Targeting an enzyme may provide metabolic treatment for pancreatic cancer

A new study released by our 2016-17 Seed Grant Awardee, Nada Kalaany, PhD shows evidence that targeting an enzyme that tumors use to get rid of nitrogen can slow tumor growth. These innovative therapeutic strategies are precisely why our Seed Grant Program is crucial in the fight against pancreatic cancer.

Chemotherapy nanoparticles offer breakthrough in pancreatic cancer drug delivery

Originally published at http://www.cancer.ucla.edu

UCLA scientists combine a peptide with a nano cancer drug formulation to improve treatment effectiveness and prevent metastasis in pancreatic

cancer

Study shows the peptide enhances a vascular access pathway for nanocarriers in pancreatic cancer

UCLA scientists have unlocked an important mechanism that allows chemotherapy-carrying nanoparticles—extremely small objects between 1 and 100 nanometers (a billionth of a meter)—to directly access pancreatic cancer tumors, thereby improving the ability to kill cancer cells and hence leading to more effective treatment outcome of the disease. The researchers also confirmed the key role of a peptide (an extremely small protein) in regulating vascular access of the nanoparticle to the cancer site.

The discovery is the result of a two-year study co-led by Drs. Huan Meng and André Nel, members of UCLA's Jonsson Comprehensive Cancer Center and the UCLA California NanoSystems Institute. The findings are important as they demonstrate how the delivery of chemotherapy to pancreatic cancer can be improved significantly through the use of smart-designed nanoparticle features.

The study is published online in the Journal of Clinical Investigation.

Pancreatic ductal adenocarcinoma is generally a fatal disease, with a five-year survival rate of less than 6 percent. The introduction of nanocarriers as delivery vehicles for common chemotherapy agents such as the drug irinotecan, has led to improved survival of patients with this disease. However, the reality is that nanocarriers may not always reach their intended target in sufficient numbers because of a constraint on their ability to transit through the blood vessel wall at the tumor site, leading the encapsulated drugs to be diverted or lost before they can deliver their payload.

A key challenge for scientists is how to help nanoparticles travel to and be retained at tumor sites. This can be accomplished by custom-designed or engineered nanoparticles that overcome common challenges, such as the presence of a dense tissue surrounding the pancreas cancer cells. Prior research has identified a major vascular access mechanism that relies on a vesicle transport system, which can be turned with a peptide called iRGD in the blood vessel wall. iRGD is therefore potentially useful to optimize the delivery of cancer drugs by the nanoparticle to the tumor.

The use of electron microscopy allowed UCLA scientists to visualize the silica nanoparticle transportation mechanism from the tumor blood vessel interior (left, pink region) to the space in between the tumor cells (right, cyan region). The images on the top-left show the nanoparticle morphology.

The UCLA research team designed a nanoparticle comprised of a hollow silica core surrounded by a lipid bilayer to enhance the delivery of irinotecan in an animal model with pancreatic cancer. The invention is called a silicasome. The researchers proposed that the therapeutic benefit of the irinotecan containing nanoparticles may be enhanced when combined with the injection of iRGD. The investigators used the nanoparticle plus the iRGD to deliver irinotecan in a robust animal model for pancreatic cancer that closely mimics human disease.

“We demonstrated that the co-administration of the iRGD peptide with the particles can enhance the effectiveness of pancreatic cancer treatment in the tumor model, leading to increased tumor shrinkage, disappearance of metastases and enhanced animal survival” said Meng, an adjunct assistant professor of nanomedicine.

“Utilizing the nanoparticle carrier with a core made of gold

nanoparticles also made it possible to obtain evidence for the entry of nanoparticles into the tumor; we looked at the tumor under the electron microscope and observed the particles", said post-doctoral fellow and first author Xiangsheng Liu. This helped to confirm that in addition to relying on leaky blood vessels for nanoparticles to gain access to the tumor, a major inducible vascular transit pathway is available in the form of the vesicle transport system.

Meng and Nel also collaborated with Dr. Timothy Donahue, chief of gastrointestinal and pancreatic surgery and a Jonsson Comprehensive Cancer Center member, to demonstrate that treatment with the iRGD peptide can enhance tumor cell killing for patient-derived pancreatic cancers, growing subcutaneously in a mouse model. The ability to enhance nanoparticle uptake is dependent on the level of expression of a molecule, called NRP-1, to allow the peptide to bind to the tumor blood vessels.

"In the tumor sample from a patient with high NRP-1 expression, there was a significant improvement in the efficacy of the nanoparticle to induce tumor shrinkage," said Nel. "The enhancing effect was not seen in a patient tumor sample with a low level of NRP-1 expression on the vasculature. This allows for a personalized approach to the treatment of pancreatic cancer with the iRGD peptide in combination with the nanoparticle."

The paper by Nel and colleagues is accompanied by a commentary in the Journal of Clinical Investigation that explains the utility of co-administrating iRGD with the silicasome. This commentary also points out that in order to obtain effective treatment outcome with the peptide, it is important to consider the biological variation from patient to patient and one tumor model to another in obtaining success by iRGD treatment, as shown in the UCLA led study.

The research was supported by the National Cancer Institute and the Hirshberg Foundation for Pancreatic Cancer Research.

13th Annual Symposium Video Presentations

We're happy to announce that the video presentations of the 13th annual Symposium on Pancreatic Cancer are now available to view on our website. This year the Symposium was titled, 'Mission to Cure Pancreatic Cancer' and when you hear the speakers you'll share our confidence that our esteemed doctors and scientists are truly making a difference. From advances in chemotherapy, robotic surgery, treatment, and genetic testing, top experts from across the U.S. shared the latest information on pancreatic cancer to over 225 patients, families and caregivers. This year two new subjects were introduced: the challenges in treating pancreatic cancer and the genetic/hereditary factor.

"The symposium this year marks the highest attendance recorded in our 13-year history hosting this event," said Agi Hirshberg, Founder and CEO of the Hirshberg Foundation for Pancreatic Cancer Research. "The foundation wants to ensure that patients have the best information available to win the battle against pancreatic cancer. We are privileged to have the capability of offering this type of resource free to the public. We will relentlessly continue to move forward until our mission is complete."

A major highlight of the symposium was a transparent and inspirational Q & A panel discussion with pancreatic cancer

survivors who continue to defy the odds (along with 30 other survivors who were in attendance). The survivor panel featured actress/comedian Wendy Hammers who added levity to the lively discussion. Actress and pancreatic cancer survivor Charlotte Rae (Facts of Life) made a special guest appearance.

Study Explains Genetic Connection Between Aging and Cancer

David Gius, MD, PhD from Northwestern University was funded in the 2012 cycle of the Hirshberg Foundation's annual Seed Grant Program. The results of the study explain the genetic connection between aging and cancer.

Gius is the Vice Chair of Translation Research in the Department of Radiation Oncology and Pharmacology at Northwestern University Feinberg School of Medicine and has been studying the relationship between aging and cancer. A fundamental observation in oncology is that the rate of malignancies increases significantly as a function of age and the development of cancers. In fact, advanced age is the single most important predictive variable for cancer incidence in pancreatic cancers. Dr. David Gius and his colleagues have investigated and found that this relationship involves one of the primary anti-aging genes, SIRT2, which interacts with KRAS and alters KRAS activity establishing a cellular environment in the pancreas favoring proliferation and genomic instability. KRAS mutations are

observed in 95% of patients with pancreatic adenocarcinoma. Thus there is a genetic connection between aging and the early events that put humans at risk for pancreatic cancer. They have published their work in Oncotarget, 2016, Vol. 7, (No. 49): pages: 80336-80349.

Hirshberg Funded International Researcher Publishes Findings

2011 Seed Grant Recipient Ido Wolf, MD from University of Tel Aviv, Israel, recently published his findings that will offer novel approaches towards development of new therapies for pancreatic cancer.

Dr. Wolf, Head of Oncology Research Laboratory at Tel Aviv Sourasky Medical Center has been investigating the role of klotho in pancreatic cancer. Klotho is a potent aging suppressor protein. Mice and humans lacking klotho suffer from early aging, while overexpressing of klotho extends lifespan. He and his colleagues identified klotho as a novel tumor suppressor in pancreatic cancer. Klotho expression is reduced in pancreatic cancer compared to normal pancreatic tissue and treatment with klotho inhibits growth of pancreatic cancer cells. Dr. Wolf and his colleagues study the role of klotho in the development of pancreatic cancer and discover mechanisms that mediate its activities by inhibiting insulin like growth hormone (IGF-1) fibroblast growth factor (FGF) signals in pancreatic cancer. They are now expanding their research work on how klotho regulates pancreatic tumor metabolism. Since klotho is an endogenous hormone, its administration is potentially feasible.

Their discoveries may identify new therapeutic targets and aid in the development of novel therapies for pancreatic cancer.

Richard Hatch Memorial Fund

Richard Hatch, star of the original “Battlestar Galatica” passed away on February 7, 2017 after a battle with pancreatic cancer.

Hatch was best known for his role as Captain Apollo in the original “Battlestar Galactica” sci-fi series, which earned him a Golden Globe nomination for Best Actor in a TV drama series. He played Tom Zarek, a different character on the Syfy remake in 2003. Hatch started acting in Off Broadway productions but his career took off after landing a leading role in “All My Children.” He has a lengthy list of TV credits, including many guest roles in ’70s and ’80s television favorites like “Baywatch,” “MacGyver,” “CHiPS,” and “Murder She Wrote.”

The Hirshberg Foundation, with the blessing of Richard’s family, is honored to invite fans, family & friends to pay special tribute to Hatch on March 19 at the Los Angeles Marathon. The Hirshberg Foundation, an official charity of the Los Angeles Marathon, hosts a cheer station in Brentwood, along the course. Dubbed the Purple People Party, our cheer station brings out hundreds of volunteers to cheer on the runners and raise awareness for pancreatic cancer. We invite you to join us as we honor Richard Hatch at the Purple People Party.

Memorial Fund ➤