ISTF Project # 15-3056 was developed in response to the 2015-2016 Internet Science and Technology Fair\*

Project Title: NanoWarriors

National Critical Technology (NCT): Living Systems

Sub Category: Biocompatible Materials

Specific Technology Application: Microcapsules

Statement:

Pancreatic cancer has almost a 100% mortality rate. Most treatments are ineffective and cannot target the specific area that significantly treats the cancer. Nanocapsules can be created to detect pancreatic cancer and apply treatments that are targeted specifically to the tumor. These will increase the effectiveness of preexisting treatments.

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ISTF Component Answers

Component 1

Task 1 - Describe in detail the problem your team selected and explain why it is important for your team to investigate the problem:

Only 23% of people diagnosed with pancreatic cancer live at least one year after their diagnosis and only 4% of people live at least five years after their diagnosis. These numbers reveal the startlingly high mortality rate of pancreatic cancer, a number nearly as high as the the rate of the disease. In addition, traditional cancer treatment methods are ineffective against pancreatic cancer which reveals the need for a more effective method of treating pancreatic cancer that is specific to this type of cancer. With the development of targeted medicines that will be delivered in the early stages of cancer comes the hopeful decline in the mortality rate of pancreatic cancer. Because of the high mortality rate of pancreatic cancer and its rising prevalence in today’s society, it is imperative that this method of eradicating pancreatic cancer is explored.

<http://www.webmd.com/cancer/pancreatic-cancer/digestive-diseases-pancreatic-cancer>

<http://www.mayoclinic.org/diseases-conditions/pancreatic-cancer/basics/treatment/con-20028153>

<http://chemocare.com/chemotherapy/drug-info/erlotinib.aspx>

Task 2 - Describe how your team decided on the problem you are investigating and explain what steps you took to narrow the focus of your investigation:

Pancreatic cancer is set to be the second most deadly cancer in the world by 2030. Pancreatic cancer would be second only to lung cancer and it is catching up. While cancer rates in the US have been in declining in recent years, pancreatic cancer is one of the few cancers that does not follow this trend and little progress has been made in research for pancreatic cancer. On top of this, pancreatic cancer is a unique cancer in that it originates deep within the abdomen which makes it hard to reach. Additionally, the pancreas is surrounded by thick drug-blocking tissue and proliferates at early stages. This makes it hard to deliver common cancer treatments in order to stop its spread. Because of all of these difficulties in treating pancreatic cancer, pancreatic cancer calls for an innovative solution.

The usage of nanocapsules have also been studied in the drug field in recent years. Most often, they are a delivery method for drugs, where the drug is inside or on the surface of metal nanocapsules, such as aluminum. By using nanoparticles to deliver drugs, degradation of otherwise quickly-degrading drugs or a short-lived immune response without immunity being built may be avoided.

<http://www.webmd.com/cancer/pancreatic-cancer/news/20140519/pancreatic-cancer-will-be-2nd-deadliest-cancer-by-2030-study>

Task 3 - Locate and document (using facts and figures) and describe how: two organizations, educational institutions or research facilities are doing significant research to solve the problem your team identified:

The Lustgarten Foundation is one of many such major researchers in the field that are studying pancreatic cancer and attempting to create methods for its treatment. This research institution is specifically studying the genetic makeup of pancreatic cancer and is also attempting to find the genes within the cancer that cause it to become hereditary. In addition, they are attempting to make tests that will be able to detect pancreatic cancer in the early stages, which would make it more treatable. They have spent over $110 million on more than 200 research projects in over 60 different research centers worldwide, due to the lack of federal funding in pancreatic cancer - around 2% of all research money. They recognized the paucity in funding and stepped in to aid research projects everywhere. Additionally, the Hirshberg Foundation for Pancreatic Cancer is attempting to perform research on pancreatic cancer. The Hirshberg Foundation began research in 1997, and focused on physiology, early diagnosis, treatment, and prevention of pancreatic cancer. The foundation of their research focuses on basic science, translational research, and the creation of a pancreatic tissue bank. The Hirshberg Foundation attempts to identify novel genetic and epigenetic alterations responsible for the development and progression of pancreatic cancer, understanding cell signaling pathways in promoting or inhibiting pancreatic cancer, and identifying biomarkers towards to goal of personal treatment of pancreatic cancer. The Hirshberg Foundation operates on a budget of $4,725,000 from 2009-2014 for their basic sciences and $7,500,000 from 2012-2017 for their translational research. To help sponsor other research in pancreatic cancer, the Hirshberg Foundation also provides start-up funding for basic scientists and clinicians.

