Stories of Discovery:

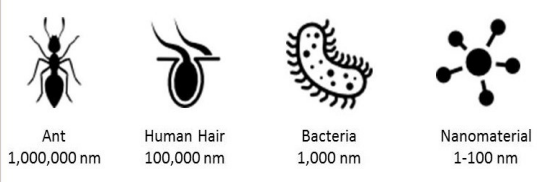
Nanotechnology Turns Chemotherapy into a Breast Cancer-Seeking Missile

The State of the Art

Every day, breast cancer patients are treated with a combination of well-known chemotherapy drugs such as cisplatin or carboplatin, docetaxel and doxorubicin. While these drugs help many patients, they often come with serious side effects such as hair loss, severe nausea, weight loss, even kidney and heart problems. This occurs because these drugs not only kill cancer cells, but also attack healthy tissues without discrimination. However, Komen grantee Dr. Mark Cohen, has found a way to deliver these drugs directly to cancer cells, improving the drug's effectiveness while reducing its side effects.

What is Nanotechnology?

Nanotechnology is the use of very small objects. How small is very small? Objects used in nanotechnology are measured in nanometers. One nanometer (nm) is equal to one billionth of a meter – about one hundred-thousandth the size of a human hair. Scientists are using nanotechnology in a wide range of fields including medicine, electronics, and manufacturing.



In Dr. Cohen's Komen-funded research, nanotechnology is being used to combine potent drugs with cancer-seeking molecules to specifically kill cancer cells.

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Better Therapy through Nanotechnology

The key to Dr. Cohen's work is nanotechnology, the science of very small materials. Specifically, Dr. Cohen uses nanotechnology to combine chemotherapy drugs (such as cisplatin, doxorubicin, docetaxel or others) with a "nano"-sized carrier molecule that allows the drug to specifically target the tumor and its nearby lymph nodes. Because the drug is specifically delivered to the cancer cells, patients could benefit from lower doses of the drug and fewer side effects. With the help of a Komen Career Catalyst grant (a grant for early-career researchers), Dr. Cohen, along with his colleague, Dr. Laird Forrest, has developed nanocarriers from hyaluronic acid (HA) that can effectively be combined with chemotherapy drugs. HA is small molecule that is naturally found in the body and is involved in cell movement and growth. Because it is a compound already in the body, the immune system does not attack HA-drugs when they are injected.

Cancer Seeking Missile

A new finding learned from these studies, is that HA specifically attaches on the surface of cells to a protein called CD44, which is found at high levels on the outside of many breast cancer cells, including Triple Negative Breast Cancer (TNBC) cells. Because HA specifically binds to CD44 on the surface of breast cancer cells, drugs attached to the HA-based nanocarrier are then taken into the cell where they attack and kill the cancer cells like a heat-seeking missile. Many aggressive breast cancer cells, including cancer stem cells, have high levels of CD44 compared to normal cells. This means that the HA-drug nanoparticle more readily targets these tumor cells, while leaving normal cells unharmed. This makes the drug more effective and less toxic. Another huge benefit of this technology is that drugs given through an i.v. infusion, like cisplatin, doxorubicin and docetaxel, can be converted into a simple shot injected right at the tumor site.

To test his nanocarrier drugs, Dr. Cohen compared his HA-nanocarrier therapy with traditional chemotherapy in mice with advanced triple negative breast cancer. Cisplatin, docetaxel and

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doxorubicin were each attached to HA nanocarriers, and mice were given either the standard drug (e.g. cisplatin alone) or the HA-nanocarrier version (e.g. HA-cisplatin), and the responses of the mice were compared. In all cases, the mice receiving the HA-nanocarriers survived longer and had fewer side effects than those receiving standard chemotherapy. Recently, Dr. Cohen found the same effect when mice were given a cocktail of all three drugs. The HA-nanocarrier cocktail was both more effective and safer than the standard cocktail.

