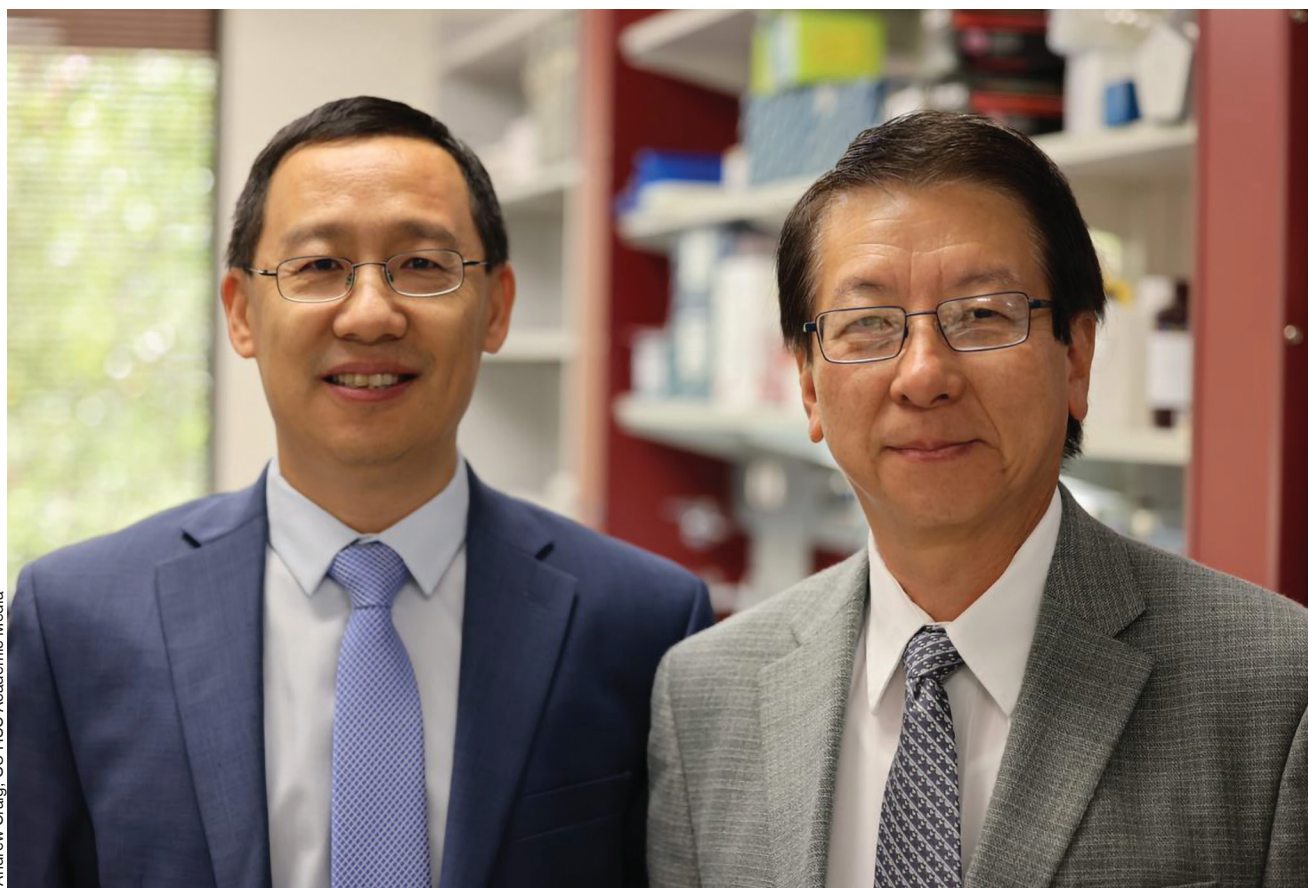


Outsmarting the Foe

*Two of OU's leading researchers join forces
to beat the odds against pancreatic cancer.*

BY APRIL WILKERSON



Andrew Craig, OU HSC Academic Media

OU researchers Min Li, left, and Wei R. Chen are using a groundbreaking combination of laser ablation and immunostimulant drugs to confront pancreatic cancer.

Rex Tullis kept receiving news that left little room for hope.

After his diagnosis of stage four melanoma in 2011 and surgery to remove the 5-millimeter tumor from his head, he learned nine months later that it had metastasized to his lungs. An oncologist estimated his time left would be short. Tullis, then chair of Southern Nazarene University's School of Education in Bethany, Okla., began planning his own funeral service, picking out the songs he thought would be meaningful to his loved ones.

Then, through a serendipitous series of connections, he discovered a clinical trial testing an innovative treatment for



J. Pat Carter

Handed a death sentence, Rex Tullis of Edmond, Okla., was among the first to participate in a clinical trial using the protocol OU's team is now testing on pancreatic cancer.

metastatic melanoma. The combination of laser ablation to irradiate the tumor, along with an existing immunostimulant and a new immunotherapy drug, was showing tremendous promise in killing not only original tumors but cancer cells that spread throughout the body. Tullis enrolled in the trial and, 10 years later, remains cancer-free.