<http://www.curepc.org/index.cfm?objectid=C11C7D70-1964-11E2-B663000C296BA163>

<http://www.pancreatic.org/site/c.htJYJ8MPIwE/b.887629/k.DBFB/Research.htm>

Task 4 - Document (using two different sources based on facts and figures) what effect this problem has on people's lives:

Because of its low survival rate, and devastating effects upon the body, pancreatic cancer often has a highly detrimental effect upon people’s physical and emotional health. Emotionally, people think more of death and dying. They become more aware of the effect that it is having on their family, friends, and career. This leads to people being more stressed and needing more guidance than other forms of cancer and often seek external guidance from groups like cancer support groups, churches, and spiritual groups. Physically, PC causes a myriad of symptoms, which include yellowing of the skin and eyes, pain in the upper or middle abdomen or back, unexplained weight loss, loss of appetite, fatigue, or depression. In addition, a huge number of patients die from PC, which means that it ends the life of whoever has it. Only 4% of people are living 5 years after diagnosis, and this number gets even closer to 0% as time goes on. In the end, death is almost inevitable from PC. Pancreatic cancer has many effects on people’s lives and the ones around them, both physical and emotional.

<http://www.cancer.org/cancer/pancreaticcancer/detailedguide/pancreatic-cancer-after-emotional-health>

Task 5 - Document (using two different sources based on facts and figures) the impact the problem has on the economy of our nation or on your community:

There are significant economic costs upon the economy that are imparted when a person has pancreatic cancer no matter what health system a person is. In Sweden, for example, on average the medical costs from pancreatic cancer when adjusted for inflation is $30,547.08. 55% of this comes from the cost that was attributed to hospitalization, 20% due to long term care, 11% due to chemotherapy, 9% due to diagnostics, and 4% due to radiotherapy. This led to an overall cost of $20.9 million on the health care system of Sweden. Similarly, in the USA in a study of over 15,000 people of which 97% were observed to death, the mean cost of pancreatic cancer per person was $65,500. Thus, despite poor prognosis and short survival, the economic burden of pancreatic cancer in the elderly is substantial.

<http://www.tandfonline.com/doi/pdf/10.1080/02841860310000386>

<http://www.ncbi.nlm.nih.gov/pubmed/22415469>

Component 2

Task 1 - Provide a history of the National Critical Technology (NCT) technical application your team is researching. Include at least three significant scientific discoveries, advances and milestones using documented facts and figures:

In 1953, Barrett Green described the process of creation of oil-containing microcapsules. He used a method called salt-coacervation to produce these capsules. The microcapsules that he produced were several microns in diameter, and each one contained oil surrounded by a relatively thick wall of gelled colloid material. Through his observations, he found that the capsules could be dispersed in water, but they tended to agglomerate like bunches of grapes when water was removed.

James Hayward, along with other scientists in 1986, created a new type of microcapsule that was more conducive for the delivery of drugs. He created a capsule that would encapsulate its payload with liposomes, which were encapsulated in a hydrocolloid matrix that could be composed of gelatin. This type of microcapsule could be used for drug delivery because of the structure of the liposomes. Previous microcapsule designs would only be able to carry larger components due to the relative leakiness of the design.

Another advancement in the use of nanoparticles to deliver treatments was the creation of nanocapsules. Nanocapsules had a similar structure to microcapsules, but they were significantly smaller, on the order of nanometers instead of microns. These nanocapsules were useful because cells could take them in because of their relatively small size. Because of the similarities between microcapsules and nanocapsules, advancement in nanocapsules can also apply to microcapsules.

