Whole-Body Computational Design of Biomimetic Cells that Inhibit Circulating Tumor Cells

Tanishq Abraham[1] and Cheemeng Tan[1]
[1]University of California, Davis, Davis, CA

Introduction: Circulating tumor cells (CTCs) cause metastasis, which is responsible for over 90% of cancer deaths. There are multiple CTC-destroying therapies for the prevention of metastasis, but they often require extracorporeal devices or implanted stents. We propose a new nanoparticle-based approach for detecting and destroying CTCs in human circulation. The liposome-based multifunctional artificial cells bind to the CTCs and release a drug payload onto the CTCs. Such biomimetic cells have been previously used to produce therapeutic proteins within solid tumors. To better evaluate the efficacy of this proposed therapy and optimize the formulation, we develop whole-body pharmacokinetic models (WPBPK) for various types of liposomes and the CTCs.

Materials and Methods: We developed three WPBPK models, each with 12 organs, to describe the liposome bioavailability. All models were mass-balance ordinary differential equations of liposome concentration in organ compartments. The first two models were blood-flow limited models of small unilamellar liposomes (SUVs), and large unilamellar liposomes (LUVs), respectively. The third model was a model for SUVs, incorporating transvascular transport. Literature data were used to validate the liposomal mathematical models. A mathematical whole-body model for circulating tumor cells was also developed using similar principles as the WPBPK models. The CTCs entered the circulation in our model based on the shedding rate of the primary tumor. Rate constants described clearance of the CTCs from circulation, extravasation, and arrest in a secondary organ. Literature data were used to fit CTC-specific parameters. The two models were combined, and a binding reaction between the CTCs and the liposomes was incorporated with a simple kinetic rate constant. This reaction simulated the interaction between the artificial cell with the CTCs in circulation. We assumed that the liposomes have an anti-EpCAM antibody on their surface that binds to the CTCs.

Results and Discussion: Figure 1 is a plot of the simulation of the first model. The model shows that increasing the size decreases transport of the liposomes, and so does organ clearance. However, the system is more sensitive to liver clearance than reticuloendothelial clearance. To determine model parameters (e.g., the RES clearance), we compiled data from the literature. The data will be useful for future work on mathematical modeling of liposome pharmacokinetics. For the CTC model, literature data was used to fit CTC-specific parameters such as arrest rate in each organ and clearance by the immune system. The combined CTC-liposome model showed the efficient capture of the liposomes with the CTCs. The computational model suggests that biomimetic cells may, therefore, be used to capture and destroy circulating tumor cells.

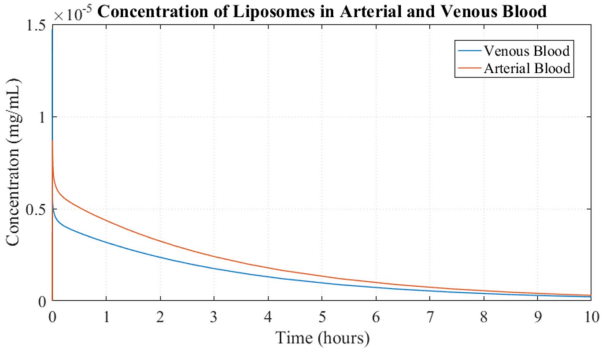

Figure 1: SUV model concentration profiles

Conclusion: Much of the work regarding mathematical models of liposome transport have focused on intra-tumoral transport due to their application for tumor drug delivery. In addition, the current whole-body models focus on the bioavailability of the encapsulated drug, not the transport and circulation of the liposome itself. This work is important for whole-body mathematical modeling of liposomes *a priori*, especially for investigating liposomal drug delivery in locations apart from tumors. This work also provides a platform to develop a model for circulating liposomes from experimental data. The results of this work provide an analysis of the effect of the liposome size and the vascular physiology of the tissues. Furthermore, this work has resulted in the determination of several new parameters that can better describe the distribution of CTCs within the body. The mathematical model for CTCs developed here can, therefore, be used to study the formation of metastases quantitatively. Based on the computational work, we aim to engineer multi-functional biomimetic cells that attack and provide therapeutics to the primary tumor, as well as prevent metastasis by destroying circulating tumor cells. While there are multiple CTC-destroying therapies for the prevention of metastasis, there is no systematic comparison between these methods. We plan to address this gap of knowledge by comparing our proposed biomimetic cells with other CTC-targeted therapies using the mathematical models.