"I sit here today with no evidence of disease," he says. "I'm thankful for good people, good medical care and good outcomes."

University of Oklahoma researcher Wei R. Chen conceived of the combination of therapies that led to Tullis' cancer remission. He since has expanded his focus to pancreatic cancer, which has long eluded successful treatment as one of the deadliest malignancies and most quickly metastasizing cancers.



As in Tullis' case, Chen says, it is the metastasis to other organs that poses the biggest threat, not the original tumor itself.

Working with fellow researchers, Chen created his own, novel immunostimulant drug and pioneered pairing its use with laser ablation. He then formed a collaboration with OU Health Sciences Center researcher Min Li, who is internationally known for his studies of the biology of pancreatic cancer.



Li's team created both cell culture and mouse models of pancreatic cancer for the study. By implanting human pancreatic cancer cells into the pancreas of mice, a tumor grows that closely mimics human disease. Li's laboratory features instruments that his team of researchers uses to monitor tumor progression and evaluate the effectiveness of Chen's treatment regimen.

Estimated New Cases and Cancer Deaths in 2022

Estimated New Cases

		Males	Females		
Prostate	268,490	27%		Breast	287,850 31%
Lung & bronchus	117,910	12%		Lung & bronchus	118,830 13%
Colon & rectum	80,690	8%		Colon & rectum	70,340 8%
Urinary bladder	61,700	6%		Uterine corpus	65,950 7%
Melanoma of the skin	57,180	6%		Melanoma of the skin	42,600 5%
Kidney & renal pelvis	50,290	5%		Non-Hodgkin lymphoma	36,350 4%
Non-Hodgkin lymphoma	44,120	4%		Thyroid	31,940 3%
Oral cavity & pharynx	38,700	4%		Pancreas	29,240 3%
Leukemia	35,810	4%		Kidney & renal pelvis	28,710 3%
Pancreas	32,970	3%		Leukemia	24,840 3%
All Sites	983,160	100%		All Sites	934,870 100%

Estimated Deaths

		Males	Females		
Lung & bronchus	68,820	21%		Lung & bronchus	61,360 21%
Prostate	34,500	11%		Breast	43,250 15%
Colon & rectum	28,400	9%		Colon & rectum	24,180 8%
Pancreas	25,970	8%		Pancreas	23,860 8%
Liver & intrahepatic bile duct	20,420	6%		Ovary	12,810 4%
Leukemia	14,020	4%		Uterine corpus	12,550 4%
Esophagus	13,250	4%		Liver & intrahepatic bile duct	10,100 4%
Urinary bladder	12,120	4%		Leukemia	9,980 3%
Non-Hodgkin lymphoma	11,700	4%		Non-Hodgkin lymphoma	8,550 3%
Brain & other nervous system	10,710	3%		Brain & other nervous system	7,570 3%
All Sites	322,090	100%		All Sites	287,270 100%

Rebecca Siegal et al. Cancer Statistics, 2022 CA J Clin 2022; 72:7-33

The data they have gathered thus far is so promising that the National Cancer Institute this year awarded the duo a \$2.5 million grant to continue the work. They hope the results of their five-year project will pave the way to a clinical trial to study the treatment in humans.

"We are a good team, and our expertise complements each other," says Chen, Stephenson Chair and Professor of Biomedical Engineering in OU's Gallogly College of Engineering. "We need a new way to treat pancreatic cancer because, right now, there is almost no way to prevent a quick, and often painful, death. Although surgery is the first option, it is not effective in about 80% of patients. In more than half of patients at the time of diagnosis, the cancer has already metastasized to other parts of the body, and the five-year survival rate for such patients is only 3%."

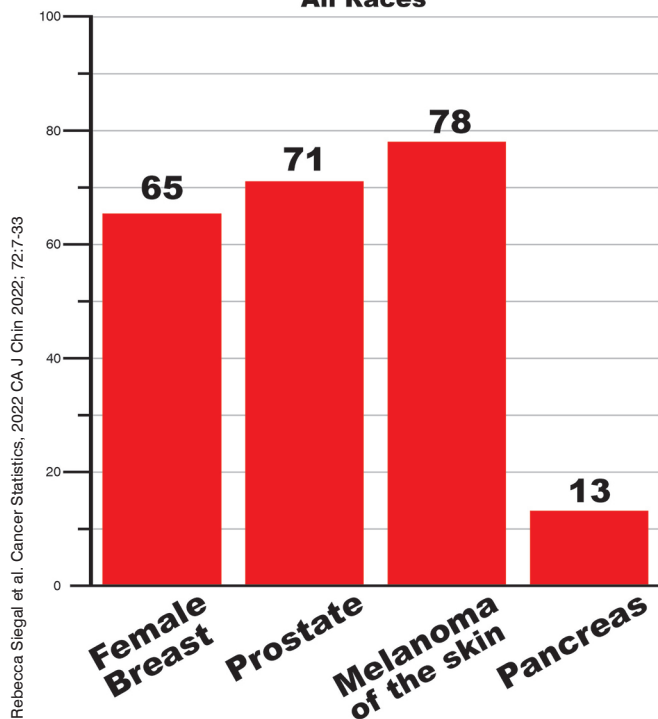
Li is an OU George Lynn Cross Research Professor of Medicine, Surgery and Cell Biology and the Virginia Kerley Cade Endowed Chair in Cancer Treatment at the OU Health Sciences Center in Oklahoma City. Li and Chen's research collaboration began about six years ago, and the results of their initial study, published in the journal *Clinical Cancer Research*, led to their current federal grant.