<http://onlinelibrary.wiley.com/doi/10.1016/0014-5793(77)80717-5/epdf>

<https://patentscope.wipo.int/search/en/detail.jsf?docId=WO1987001587>

<http://patft.uspto.gov/netacgi/nph-Parser?Sect2=PTO1&Sect2=HITOFF&p=1&u=/netahtml/PTO/search-bool.html&r=1&f=G&l=50&d=PALL&RefSrch=yes&Query=PN/2800458>

<http://www.pbs.org/wgbh/aso/databank/entries/dm52sa.html>

<http://www.salk.edu/about/history-of-salk/jonas-salk/>

<http://www.historyofvaccines.org/content/timelines/hilleman>

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3648923/>

Task 2 - Identify two scientists or engineers who have made major contributions to the development of the technical application your team selected and explain how their work is related:

One scientist who made great strides in the field of nanocapsule delivery of targeted medicines is Peter Burkhard from UConn. Dr. Burkhard had managed to make a treatment using nanocapsules for the deadliest form of malaria parasite known as *Plasmodium falciparum.* The standard problem with making treatments for malaria lies in the ability of the malaria parasite to hide and avoid detection from the immune system. The treatment that Dr. Burkhard made, though, is able to find the parasite utilizing the perfect symmetry and 60 faces of nanoparticles that can seek the parasite out. The particle then induces the immune system to attack the parasite leading to the death of the parasite. This method has been shown to be very effective in mice with a 90-100 percent success rate of eradicating the parasite. Another researcher who made great strides in the study of nanocapsules in medicine is Yuan Ping from Nanyang Technological University in Singapore who has created an oral treatment that has bacteria coated with nanoparticles that serve as a nanocapsule delivering the treatment. This is done in order to make sure that the bacteria can make it through the digestive tract and into the area of the tumor. Then the bacteria induces a surge in the immune system in order to block off the blood vessels and inhibit tumor angiogenesis ([blood vessel formation](http://medicalxpress.com/tags/blood+vessel+formation/)). This will starve the tumor of the resources it needs and prevent it from metastasizing.

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3559243/>

Task 3 - Explain how the technical application your team is researching is currently being used to solve the problem in Component One. Include documentation regarding at least two benefits and two limitations:

Nanocapsules are currently being used to solve the issue by being marked with surface properties of specific cells, using nanoconstructs that are targeted to specific cellular receptors. These nanocapsules can carry drugs to be delivered to the cancerous cell in order to kill it. There are certainly many advantages to this method of attacking pancreatic cancer such as increasing the accuracy of intracellular drug delivery, helping to destroy tumor stromal fibroblasts, and facilitating the penetration of the tumor endothelial cell layer. Additionally, nanocapsules are superior to other vectors such as viral vectors because they have greater potential when carrying treatments other than genetic treatments and also do not stimulate an immune response. Another method of treating pancreatic cancer involves a drug housed by a biodegradable nanoparticle. This method though is disadvantageous though, because these nanoparticles are hard to produce, and when used, are somewhat ineffective at raising the concentration of drugs.

<http://www.epo.org/learning-events/european-inventor/finalists/2013/couvreur/feature.html>

<http://nano.cancer.gov/action/programs/platforms/emorysm.asp>

<http://www.medicalnewstoday.com/articles/270100.php>

Task 4 - Based on what you have learned in Component Two, explain how science has advanced technology regarding the technical application your team has researched:

Science has made many advancements in nanocapsule and microcapsule technology. Scientists began by creating basic microcapsules that could contain a specific item inside. As time progressed, microcapsule use began to become more feasible and stable, and drugs with even smaller components were able to be carried by them. Eventually, changes in capsule production allowed scientists to create nanocapsules, an even smaller version of a microcapsule. By adding surface markers and attaching antibodies to these nanocapsules, scientists were able to create targeted treatments that would attach to a specific type of cell, such as Dr. Burkhard’s approach to seeking parasites out, which had higher efficiencies and different approaches than other, more conventional treatments. The field of nano and micro encapsulation enables unique and effective approaches to the most pressing problems of today.

