Development of targeted drug carriers for breast cancer therapy

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OBJECTIVES AND WORK PLAN

Current cancer treatments include surgical intervention, radiation and chemotherapeutic drugs; however these therapies are non-specific resulting in the destruction of both tumor and healthy cells. In this sense, the development of a targeted drug delivery system is highly desirable. This approach consists essentially in designing smart new anticancer therapeutics meant to specifically target some unique aspects of tumor biology. Such drug delivery systems should enable improved biodistribution, tissue uptake and pharmacokinetics of therapeutic agents. Nanocarrier-based drug delivery offers several advantages such as an increase of drug stability and bioavailability, by preventing its early degradation, the ability to deliver therapeutic agents, and thus reduce non-specific toxicity. The aim of this PhD project is to develop a targeted therapeutic nanocarrier for the treatment of cancer. The isolation of novel targeting moieties – aptamers - for cancer cells shall be achieved through the SELEX technique. This methodology consists in the use of a random library of single-stranded DNA or RNA, flanked by two primer-binding regions, and uses an iterative process that specifically amplifies sequences that have high binding affinity to a given target. In several selection rounds, binders are amplified and nonspecific binders are removed in a partitioning step. Furthermore, a rationally designed gene silencing siRNA will be used as a therapeutic agent, directed to targets in relevant pathways involved in the development and proliferation of breast cancer cells. The siRNA will follow conjugation to previously isolated aptamers. This may be achieved either directly or to an encapsulated form of the therapeutic agent in a nanocarrier. In the case of nanocarrier encapsulation, these will enhance the stability, bioavailability and selectivity of these constructs. But more importantly, the ability to design materials with controlled crosslinking density determining material fate would enable to program the delivery rate of the therapeutic agents and prolonging its duration *in vivo*. The delivery and internalization of the conjugated aptamer-siRNA or nanocarrier will be studied and ultimately, the optimization of the delivery system is predicted. These studies will primarily undergo *in vitro* validation using various cancer cell models. Eventually, in vivo studies shall also be conducted.

RESULTS

Ongoing cycles of SELEX. Culture optimization of different cell lines and establishment of procedures for siRNA transfection and protein expression.