Innovation is required to outsmart a foe like pancreatic cancer, Li says.

"Tumors are considered either 'hot' or 'cold.' Hot tumors, like melanoma and some types of lung cancer, often respond well to immunotherapy drugs that prompt the immune system to attack cancer cells. But pancreatic cancer is considered a cold tumor because it is better able to keep the immune-

Distribution of Cancers 2011-2017

All Races



Rebecca Siegel et al. Cancer Statistics, 2022 CA J Clin 2022; 72:7-33

responsive cells suppressed.” In particular, he says, the immune system’s T cells—known as “killer cells” for their ability to attack invaders—are sidelined.

Chen’s combination therapy appears to have found a way around that problem. The immunostimulant drug he created is derived from chitosan, an extract from the shells of crustaceans like lobsters, shrimp and crabs. The drug’s function is to stimulate, enhance and direct the immune system to fight cancer cells. In essence, the drug wakes up the immune cells and gives T cells new weapons to use in the fight against pancreatic cancer cells. However, the drug is not doing all the work itself.

“It is the combination of the immunostimulant with the laser ablation that is effective. Neither achieves the desired therapeutic effects alone,” Chen says. “We have proved it again and again in our experiments. In our current study, we are looking at the mechanisms of how that occurs. There appears to be a systemic effect, because our treatment not only triggers immune reactions against the local tumor, but against the metastasis as well.”

Their research goes a step further by testing an existing immunotherapy drug, called a checkpoint inhibitor, in concert with the laser ablation and immunostimulant combination. Checkpoint inhibitors work in a related way to other immunotherapy drugs by freeing the T cells to kill cancer cells.

“Even though our laser ablation and immunostimulant approach is very promising, we believe it can be even more potent when it is synergized with other available therapies,” Chen says. “The good thing about combining several therapies is that you can reduce the dose of each therapy, thereby

decreasing the overall toxic side effects.”

In addition to their collaboration, Li and Chen are contributing individually to the understanding of cancer biology and treatment of cancer metastasis. About 10 years ago, Chen co-founded the company Immunophotonics Inc. to commercialize the laser ablation-immunostimulant combination. The company has since conducted clinical trials in South America, Europe and the United States in melanoma, breast cancer, soft tissue sarcoma and liver cancer. Chen says he hopes the next step is for the immunostimulant he created to be approved by the U.S. Food and Drug Administration so that clinical trials using this novel combination therapy for pancreatic cancer can start in the United States.

Basic science research to better understand the biology of pancreatic cancer also remains critical. Li’s own work is highly funded by the National Institutes of Health, and he has published articles for several consecutive years in *Gastroenterology*, the world’s leading journal on GI tract diseases. His latest publications have focused on the protein ZIP4, which transports zinc throughout the body and serves as a “master switch” for several things to occur in pancreatic cancer.

Li discovered that the overexpression of ZIP4 causes pancreatic cancer cells to be more resistant to chemotherapy, as well as prompting tumor cells to transform themselves in a manner that allows them to stealthily travel to the body’s other organs. “We also found that ZIP4 plays a role in the onset of cachexia, a muscle-wasting condition that affects at least 80% of people with pancreatic cancer,” he says.

Li is leading the growing pancreatic cancer research enterprise at the OU Health Sciences Center and OU Health Stephenson Cancer Center. He soon will serve in a national role upon becoming president of the American Pancreatic Association in November.

Ironically, pancreatic cancer also links the series of connections that brought metastatic melanoma patient Rex Tullis to Chen’s door. His brother, K.J. Tullis, died from the disease in 2020. Years before he died, however, K.J. was one of the people who referred Tullis to Chen’s lifesaving research. At the time, Chen was a faculty member at the University of Central Oklahoma, where K.J. served as associate dean of UCO’s College of Business.

Tullis says he is grateful the treatment that sent his melanoma into remission may one day bring the same good news to people like his late brother.

“I have a great amount of thankfulness for every day. And I am grateful for the researchers and doctors who devote their time to making these discoveries.”

April Wilkerson is the editor of OU Medicine.