Component 3:

Task 1 - Propose an original improvement or new use regarding your team's technical application. Explain in detail how it works and provide a link to your design requirement:

We propose the delivery of a cancer treatment through a nanocapsule. The nanocapsules will be created with Poly(amidoamine) (PAMAM) dendrimers, which have large potential in the field of drug delivery though nanocapsules, through their biocompatible attributes and their predictable surface and container properties. The nanocapsules will specifically bind to pancreatic cells that are cancerous using antibodies specifically marked for proteins found on the surface of pancreatic cancer cells. Antibodies can be used for the identification of proteins like the 99 proteins specific to pancreatic cancer cells below. In addition, folate receptor antibodies/folic acid can be used because pancreatic cancer cells contain a larger number of these receptors. When the nanocapsules are attached to the pancreatic cancer cells, a gene inside the nanocapsules, like a functioning copy of a tumor suppressor gene such as p53 may be inserted for the promotion of apoptosis to prevent pancreatic cancer growth. Because working copies of p53 will be inserted, this treatment should have little to no side effect on other cells even if it is taken up by them, as normal cells already have working copies of p53. An approach where p53 was used has not been applied before to pancreatic cancer, and also has had extremely limited application in the field of nanoparticles. Additionally, this nanocapsule may be inserted before the first signs of pancreatic cancer because of its ability to only bind to proteins found on pancreatic cells that are cancerous. Afterwards, these nanocapsules may also be able to invade cancer cells that have metastasized, if it has gotten that far.

<http://www.sciencedirect.com/science/article/pii/S1359644601017573>

<http://www.genecards.org/cgi-bin/carddisp.pl?gene=TP53&keywords=p53>

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2949717/>

<http://www.ncbi.nlm.nih.gov/pubmed/22350599>

Task 2 - Explain what economic impact your team's proposed improvement or new use would have as it relates to the problem you identified in Component One:

One of the promises that this new system of treating cancer brings about is the possibility for the cost of cancer treatment to go down considerably. This is because the treatment only has to be used a few times in order to attack the cancer effectively. One or two injections of the treatment should be extremely effective against this type of pancreatic cancer. This is a major improvement of current treatments that need to be repeated and are also very expensive. Initially buying the machinery need for radiation is expensive, as is maintaining it. This treatment will reduce the need for those machines. It will also make treating cancer more affordable for insurance companies and will reduce insurance premiums for all making it a huge positive impact on the economy.

Task 3 - Identify and describe a company, federal agency or academic research laboratory that could carry out your team's proposed new improvement or new use:

There are several different entities that can provide the infrastructure and resources that are necessary for the research and the clinical trials that must take place for this solution to come into play. One such institution is the National Institute of Health (NIH), specifically the Nanotechnology Characterization Lab, which has both done research in nanotechnology and cancer. In addition to the NIH, there exist many pharmaceutical companies that have the resources required to undertake such a research project, with two such examples being Pfizer and Novartis. Finally, the clinical trials that need to take place for this drug can take place at companies like PRC Clinical and Datapharm Australia, which have previously directed clinical trials.

<http://ncl.cancer.gov/>

Task 4 - Using e-mail, obtain the opinion of a scientist or engineer about your team's proposed improvement or new use for the technical application. Add this information to your website by including the individual's name, organization, copies of the e-mail the team sent and the reply it received from its inquiry.

If your team is not able to obtain a response to your inquiry, provide an example of the e-mail request you sent and the names of those whom you sent the request:

To Nanotechnology Characterization Lab, National Institutes of Health

To Whom It May Concern,

My name is Edward L. and I am a freshman at the Bergen County Academies in New Jersey. I am working with Ciro R. and Shalin P. in an online science fair called ISTF (Internet Science and Technology Fair) where students are encouraged to think about future ideas. We heard about your research in the cancer area and the work that you’ve done in the Nanotechnology Characterization Lab, and we’re wondering if you could provide some feedback about our idea.

In our research, we realized that correct pancreatic cancer treatments were extremely ineffective, as pancreatic cancer has almost a 100% mortality rate over a longer period of time. Our idea is a type of nanocapsule that will house certain genetic treatments for pancreatic cancer, such as a working copy of a tumor suppressor gene like p53. It will be coated with antibodies specifically for surface markers occurring mostly on pancreatic cancer cells. These capsules could be introduced before the onset of pancreatic cancer symptoms, which could allow the instant recognition of these cells after such surface markers appear.

We believe that this solution will be superior to other viral vectors as a nanocapsule is capable of carrying other treatments besides genetic treatments, and because nanocapsules do not stimulate an immune response, which will enable them to be introduced in the body before any symptoms appear.