Stop the Stem Cells, Stop the Cancer

In addition to reducing the dose and side-effects of chemotherapy, Dr. Cohen's HA-nanocarriers could also become one of the first therapies to directly attack cancer stem cells. CD44, the molecule that binds HA-nanocarriers is also found at high levels in breast cancer stem cells, which contribute to drug-resistance and have the ability to reform a tumor from just a single cell if not killed. New research from Dr. Cohen's lab suggests that by attacking breast cancer stem cells, these HA-nanocarrier drugs can cause a tumor to become less aggressive and invasive, slowing down or even stopping the disease from progressing, and in some cases even preventing the cancer from coming back (recurrence). Future studies conducted by Dr. Cohen's laboratory in collaboration with other experts, like Dr. Max Wicha at the University of Michigan, will focus on targeting breast cancer stem cells with HA-nanocarriers.

Looking to the Future

Dr. Cohen notes that nanotechnology can be applied to a number of drugs and diseases. The technology, developed with Komen funding, is now being tested in other tumors including lung, bladder, and head and neck cancer. Indeed, HA-cisplatin has shown great promise against squamous cell carcinomas. In addition, Dr. Cohen is working with collaborators to develop a clinical trial of HA-nanocarriers for patients with locally advanced or recurrent breast cancer. If successful, Dr. Cohen's Komen funded research could revolutionize the treatment of breast cancer for patients at multiple stages, including metastatic disease (cancer that has spread to other parts of the body) and triple negative breast cancer, both areas in need of newer treatments with improved outcomes.

"Komen funding was a huge catalyst that has allowed us to develop a new platform for cancer drug delivery" said Dr. Cohen. In addition to its application for breast cancer, this technology is being applied to improve the delivery of other drugs and benefit patients with other diseases.

What It Means for Patients

The side effects of chemotherapy are a major concern for cancer patients. These include hair loss, severe nausea, weight loss, even kidney and heart problems. These issues can compromise quality of life and may limit the duration and dose of therapy a patient can take. Dr. Cohen's nanocarrier technology promises to reduce the severity of these side effects by focusing chemotherapy on the tumor itself, rather than distributing it throughout the entire body. This will increase the strength of the drug at the tumor site, while at the same time reducing the dose of drug needed. This has the potential to significantly improve the overall experience of patients receiving chemotherapy, improving both patient response and quality of life. In addition, Dr. Cohen's recent studies suggest this technology could also prevent tumor recurrence by attacking cancer stem cells. This means tumors would become less invasive or aggressive and be less likely to return after treatment.

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Behind the Science

Dr. Cohen's work is driven in large part by his personal experience with breast cancer. His grandmother lost her battle with metastatic breast cancer while he was in college, and he saw first-hand the drawbacks of traditional chemotherapy. "She had significant side-effects from her chemotherapy" recalls Dr. Cohen, "since that time, I promised myself I would find a way to make better treatments that are less toxic to patients." Dr. Cohen carried this interest to his first faculty position at the University of Kansas. Here, he was inspired by the routine use of dyes that specifically travel to tumors. He asked, "Why can't we develop a way to focus chemotherapy drugs so they can go to the tumor locally like the dye?" This question led to his collaboration with Dr. Laird Forrest, a nanotechnology expert, and the development of HA-nanocarriers.

Mark S. Cohen, M.D. F.A.C.S., is Associate Professor of Surgery and Pharmacology, Director of Endocrine Surgery Research, and a Principal Investigator in the Translational Oncology Program at the University of Michigan.

In addition to his clinical and research duties, Dr. Cohen serves as a reviewer for several scientific journals including, *Cancer Research, Surgery, JACS,* and *is on the editorial board for BMC Cancer.* He also serves as a grant reviewer for the National Comprehensive Cancer Network Young Investigator Award.

Dr. Cohen sees community outreach as an essential part of his role as a clinician and educator. He has spoken at a number of events for his local Komen affiliates and other local cancer organizations. In addition, Dr. Cohen and his colleagues in the Translational Oncology Program at the University of Michigan, sponsor an annual "One Day Closer" event to educate the local community about cancer research taking place in their community, and how they can contribute to the fight against cancer.

As a result of his Komen Catalyst Grant funding, Dr. Cohen's research on HA-nanocarrier cancer drugs has been published in 14 peer-reviewed journals and he has given 15 national and international talks on this topic. When he is not in the lab or clinic, Dr. Cohen enjoys playing the trumpet, singing in his local choir, traveling and spending time with his family.

The Susan G. Komen® promise is to save lives and end breast cancer forever.

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