

Cellular Processing of Drug and Gene Delivery Biomaterials

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Drug and gene therapies have the potential to deeply alter human disease treatment by providing safe and permanent cures to a variety of debilitating diseases, enabling the genetic manipulation of stem cells, and facilitating regenerative medicine, yet in many cases, therapeutic efficacy has yet to be realized. Tissue and cell targeting are crucial to maximize therapeutic efficacy and limit off-targeting effects. Simultaneously, improved control over subcellular processing/trafficking, especially in the context of the *in vivo* environment, has been identified as an absolutely critical hurdle. The broad goal of our work is to develop simple strategies for targeted and efficient delivery within remodeling tissues. Tissue repair and extracellular matrix (ECM) turnover are profoundly important in a variety of pathological processes, including hypertension, restenosis, fibrosis, and cancer. Thus, because successful delivery materials must selectively partition into these tissues and enter diseased cells, our approach is to exploit natural ECM remodeling processes for delivery into diseased tissues. To that end, we have developed new methods for the presentation of cell-targeting peptides that rely on the natural upregulation of proteins involved in cellular migration and ECM turnover to facilitate utilization. Work on the coupling of cell targeting with programmed subcellular trafficking and processing will also be presented, including recent studies demonstrating the efficacy of histone-derived peptides to enhance nuclear delivery and processing of DNA.