DISCOVERY TO CURE

2016-Quarterly News Yale School of Medicine

Compound Developed in Yale Lab Provides Hope for Ovarian Cancer Cure

NV-128/ME-344 now in Phase 1 Clinical Trial

*(Editor's Note: **Ayesha Alvero, M.D., MSc**, led the research team in the Yale School of Medicine, Department of Obstetrics, Gynecology and Reproductive Sciences lab of Gil Mor, M.D., Ph.D. MSc, that identified and characterized ovarian cancer stem cells – and identified the novel compound NV-128 as a potential inducer of death in cancer stem cells by circumventing apoptosis resistance. A newer, more potent compound, NV-128/ME-344, is currently in Phase 1 Clinical Trial.)*

The first potential new therapy for treatment of ovarian cancer in over 30 years

In 2003, when Dr. Ayesha Alvero joined Dr. Gil Mor's scientific research lab in the School of Medicine's Department of Obstetrics, Gynecology and Reproductive Sciences, Dr. Mor had already become the first researcher to isolate ovarian cancer cells. No new therapies for ovarian cancer had been developed in decades, in fact as of today, it's been more than 30 years. Moreover, research had failed to significantly improve the survival rate -- and Dr. Mor was determined to isolate the cancer stem cells responsible for ovarian cancer recurrence and end the approximately 70% mortality in recurrent patients, due to cancer stem cells chemo-resistance.

Dr. Alvero dedicated herself to the crucial task of leading the Mor Lab team that successfully identified and characterized ovarian cancer stem cells. But the path to success in scientific research is long and arduous. Failure is a fact of everyday life in the lab, Dr. Alvero points out. “The failure rate in this business (i.e. research and development of new treatments for disease) is so much higher than the success rate.” Yet, she and her team pressed on, undeterred in pursuing the quest to find a cure for ovarian cancer.

UPCOMING EVENTS

Discovery to Cure High School Internship Program

Orientation Day is Monday, March 7th!

For program details click here

Day of Discovery

Saturday, May 7th

The event will include a tour of Yale labs, viewing of the Da Vinci Robot, guest speakers, etc.

Annual Discovery To Cure Walk

Sunday, September 25th

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

Donations are being accepted on the walk website

Since 2013, Dr. Alvero and the Lab Team have screened more than 100 compounds for ability to kill ovarian cancer stem cells

In 2013, Yale University and the Mor Lab partnered to form CanTx, Inc.* with Novogen, an Australian-U.S. biotec firm which had submitted novel compounds for killing ovarian cancer cells to be tested in Dr. Mor's lab. Since that time, in seeking an effective way to destroy the deadly ovarian cancer stem cells, says Dr. Alvero, she and the lab team “have screened more than 100 compounds from both large and small pharmaceutical firms, and even from Yale's Department of Pharmacology and Department of Chemistry. Of all the compounds we have tested, NV-128/ME-344 and TRX-E002-1 (from CanTx) are the most potent.” Both of these compounds are specified to be able to kill ovarian cancer stem cells.

NV-128/ME-344 met the qualifications for Phase 1 clinical testing and is now in Phase 1b clinical trial for ovarian, cervical and non-small-cell lung cancers. “Phase 1,” explains Dr. Alvero is designed to answer the question 'Is the drug safe to use in humans?' Data from this phase will tell us the highest dose we can use and also the schedule for dosing and any side effects. If Phase 1 is successful, NV-128/ME-344 will go on the rest of the Phases II – IV, until we can demonstrate its value as a therapy.”

What gives NV-128/ME-344 the ability to kill ovarian cancer stem cells, when other compounds have failed?

NV-128/ME-344 overcomes the chemo-resistance of the ovarian cancer stem cells that cause recurrence of the disease by “circumventing apoptosis resistance.” For our readers who are not familiar with medical terms, Dr. Alvero explained that “apoptosis” is a property of all cells. It is a way that cells have of committing suicide. “When a cell senses that it is unwell, it activates the apoptosis program to sacrifice itself for the well-being of the whole organism. Because ovarian cancer stem cells cancel out apoptosis, our research finds compounds that induce cell death in another way.”

