1. Study on the effector domain of MARCKS protein as a cell penetrating peptide.

2. Development of the photoactivatable prodrugs of doxazolidine.

by

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Abstract

Exosomes are natural nanocarriers that deliver signaling molecules, such as DNA, RNA, proteins and lipids, and play significant roles in cell-to-cell communications. Cancer cell derived exosomes promote cancer progression and metastasis by spreading oncogenic materials to neighbors or future sites of metastases. We developed a novel drug delivery system, MARCKS-ED-Photodoxaz, consisting of an exquisitely cytotoxic agent doxazolidine (doxaz), a photoactivatable linker that provides spatiotemporal prodrug activation to minimize unwanted side effects, and the MARCKS-ED peptide that binds exosomes secreted from cancer cells. MARCKS-ED-Photodoxaz is membrane permeable and releases highly potent doxaz with low nM IC_{50} value under near UV irradiation potentially available inside cancer cells as a component of Cerenkov radiation. Our system targeting exosomes and utilizing photochemistry will potentially provide a new approach for the treatment of cancer, especially for highly progressive and invasive metastatic cancers imaged with PET scans. Furthermore, we also explored the glucose transporter targeted prodrugs as well as nontargeted prodrugs of doxazolidine. This thesis consists of four chapters: Chapter 1: the review of exosomes and extracellular vesicle sensing peptides, Chapter 2: the study of the effector domain of MARCKS protein for the development of a targeted photoactivatable prodrug of doxazolidine, Chapter 3: the development

of the targeted and nontargeted prodrugs of doxazolidine, and Chapter 4: conclusions and future directions.