

# **Collegiate Inventors Competition®**

## **Sample Abstract**

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## **Part 1: Summary of Invention**

### **Liposomase for Generalizeable Drug Delivery**

The major challenge facing cancer therapy is achieving specificity. Current efforts are focused on developing targeted therapeutics specific to cancer. Another approach is to selectively deliver cytotoxic agents to the tumor site. Here, I describe an invention using a previously unknown protein named liposomase, which is secreted by the tumor-colonizing anaerobic bacterium *Clostridium novyi-NT*, to induce the targeted rapid release of liposomal payloads within tumors. This technology is not limited to a particular drug or tumor type and could potentially be incorporated into diverse experimental approaches for the specific delivery of chemotherapeutic agents to tumors.

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## **Sample Student Essay**

## Part 2: Background Information

### The Problem

The challenge for cancer therapy is killing cancer cells without damaging healthy tissue. In this regard, cancer drugs are akin to pizza: To target your specific audience, you can make better pizza, or you can deliver pizza more efficiently. Both approaches are not mutually exclusive, but the 'better drug' strategy is currently dominant, giving us targeted therapies like Gleevec, whereas the 'better delivery' strategy is still in its infancy. Here, I describe a generalizable method for specifically and rapidly delivering large bioavailable quantities of your drug of choice specifically to tumors.

### The Solution

There are three ingredients which make up this invention: (1) the spores of *Clostridium novyi-NT*, a strictly anaerobic bacterium which germinates only within tumors and not normal tissue; (2) a protein secreted by this bacterium named liposomase which is able to disrupt lipid membranes and release their contents; and (3) your drug of choice packaged within liposomes which have been optimized for physical robustness.

How does this recipe work conceptually? Tumors grow so quickly that they exhaust oxygen which their abnormal vasculature is unable to replenish. This low-oxygen tumor environment is the perfect niche for *Clostridium novyi-NT*, a bacterium which is unable to grow in the presence of oxygen. When spores of *C. novyi-NT* are intravenously injected into a mouse bearing an established tumor, this bacterium will germinate only within the tumor and nowhere else. *C. novyi-NT* also happens to naturally secrete a previously unknown protein termed liposomase which can physically disrupt lipid membranes. Drug-loaded liposomes injected intravenously will thus rapidly burst and release their payloads only within the liposomase-rich tumors but otherwise remain intact in healthy tissues. Essentially, this invention combines the selective tumor toxicity of the drug, the passive leakage of liposomes through the characteristic fenestrations found in tumor vessels and the exquisite ability of *C. novyi-NT* to germinate and exert its liposome-releasing properties only within tumors and not healthy tissue. This invention is akin to a precision rifle where *C. novyi-NT* is the scope and liposomase is the trigger which releases liposomal ammunition on command at the tumor target.

### What is new about this invention?

There are several novel aspects to this invention. This is the first instance demonstrating the combined use of *C. novyi-NT* (or any bacterium) and liposomes for the purpose of targeted drug delivery (See Appendix). Further, the secreted factor responsible for liposome disruption has been purified and identified as a previously unknown lipase which we named liposomase. This opens the door to therapeutic strategies in addition to those based on bacteria. For example, liposomase could be attached to antibodies or encoded within vectors used for gene therapy. As virtually any therapeutic agent can be packaged in liposomes and can thereby act as a "prodrug", liposomase offers a number of interesting possibilities for the specific delivery of drugs to tumors. Remarkably, while lipases (including liposomase) are generally unable to hydrolyze phospholipids, experimental evidence suggests that liposomase disrupts liposomes using a physical mechanism. This is not an intuitively obvious phenomenon. It is therefore not surprising that the use of neutral lipases for the triggered release of liposomal drugs has never been documented.

## What is the story behind the invention?

*Clostridium novyi-NT* is a strictly anaerobic bacterium identified in a screen by the Vogelstein lab for its ability to selectively colonize hypoxic areas within experimental tumors. While characterizing *C. novyi-NT* as a graduate student, I observed that it was able to cause hemolysis when cultured on blood agar plates. Because enzymes that rupture red blood cells can disrupt lipid bilayers, I hypothesized that the bacterium's hemolytic properties might be exploited to enable the rapid release and enrichment of liposome-encapsulated drugs within tumors. Under the mentorship of Professor Bert Vogelstein, I initiated experiments to test this theory. In accord with this hypothesis, large, established tumors were often cured when treated with *C. novyi-NT* plus a single dose of liposomal doxorubicin or liposomal irinotecan. Much to our surprise, we discovered that the secreted factor responsible for this phenomenon was not a conventional hemolysin but an unknown member of the lipase family. We named this gene liposomase. Details of this invention are given below.

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## Why is this invention important?

Most cancer drugs fail in the clinics not because they are ineffective in killing cancer cells. Rather, the problem is that one cannot give a dose high enough to eradicate the tumor without also killing the patient. In essence, they are effective but not very specific. We have often heard that we need to find the cure for cancer. We in fact already do have many drugs which will effectively kill cancer cells. The challenge is getting enough of the drug into tumors without collaterally damaging healthy tissue. Not only does the described technology accomplish this goal, it is also not limited to any one particular tumor type or drug. Its potential to 'rescue' toxic drugs and improve already successful drugs is therefore very broad.

## References and Notes

1. Papahadjopoulos, D. et al. Sterically stabilized liposomes: improvements in pharmacokinetics and antitumor therapeutic efficacy. *Proc Natl Acad Sci U S A* 88, 11460-4 (1991).
2. Sakurai, J., Nagahama, M. & Oda, M. Clostridium perfringens alpha-toxin: characterization and mode of action. *J Biochem (Tokyo)* 136, 569-74 (2004).
3. Cheong, I. et al. A bacterial protein enhances the release and efficacy of liposomal cancer drugs. *Science* 314, 1308-11 (2006).