While NV-128-ME-344 moves through clinical trial phases, screening of potential therapy compounds continues. “We are continually screening,” Dr. Alvero concludes. “We've finished all the pre-clinical studies for TRX-E002-1 (from CanTx), which should start Phase 1 clinical trial this year. But if it fails Phase 1, the ongoing screening program should give us another compound, better one, ready to go.”

at: Discovery To Cure website

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.

Please view schedule here

Discovery to Cure Survivor Sessions

This 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.

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.

*CanTx = Can for “cancer” and Tx for “therapy.”
The upper case “C” and “T” represent Connecticut.

Interview with Ayesha Alvero, M.D. MSc
Article by Janice P. Marcus, Associate Editor

The Yale University Reproductive Sciences Biobank Research Team

A Vital Link Between Labs and Clinic

Yale University
Reproductive Sciences Biobank

Unless you've been a patient in the School of Medicine Department of Obstetrics, Gynecology and Reproductive Sciences clinic and were approached about donating a medical specimen for research...are a Yale scientific researcher or investigator...or a member of the Yale medical community...you may be learning about the YURS-Biobank here for the first time.

Recently re-branded from the “OB-GYN Biospecimen Repository” to the Yale University Reproductive Sciences “YURS”- Biobank, this operation coordinates the important mission of collecting, annotating, storing, and distributing human biological materials to support translational research throughout the medical school.

Under the direction of Gil Mor, M.D., Ph.D. MSc, the research team is ably guided by Biobank Co-Directors Clare Flannery, M.D., and Michelle Silasi, M.D., and aided by the YURS-Biobank coordinators. The highest standards are meticulously maintained in every aspect from the initial collection of biological materials to their equitable distribution. The research team identifies potential specimen donors, with diligent safeguards to protect their privacy. The team procures and processes individual donor specimens, annotating them with relevant clinical information. The team also coordinates the prompt and secure storage of human biospecimens from participants for future use in scientific research projects that are purposed to one day benefit – perhaps save lives – of patients in clinical practice. “We pride ourselves on rapid, uniform, and precise processing and storage – within 30 minutes!” says Lauren Perley, YURS-Biobank Coordinator.

“An Invaluable Service...Accessible to All”

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

Join Our Mailing List!

Please consider forwarding this e-mail to a friend.

CONNECT WITH DISCOVERY TO CURE!

“We help reduce the time it takes to conduct research involving human biospecimens,” Lauren Perley explains. “This is an invaluable service, offered at a very low cost to all investigators here at Yale, and also for external researchers. They can take advantage of this resource even prior to receiving research funding. This expedites preliminary studies and maximizes project productivity.” Perley and her Research Team associate, Nicole Martin meet several times each week to discuss plans and develop strategies to optimize the effectiveness of collection protocols. They are encouraged to support interdisciplinary and interdepartmental relationships, and to seek out specimens that may not be typical for the Ob/Gyn Department.

Given the broad responsibilities of the YURS- Biobank research team, the opportunities to learn and grow are endless, keeping the job interesting and the team on its toes. There's no typical day for Perley and Martin. “For example,” Perley elaborates, “we may collect blood samples for a researcher who is exploring the effect of diabetes on pregnancy – or we may provide placental samples from various donors for research on the effect of obesity on placental function. Depending on the day,” she continues, “we may collect and process donor materials, or we might run internal quality-control experiments of medical biospecimens, write reports, or develop budgets.”

A Potentially Life-Saving Mission

Whatever the task at hand, Lauren Perley and Nicole Martin never forget the absolute value of human biological materials. The biospecimen donations that are painstakingly solicited, processed and stored by the YURS-Biobank research team every day may well hold the key to new clinical therapies and life-saving discoveries for families with reproductive conditions and disease.

