaneously. Clinical studies, on the other hand, suggest that although combined therapeutic modalities are more effective than single-agent therapies, they still do not demonstrate synergistic tumor killing. There is a fundamental difference between studies *in vitro* and clinical studies: *in vitro* all therapeutic modalities are designed to be present simultaneously at the cell microenvironment, and, also intracellularly, both in adequate amounts and for adequate periods of time. *In vivo*, however, it is more challenging to control accumulation and retention of therapeutic compounds at the tumor sites. In strategies that involve combined therapeutic modalities, different compounds may have different transport characteristics (blood circulation times, tumor accumulation, tumor retention times) that result in different 'profiles' at the tumor sites. Thus, the prerequisite for synerstistic killing (i.e. adequate simultaneous presence of all therapeutic modalities at the tumor site) may not be fulfilled. A vehicle is required that will enable simultaneous *in vivo* accumulation and adequate retention times of all combined therapeutic modalities in the tumor interstitium (microenvironment) and also intracellularly.

Working under the hypothesis that simultaneous use of multimodal therapies has synergistic effects on tumor killing (1) only when all modalities are combined at the tumor cell microenvironment, cell surface or intracellularly, and (2) only when all modalities are retained at the target for adequate periods of time, we designed a novel nanoscale vehicle that can (a) simultaneously deliver any combination of therapeutic and imaging modalities at specifically targeted tumor cells, *in vivo*, (b) simultaneously retain all modalities at the tumor microenvironment for adequate time, and (c) simultaneously deliver all modalities into the cytoplasm of cancer cells. This targeted vehicle is an antibody-labeled liposomal structure with different compartments, each containing different modalities, that we call lipid-based 'polysome'.

PEGylated liposomal structures with different compartments were developed and characterized for size and content retention. These structures were then immunolabeled with an anti-HER2/neu antibody and their targeting properties on cancer cells were evaluated *in vitro*. Preliminary results are discussed regarding the cytotoxicity of multimodal therapies delivered by targeted 'polysomes'.

Simultaneous encapsulation and targeting of multiple therapeutic modalities by lipid-based 'polysomes' can potentially result in a highly promising and completely new treatment approach ideally suited for the therapy of disseminated metastatic cancer.