Innovation: A method which bypasses the multi-year *in-vitro* (test tube) approach to drug discovery by creating a bullet directly *in-vivo* (inside an animal carrying the relevant disease). That bullet carries an appropriate payload and delivers it only to the targeted tumor. The combination of the bullet and payload is the "aptabody."

Functional Group	Function	Antibody	Aptabody
Amino acids	affinity and specificity	✓	✓
Fatty acids	tissue delivery and bioavailability		✓
Sugars & Carbohydrates	specificity and tissue targeting		✓
Small Organics & Metals	enhanced chemical activity		✓

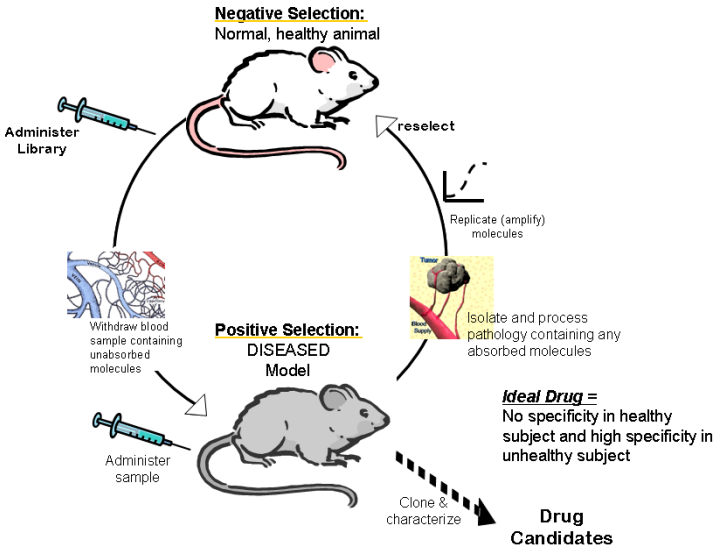
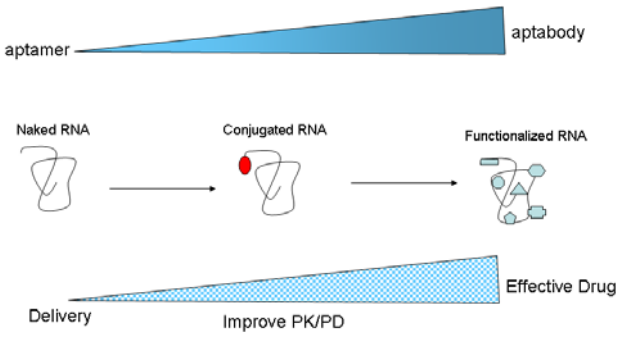


Figure 1. Selection of highly specific aptabody ligands in a diseased-animal model. A library of aptabodies is pre-exposed in negative selection to a normal, healthy mouse followed by positive selection in a diseased mouse to maximize specificity to diseased tissue. As selection progresses, the library pool is enriched with aptabodies specific to the diseased tissue. These aptabodies can be used as delivery vehicles or screened for pharmacological activity.

Hypothesis/Rationale/Purpose: Heading against conventional wisdom, we question whether drug discovery can be initiated directly in whole-animal models, thereby bypassing *in vitro* testing entirely. The method has been previously applied using antibody/peptide-phage display platforms with some success[4,5].

Figure 2. Conceptual Relationship Between Aptamers and Aptabodies. Aptamers[1-3] are unmodified or 'naked' single-stranded DNA or RNA that form unique secondary structures. They act as ligands for target delivery. These nucleic acid ligands tethered to a known drug or compound may improve the pharmacokinetic properties of the drug or compound. Aptabodies are supramolecular structures formed by the tethering of more than one drug, compound, or functional group to single-stranded nucleic acid scaffolds. These macromolecules may posses effective ADME and drug-like properties, and represent a new class of pharmaceutical molecules.



Objectives: 1) Create a combinatorial library of aptabodies, 2) Perform selection in a Xenograft breast cancer mouse model, and 3) Characterize the "enriched" polyclonal pool of aptabodies.

Methods: A random library of 10^{14} RNA aptamers will be functionalized with 20 unique amino acids, 10 unique fatty acids, and 15 unique carbohydrates forming the aptabody library (using established patent pending techniques). As described in Figures 1 and 2, the assembled aptabody library will be administered by tail-vein to a breast cancer Xenograft mouse model for multiple rounds of selection to enrich for tumor-targeting aptabodies. Final round characterization of pool clones for tumor-targeting properties will be as described previously using established methods.

Significance/Relevance: Because the proposed method is an *in-vivo* (directly tested in the animal model) approach, it avoids the majority of the bench testing for breast cancer research, saving several years and approximately 35% of the R&D cost. By using a breast cancer mouse model, the approach reduces the false starts in drug development.