Interview and Article
by Janice P. Marcus, Associate Editor

2016 Discovery To Cure Grant Recipients

Four Yale School of Medicine researchers 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.

This year's awarded recipients are: **Clare Flannery, M.D.; Roslyn Tedja, Ph.D**.; **Yang Yang-Hartwich, Ph.D.** and **Z. Ping Lin, Ph.D.**

CLARE FLANNERY, M.D.

Project: The Clinical Question of Why Some Women with Obesity Develop Endometrial Hyperplasia and Adenocarcinoma, While Other Women Are Protected Despite Also Having Obesity

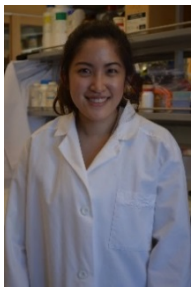
Our goal is to determine whether the endometrium of women with endometrial hyperplasia and adenocarcinoma fails to develop resistance to the effects of insulin, and is exposed to chronic mitogenic stimulation through IR-A. The examination of tissue specificity in insulin sensitivity is novel, especially in a clinical study.

The broader implications of this research is to understand the mechanisms for how clinical states of insulin resistance affect organs other than the classic metabolic organs—muscle, liver and adipose tissue. Weight loss is effective to reduce cancer risk, but challenging for most people. With a better understanding of underlying mechanism, future therapy will hopefully entail a medical means to block the mitogenic effects of insulin, while maintain insulin's metabolic effects.

In this study we aim to metabolically characterize women with either endometrial hyperplasia or endometrioid adenocarcinoma, relative to women without these conditions who are undergoing surgery for benign gynecological conditions. Women will be matched by body mass index (BMI), presence of Type 2 diabetes, menstrual cycle phase or menopausal status. Metabolic testing will include Testing includes 2) measurements of waist circumference and body composition by Tanita, b) fasting serum profile of lipids, estrogen metabolites, other sex hormones, and inflammatory cytokines, c) 2-hour glucose tolerance testing with glucose and insulin measurements at multiple time points to determine insulin sensitivity and d) quantification of visceral and peripheral body fat by MRI.

Second, we aim to determine the insulin sensitivity of endometrial hyperplasia and endometriod adenocarcinoma as compared to both normal endometrium and adipose tissue, by quantifying the mitogenic and metabolic insulin receptor isomers, IR-A and IR-B respectively, and activation state of

insulin signaling proteins in each tissue, from each case and control woman. Adipose tissue serves as a control since it is a well-characterized metabolic tissue which develops resistance to insulin in the setting of obesity.



ROSLYN TEDJA, Ph.D.

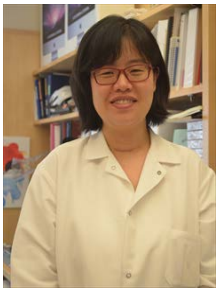
Project: Determine The Efficacy of Trans-immunization Regimen In Preventing Recurrence In An Ovarian Cancer Animal Model

Despite an initial 80% response rate, the 5-year survival rate is only 15% as most patients develop recurrence. In the recurrent setting, co-presentation with micrometastasis and chemoresistance limits the value of the available treatment options. We have shown in several studies the presence of chemoresistant ovarian cancer stem cells that can survive chemotherapy can eventually rebuild the tumor leading to recurrence. Targeting these chemoresistant cells is thus imperative in preventing recurrence. More importantly, the time after 1st-line chemotherapy therefore represents a critical period wherein additional treatment can be administered with the goal of eliminating residual disease that is composed of chemoresistant cancer cells. We hypothesize that activating the immune system against these surviving cancer stem cells can prevent recurrence and therefore improve patient survival.

