Identifying Key Properties of Effective Targeted Cancer Therapeutics

Introduction: As next-generation biotherapeutics begin to play a more central role in the targeted treatment of disease, it becomes increasingly important to understand the molecular requirements of drug efficacy, both in terms of the disease tissue as well as the therapeutic itself. Mecahnistic models present a unique opportunity to simulate the new therapeutic in the context of various disease indications to determine which attributes of the drug and the disease tissue are most advantageous or desired.

Goal: This study was undertaken to understand which attributes of a next-generation bispecific antibody biotherapeutic and which properties of the tumor tissue itself are desirable for maximum treatment efficacy (specific toxin deposition in tumor tissue).

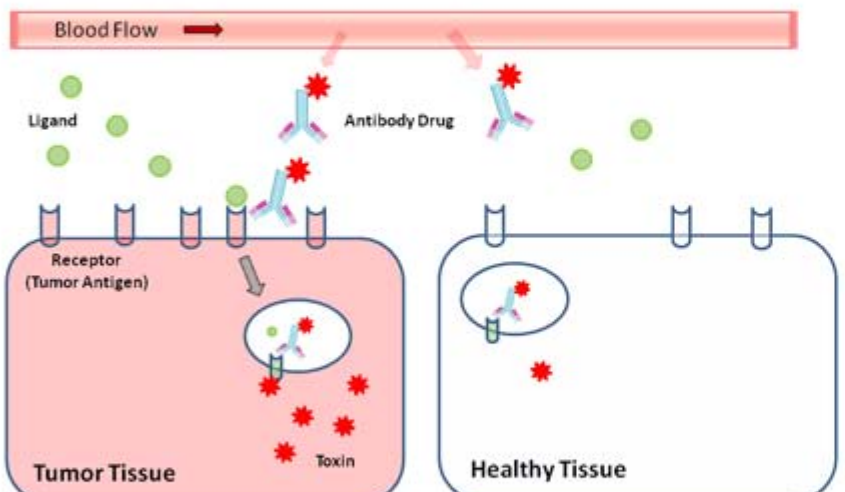

Figure 3. Illustration of the tumor-toxin targetting strategy in which an antibody-toxin molecule are sepecifically targeted to tumor tissue while minimizing impact on healthy tissue.

Model: Consisted of ~30 reactions, ~50 parameters, and ~25 variables distributed among 3 compartments, "Tumor Tissue", "Healthy Tissue", and "Blood" (see Figure 3).

Sensitivity Analysis & Calibration: Parameters which were the most critical for controlling the specificity of drug deposition in the Tumor Tissue compartment were identified/ranked via Global Sensitivity Analysis. This provided a good starting point toward understanding which biotherapeutic/tumor properties (parameters) will dominate therapeutic outcome.

Results: Following extensive parameter sweep analysis of properties such as receptor expression level, receptor half-life, receptor expression ratio, drug transport, and drug binding affinity, a thorough understanding of desirable drug/tumor properties for therapeutic index was obtained.

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