ANTIBODY SPLIT-ENZYM CONJUGATES COUPLING HIGH DRUG DELIVERY WITH LOW OFF-TARGET TOXICITY

Elham Hatami (Shawn C Owen)
Department Of pharmaceutical Chemistry

The objective of this project is to suggest an answer/methodology to the following question: *How to deliver a potent cytotoxic drug specifically to tumor cells?*

In order to solve the problem of delivering high concentrations of potent drug just on the tumor site and not the off-target sites we propose to use inactive enzyme parts which will become active when they are located next to each other at the tumor site (Figure 1). Each of the fragments of the enzyme is fused to two separate Fabs (Antibodies). After binding to the target, the enzyme halves refold to regenerate enzymatic activity. The enzyme can then catalyze inactive prodrugs into active drugs specifically at the tumor site. This method would be able to target many solid tumors - in this study we chose the HER2+ breast cancer. Our objective is to demonstrate the activation of β-lactamase on HER2+ breast cancer cells for prodrug treatment**.**

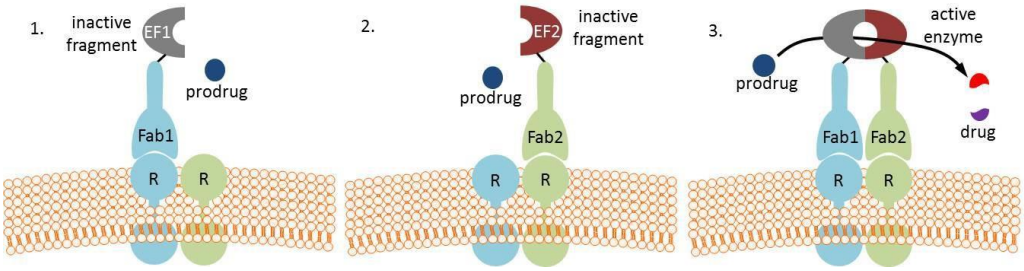

Figure 1 Illustration of proposed mechanism. 1 & 2) Fabs fused to inactive enzyme fragments (EF1/2). 3) Activation of enzyme by complementation when both Fabs bind target receptor (R).