Our team understands that you may be busy, but we would be extremely grateful if you could supply any feedback on this idea. If you need any additional information, you can find it at: <https://docs.google.com/document/d/1slASMWPOxHtd323sL0Hvh5yRKFrPW94g91JeNE8g88U/edit?usp=sharing>

Sincerely,

Eddie L., Shalin P., Ciro R.

We received a response on February 23, 2016 from Pavan P. Adiseshaiah, Ph.D., Section Head of Cancer Biology in the Nanotechnology Characterization Lab:

Hi Edward,

Thanks for the enquiry and presenting an idea to overcome pancreatic cancer development. There are several caveats based on limited information provided by you.

1. As mentioned, pancreatic cancer development takes a long time. In addition, diagnosis is usually at a late-stage when the prognosis is poor. Initial mutation is in KRAS oncogene followed by p53/other cycle genes.
2. Depositing a nanocapsule containing wild type p53 with a targeting ligand at the pancreatic site is an interesting thought.
   1. Expression of targeting ligand over different stages of tumor development.
   2. Biocompatibility of the nanocapsule (e.g., perturbs cellular functions at the site of implant, interaction with immune cells).
   3. How the introduction of nanocapsule will be determined in patient population? Initial inflammatory reaction at the pancreatic site is asymptomatic.
   4. How is the release and delivery of p53 controlled prior to disease development, delivery can be compromised due to predominant desmoplastic stroma.

I want to commend you for your idea, research the pancreatic cancer and understanding the complexity involved in the drug delivery. Please feel free to reach out to me, if you need further assistance.

Best wishes,

Pavan

Our reply to Dr. Adiseshaiah was:

Dr. Adiseshaiah:

Thank you for taking some time to reply to our email and give us some feedback.

We had some ideas pertaining to your previous feedback that we would like to share with you. We would be extremely grateful if you could provide some feedback.

1. Seeing that pancreatic cancer is usually diagnosed at a later stage, we were thinking that this treatment could be delivered before the onset of symptoms, starting from a certain age and onwards as deemed necessary. This way, the nanocapsules can begin to deliver the treatment as soon as the targeting ligand on the nanocapsule binds to a receptor on the cell. Would this approach be feasible?
2. For the stability of the nanocapsule, we were thinking that trials could be conducted to identify the longevity and effectiveness of such a treatment, which could then lead to determining the frequency of re-administration
3. One potential receptor that we were considering was the folate receptor (FRβ+) which seem prevalent in pancreatic cancer cells, as we found here: <http://www.ncbi.nlm.nih.gov/pubmed/22350599>. Would this be potentially possible to target?
4. We identified Poly(amidoamine) (PAMAM) dendrimers as a potential material for these nanocapsules, which can improve biocompatibility. Do you have any feedback on this?
5. Our group was thinking of beginning the administration of the drug after a certain age, where risk of pancreatic cancer is empirically shown to increase in a certain demographic group.
6. Regarding predominant desmoplastic stroma, would delivery still be compromised if nanocapsules specifically targeted receptors predominantly on pancreatic cancer cells?

Again, we’d like to thank you for taking your time to respond to our previous email.

Sincerely,

Eddie L., Shalin P., Ciro R.

On February 26, we received this response:

Hi Edward,

Unfortunately, none of us knows who and when anyone will get cancer. There are risk factors such as smoking, obesity, African American community, and diabetic patients are more prone from getting the disease. Most of the cancers, if detected early can be surgically resected, which provides better option from avoiding reoccurrence and using cytotoxic drugs. Most of the pancreatic tumors at an early stage remain asymptomatic and difficult to detect. Only at a later stage, symptoms manifest.

Following the initiation of pancreatic disease, initially by increased inflammatory response at the pancreas, followed by mutation in KRAS, and it takes over a decade for other mutations to occur and progress the disease to metastatic stage. At this stage, the disease is difficult to resect and function is compromised.

My suggestion would be keeping the same concept and evaluate its efficacy in a mouse model with p53 mutation. Other factors - such as release of the plasmid, immunogenicity, expression of gene and receptor (most of it stromal cells and only <20% comprises of cancer cells), and evaluating toxicity from platform (dendrimer).

I hope this information is helpful.

Pavan

**Team Assessment:**

Teaming and Communication:

Research and Innovation:

Three Lessons: