DISCOVERY TO CURE

FALL 2015

Five Yale Researchers Awarded Grants to Study Women's Reproductive Cancers

Five scientific researchers with the Yale School of Medicine Department of Obstetrics, Gynecology and Reproductive Sciences have received grants from Discovery to Cure for projects to advance the program's goals of prevention, early detection, and treatment of women's reproductive cancers, including ovarian, uterine, cervical, vaginal and vulvar malignancies.

The grant recipients are: **Ayesha Alvero, M.D., MSc.**; **Yingqun Huang, PhD., M.D.**; **Elena Ratner, M.D.**; **Alessandro Santin, M.D.**; **Xiao Xu, PhD**.

The researchers discussed their projects at a July 20 reception honoring Discovery to Cure supporters. Nearly 100 guests, including cancer survivors, philanthropists, doctors, Discovery to Cure corporate sponsors and major donors, attended the event hosted by U.S. Congresswoman and 30-year ovarian cancer survivor Rosa DeLauro (D-CT) at her New Haven home.

The research projects -- ranging from enhancing early detection of ovarian cancer metastasis to more effective combination therapy for BRCA-Wild type ovarian cancer, and a novel technique for early ovarian cancer detection -- are described for our readers by each of the grant recipients.

DISCOVERY TO CURE

ADVANCING THE PREVENTION, EARLY DETECTION & TREATMENT OF WOMEN'S REPRODUCTIVE CANCERS

OUR ANNUAL DISCOVERY TO CURE WALK WAS A SUCCESS!

Discovery To Cure, an internationally recognized program of the Yale School of Medicine, was launched in 2003 and is dedicated to advancing new methods of prevention, early detection and treatment of women's reproductive cancers in order to lead to a cure.

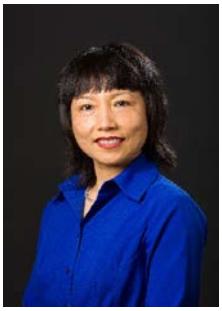
Through the efforts of over 500 participants and nearly 1,000 donors, we **raised over $165,000** to benefit the work of Discovery to Cure at Yale School of Medicine.

Donations are still being accepted on the walk website at: Discovery To Cure website until **December 31, 2015**.

AYESHA ALVERO, M.D., MSc.

Project: Enhanced Detection of Ovarian Cancer Micrometastasis for Optimum Surgical Debulking

Patients with ovarian cancer have the best prognosis when all tumors visible to the naked eye of the surgeon are removed. However, while identification of large tumors usually does not pose a challenge, metastatic tumors made up by only a cluster of cells are impossible to distinguish intra-operatively. The proposed studies aim to develop *optical enhancers* that can aid the surgeon in the identification, delineation, and removal of micrometastatic disease. This approach will ensure the best surgical effort, which will significantly impact tumor burden, quality of life, and patient survival.



YINGQUN HUANG, PhD., M.D.

Project: Genome-Wide Analysis of Metformin-Induced DNA Methylation in Ovarian and Endometrial Cancer Cells

METFORMIN, a most commonly prescribed drug for Type-2 diabetes, also elicits multiple effects on cancer cells, including inhibition of growth, migration and invasion, both in cell culture and in preclinical animal models. Despite extensive research and ongoing multi-centered randomized clinical trials on efficacy of Metformin in treating cancers, the precise molecular mechanisms by which Metformin affects cancer cells have remained elusive.

We have recently discovered that treating ovarian and endometrial cancer cells with Metformin leads to a significant reduction in their motility and invasiveness. This is because Metformin decreases the production of H19 in these cancer cells. H19 is not present in most normal adult tissue cells, but is aberrantly produced by many cancer cells. H19 is a long non-coding RNA molecule (which does not have the potential to direct the synthesis of a protein) which acts as a molecular "sponge" to soak up a tiny non-coding RNA, called let-7. Let-7 is a tumor suppressor and when it is sequestered by H19, it loses its ability to fight cancer.

The goal of the proposed research is to dissect the molecular pathways involved in Metformin-induced alteration of gene expression. Our preliminary studies suggest that Metformin

DIVISION OF REPRODUCTIVE SCIENCES SEMINARS

The Division of Reproductive Sciences Seminars are held on Tuesday afternoons, between 12:00pm – 1:00pm, in Conference Room FMB-340, Cedar Street.

October 14, 2015 – Ellen Leeds Read Sturges Lecture
Speaker, **Gil Mor, M.D., PhD., MSc.**; Host, Department of Ob/Gyn
Seminar Title: The Origin of Ovarian Cancer and Cancer Stem Cells as the Source of Chemoresistance and Recurrence
Location for October Seminar: The Brady Auditorium (BML-131)

November, 2015 – No Seminar

December 16, 2015 –
Speaker, **Akiko Iwasaki, PhD.**; Host, **Sabrina Diano, PhD.**
Seminar Title: Antiviral Immunity in the Lower Female Reproductive Tract

DAY OF DISCOVERY EVENT!

This event for will be held in January 2016!

The event will include a tour of Yale labs, viewing

inhibits H19 production by inducing modifications within a specific chromosomal DNA region that dictate the synthesis of H19. Our next step is to scan the entire genome using cutting-edge technologies including “genome-wide gene methylation profiling” to identify additional genes whose expression might be altered by Metformin. By performing these studies, we will not only gain a better mechanistic understanding of Metformin's mode of action which is key to success in its use as an anti-cancer drug, but also help to uncover novel therapeutic targets for treating ovarian and endometrial cancer.

ELENA RATNER, M.D.

Project: Targeting AKT-Associated Angiogenesis to Enhance Triapine-Olarib Combination Therapy for BRCA-Wild Type EOC

OLARIB (Lynparza) is the first PARP inhibitor recently approved for the treatment of advanced epithelial ovarian cancer (EOC) in patients who carry deleterious BRCA mutations and have received prior-line chemotherapy. The clinical approval of the first PARP inhibitor not only gives great promise for hereditary EOC patients, but also marks a milestone for the development of targeting therapy for BRCA-mutated EOC. However, a majority of EOC cases harbor wild-type BRCA and therefore are predicted not to respond to PARP inhibitor therapy.

To overcome this limitation, we have identified that triapine, a small-molecule inhibitor of ribonucleotide reductase, impairs homologous recombination repair and enhances the effectiveness of olarib against BRCA-wild type EOC in vitro. However, this combination is less effective in an EOC xenograft mouse model. Given that, we hypothesize that angiogenic and pro-survival factors produced by EOC tumors reduce the effectiveness of the olarib-triapine combination in vivo settings.

Therefore, the proposed studies are coined to investigate whether anti-androgenic drug cediranib (Recentin) can enhance inhibitory effects of the olarib-triapine combination on tumor growth and to examine the gene expression profiles of EOC tumor treated with the combination. Our findings will allow us to gain insights into the impact of pro-survival factors on the response of EOC tumor to BRCA-targeting therapy.

of the Da Vinci Robot, guest speakers, etc.

Details to follow!

Join Our Mailing List!

Please consider forwarding this e-mail to a friend.

CONNECT WITH DISCOVERY TO CURE!

ALESSANDRO SANTIN, M.D.

Project: Nanoparticles Complexed to Clostridium Perfringens Entertoxin CPE Peptide for the Early Detection of Ovarian Cancer

The goal of our study is to develop a radically different method for the early diagnosis and treatment of ovarian cancer, the most lethal gynecological cancer. Most women with the disease respond fully to traditional surgery and chemotherapy, but later develop chemo-resistant cancer. Thus, the development of effective treatments for resistant ovarian cancer is a high priority in medicine.

As cancer researchers with an understanding for the genetics and vulnerabilities of ovarian tumors and translational scientists experienced in creating highly-inventive vehicles for delivering drugs to their intended targets -- we envisioned the development of nanoparticles as microscopic “smart bombs” to latch onto ovarian cancer cells to visualize microscopic disease and unleash potent toxins to kill only the tumors. We have previously discovered that genes for making two particular proteins were highly expressed in chemotherapy-resistant ovarian cancer cells. (Gene expression is the process by which information from a gene is used to make proteins, the building blocks of cells.) These two proteins coincidentally are receptors in the surface lining of the ovaries for a potent bacterial poison found in nature, *Clostridium perfringens entertoxin,* or CPE. Thus, CPE is an effective substance for both targeting and destroying ovarian cancer cells.

Unfortunately, intravenous delivery of CPE is toxic. So, we figured that a non-toxic CPE peptide -- or protein fragment -- with an affinity for sticking to the receptors could be used as a safe targeting agent to find and lock onto ovarian cancer cells. But how could they be delivered solely to the cancer cells? We designed biodegradable nanoparticles coated with the CPE peptide to home in on the ovarian cancer cells, either carrying a fluorescent dye or a potent chemotherapy as cargo inside the nanoparticle. The binding activity of the peptide can breach the otherwise drug-resistant tumor cells, and the cargo can be unleashed only when the nanoparticle hits the target, avoiding the destruction of healthy cells -- a common problem in cancer treatment.

Using a fluorescent dye on the nanoparticles as a tracer, and utilizing female mice to ensure results as clinically relevant as possible, we demonstrated that our specially-designed nanoparticles can not only visualize but also kill resistant

ovarian cancer cells. The approach is very promising, with potential applications for the early detection and treatment of chemotherapy-resistant ovarian cancer.

XIAO XU, PhD.

Project: Gynecologic Cancer in Women Undergoing Hysterectomy and Myomectomy for Benign Indications

HYSTERECTOMY (surgical removal of the uterus) and MYOMECTOMY (surgical removal of fibroids with preservation of the uterus) are common gynecologic surgeries. They are increasingly performed via minimally invasive laparoscopic approach, providing patients with the benefit of small incisions, lower complication rate, and more rapid recovery, compared with the traditional abdominal approach. Recently, there has been concern that if a patient has uterine cancer, but undetected prior to surgery, she may experience worse cancer outcomes after *undergoing certain laporoscopic hysterectomy/myomectomy procedures.*

Our project uses a large data set to estimate the prevalence of unsuspected uterine, cervical, and ovarian cancer in women undergoing hysterectomy or myomectomy for presumed benign reasons, and to assess the characteristics of patients who were incidentally diagnosed with uterine, cervical, or ovarian cancer after hysterectomy or myomectomy. We will analyze patients in the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) Participant Use Data File who underwent a hysterectomy or myomectomy at 69 participating hospitals nationwide. The data file contains de-identified information on patient demographic (e.g., age, race/ethnicity) and clinical (e.g., body mass index, uterine weight, comorbidities) characteristics – as well as pathology report of incidental cancers identified.

Findings from this study will help us better understand the risks and benefits of laparoscopic hysterectomy and mymectomy. This will hence facilitate patient counseling and decision making in clinical care for the vast number of women undergoing hysterectomy and myomectomy each year.

Research project descriptions written by the grant recipients.
Article prepared by Janice Marcus, Associate Editor

Discovery To Cure Survivor Sessions Inspire Yale Medical Students

Since 2005 third-year students in their Ob/Gyn rotation at the Yale School of Medicine have taken a break from their usual classroom curriculum to hear ovarian cancer patients tell their stories of diagnosis, treatment and survival. **Survivor Sessions**, a Discovery to Cure educational program, brings together women of all ages who have been diagnosed at different stages of the disease in an informal presentation and dialogue with third-year Yale medical students.

Widely praised by both student attendees and Yale Medical School faculty and recipient of the 2012 Lee Buxton Teaching Award for Medical Student Education, the program provides an opportunity for future physicians to enhance their formal medical education with firsthand information about women's real-life experiences with ovarian cancer. Each hour-long session features three women presenters and a facilitator, all ovarian cancer survivors. The presentations are followed by an informal discussion and questions from the students, who treasure this chance to put a human face to cancer.

Student comments received over the years:

"This was an emotional and powerful session, and it's important that we never forget that real people are affected by these diseases."

"Thank you so much for including this in our curriculum."

"This form of experiential learning is an important adjunct to our studies. Please keep this a part of the clerkship!"

"It is impossible to truly understand fully the experience of cancer patients with only clinical knowledge alone and these stories really go a long way toward making us better physicians."

"It made me remember why I decided to become a doctor."

Survivor Sessions

If you are a survivor of ovarian cancer and are willing to share your story of diagnosis, treatment and survival, Survivor Sessions would like to hear from you. It's a rewarding experience. The program takes place once a month in the Department of Obstetrics, Gynecology & Reproductive Sciences in New Haven. Each session is approximately one hour.

Please contact **JoAnn Bilyard** on 203.785.5898
or joann.bilyard@yale.edu for more information.