In previous studies, we demonstrated that delivery of cancer cell lysate encapsulated in nanoparticles (NPs) is able to induce the activation of *in vitro* differentiated dendritic cells (DC). Our preliminary studies showed that these DC secrete pro-inflammatory cytokines that could active CD8+ cytolytic T cells. We propose to combine this approach of delivering antigens with the described transimmunization protocol, which is a novel approach for tumor immunotherapy. Transimmunization is a multi-stage personalized treatment that aims to promote an anti-tumor immune response. The goal of transimmunzation is to efficiently load patient-derived tumor antigens to patient derived dendritic cells that are capable of initiating immunization against the tumor cells and thus leading to an efficient immunotherapy. The value of transimmunization has been initially shown in patients with cutaneous T cell lymphoma.

In this proposed study, we have made slight modifications to optimize the system for ovarian cancer. Thus, we will use the

NP delivery system to deliver/present antigens from chemoresistant cancer cells to activated DC. Therefore, the objective of this proposal is to obtain proof of concept that we are able to activate the immune system using this approach in a novel ovarian cancer immunecompetent mouse model.



YANG YANG-HARTWICH, Ph.D.

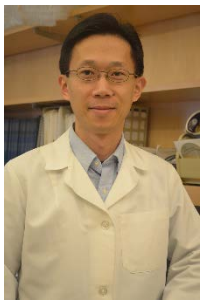
Project: Chromatin Remodeling In Ovarian Cancer

Our research focuses on understanding the chromatin remodeling in ovarian cancer cells. The long-term goal of our research is to determine the molecular mechanisms and impacts of chromatin remodeling in ovarian cancer and utilize this knowledge to discover new drug targets. To approach our goal, in this pilot study our objective is to utilize ARID1A mutation as a model to understand how chromatin remodeling globally reprograms the cellular functions in ovarian cancer cells.
ARID1A mutation is the most frequent mutation in clear cell ovarian cancer that is characterized by their aggressive behavior, high recurrent rates, and resistance to conventional chemotherapy. ARID1A belongs to the ATP-dependent chromatin remodeling complex SWI/SNF. Our hypothesis is that ARID1A mutation changes SWI/SNF complex and leads chromatin structure abnormalities in clear cell ovarian cancer cells, which leads to a global pro-tumor shift in their cellular functions. The chromatin remodeling associated with ARID1A mutation is also responsible for their resistance to chemotherapies.

We will use ChIA-PET (Chromatin Interaction Analysis by Paired-End-Tag sequencing) technique to establish comprehensive 3D chromatin structure libraries in ovarian cancer cell lines. ChIA-PET is an epigenomic approach that has become a cornerstone in exploring the 3D chromatin structure. It especially facilitates the study of higher-order chromosomal organization for transcription regulation, which is still poorly understood. We will also determine the impact of ARID1A on Chromatin remodeling by introducing wild type ARID1A back into the ovarian cancer cell lines with ARID1A-mutation. Using ChIA-PET, we will determine how the wild type ARID1A changes the chromatin remodeling. In order to explain how chromatin remodeling regulates gene expression, Human Transcriptome

Array will be utilized in our model to visualize expression changes at gene and exon levels of the ARID1A mutant ovarian cancer cell lines and these lines introduced with wild type ARID1A.

The proposed pilot study will help us establish the experimental system and collect preliminary data, which is essential for extending the study to a larger scale with the supports from federal funding agencies.



Z. PING LIN, Ph.D.

Project: p38 MAPKs as Mediator of BRCA Mutation-induced EMT and Target for Ovarian Cancer Therapy

The project is to investigate whether BRCA mutations perpetuate epithelial-mesenchymal transition (EMT) and invasive phenotypes through up-regulation of p38 MAPKs, and to investigate whether p38 MAPKs can be exploited as a pharmacological target for anti-mitotic therapy against BRCA-mutated EOC. The specific aims to be carried out in the proposed project are: *Aim 1: To elucidate the mechanisms by which p38 MAPKs promotes EMT potential and invasive phenotypes in BRCA-mutated EOC cells. Aim 2: To determine whether small molecule inhibitors of p38 MAPKs suppress EMT potential and sensitize BRCA-mutated EOC to antimitotic drugs in vitro and in tumor xenograft mouse models.*

Hereditary BRCA-mutated EOC accounts for approximately 15% of all EOC while the rest of cases are sporadic. However, up to 50% of EOC, especially high-grade serous EOC, exhibits BRCAness, a phenotype that sporadic cancer share with BRCA-mutated cancer. Notably, w*omen with deleterious BRCA mutations have about 10-30 times the risk of women in general population to develop EOC*. *Women with hereditary BRCA mutations also tend to develop disease at an earlier age of onset than sporadic cases*. Furthermore, *BRCA-associated EOC is often presented with high-grade and advanced-stage features*. Therefore, hereditary mutations of BRCA1 and BRCA2 clearly underlie predisposition to EOC and facilitate progression of the disease.

BRCA1 and BRCA2 proteins function as critical components of the homologous recombination repair (HRR) pathway to repair DNA double strand breaks (DSBs). HRR is an error-free process

to protect cells from mutagenicity and lethality of DSBs. Cells harboring deleterious BRCA mutations are defective in HRR. Therefore, the reliance of cells on error-prone repair pathways for DSBs promotes genomic instability and ultimately leads to cancer development. However, aberrant signaling pathways elicited by BRCA dysfunction remain virtually unknown. It is imperative to gain more insights into the landscape of phenotypic changes and cellular adaptations to defective HRR pathways. A better understanding of these alterations will allow identification of novel targets for devising therapeutic strategies to treat BRCA-mutated EOC.

p38 mitogen-activated protein kinases (MAPKs) belong to a subgroup of the MAPK families. Four isoforms of p38 have been identified and characterized: p38α, p38β, p38δ, and p38γ. p38 MAPKs regulate chemotactic cell migration in response to angiogenic factors (e.g. VEGF, EGF, and FGF). p38 MAPKs also promote cytoskeletal remodeling through phosphorylation of heat shock protein (HSP27). In invasive metastatic cancer, p38 MAPKs induce matrix metalloproteases (MMPs) to control matrix remodeling and degradation. Furthermore, p38 MAPKs are required for TGFβ-induced EMT. EMT is a process during which epithelial cells become mesenchymal stem cells by losing properties of polarity and cell adhesion and by gaining migratory and invasive behaviors. Among 4 isoforms of p38 MAPKs, p38γ is linked to cell motility and metastasis by regulating cytoskeletal dynamics. These pleiotropic effects of p38 MAPKs on cell migration together indicate that p38 MAPKs play a pivotal role in EMT and the invasiveness of metastatic cancers.

Paclitaxel is an antimitotic chemotherapeutic agents widely used in ovarian, breast, lung, and pancreatic cancers. Paclitaxel is highly effective as the first-line and recurrent chemotherapy for EOC. However, once patients develop platinum-resistant EOC, clinical response to paclitaxel is also low compared with that of platinum-sensitive disease. In both pre-clinical and clinical studies, a large body of evidence indicates that BRCA-mutated or BRCAness cancer cells exhibit increased resistance to paclitaxel. A very recent study demonstrates that BRCAness strongly correlates with lower rates of clinical response to taxane-based chemotherapy in triple negative breast cancer. However, the underlying mechanisms remain largely unknown and require further investigation.

Research project descriptions written by the grant recipients.

Kudos!

Please congratulate **Bobbi Blake** and **Millie Cruz** from our Gynecologic/Oncology section. They were recently awarded $1,000 grant for an idea they submitted to YNHH Auxiliary group on providing “Angel Gift Cards” to patients. They suggested that patients in

need for cab fare, gas or help with a medical bill or expenses are given a little “Angel Card”.