Josh Baxt
August 1, 2022

Sylvester Researchers Receive $9.5 Million Grant to Study Esophageal Cancer

Researchers at Sylvester Comprehensive Cancer Center at the University of Miami Miller School of Medicine have received a $9.5 million National Cancer Institute Program Project (P01) grant to investigate esophageal adenocarcinoma (EAC), the most common form of esophageal cancer in the United States.

“People with chronic gastroesophageal reflux disease, known as GERD, can develop a precancerous condition called Barrett’s esophagus,” said Wael El-Rifai, M.D., Ph.D., associate director of basic science at Sylvester, co-leader of the Tumor Biology Research Program, and principal investigator on the grant. “The cells in the esophagus adapt to protect themselves from the acid, and that increases the risk of developing esophageal cancer.”

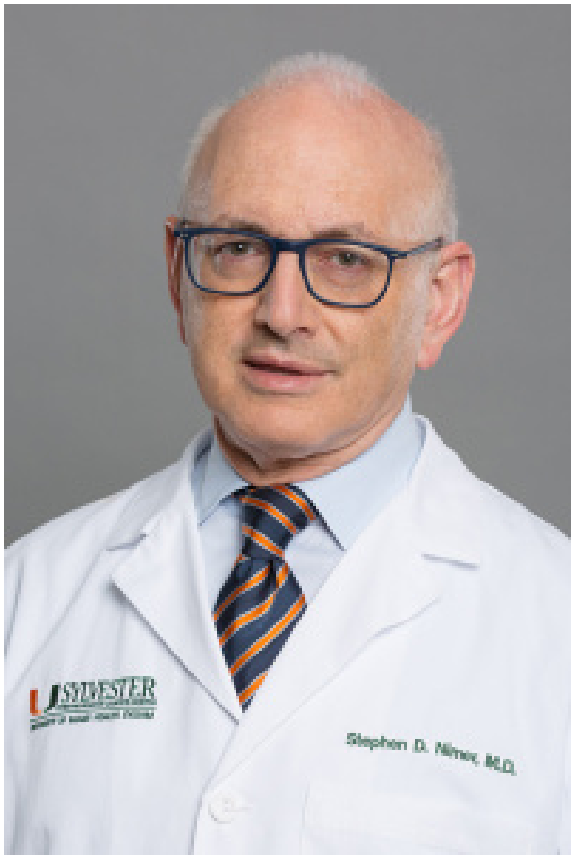
Wael El-Rifai, M.D., Ph.D., associate director of basic science at Sylvester, co-leader of the Tumor Biology Research Program, and principal investigator on the grant

“This grant is a testament to the impactful research already underway at Sylvester that is paving the way in providing patients with the best care today, and I am confident the team, under Dr. El-Rifai, will make great progress,” said Stephen D. Nimer, M.D., director of Sylvester Comprehensive Cancer Center, Oscar de la Renta Endowed Chair in Cancer Research, and executive dean for research at the Miller School. “With these resources, our researchers can learn more about this disease and create better tools to continuously

improve patient care.”

While only around 2% to 3% of patients progress from Barrett’s esophagus to EAC during their lifetimes, these cancers have a dismal, 15% five-year survival rate. In the past 30 years, EAC prevalence has increased 600%.

“Although surgery can be curative, many patients with esophageal cancer present with advanced disease that has already extended beyond the hope for complete surgical cure,” said Omaida C. Velazquez, M.D., F.A.C.S., chair of the DeWitt Daughtry Family Department of Surgery at the Miller School and surgeon-in-chief at UHealth – University of Miami Health System.



Stephen D. Nimer, M.D., director of Sylvester

Comprehensive Cancer Center, Oscar de la Renta Endowed Chair in Cancer Research, and executive dean for research at the Miller School

“Innovation is needed towards advancing early detection and adjunct medications. Together these three critical arms of care, preventative, medical, and surgery, hold great promise to reduce or eliminate deaths from this cancer,” Dr. Velazquez said. “Dr. El-Rifai and his team are providing seminal contributions that will translate to state-of-the-art, personalized lifesaving care.”

Cells Adapt, Becoming More Susceptible to Cancer

The team will focus on how esophageal cells remodel themselves in response to GERD, becoming more vulnerable to cancer-causing mutations. These cellular changes activate oncogenic transcription factors – enzymes that turn on cancer-promoting genes.

“The cells in the esophagus are not like those in the stomach – they aren’t built to withstand acid,” said Dr. El-Rifai. “However, esophageal cells adapt to this acidic environment by rewiring themselves and expressing different genes, which makes them more prone to cancer. Transcription factors are the hubs that control gene expression, and if we can control these hubs, we can control everything else in the cancer cell.”

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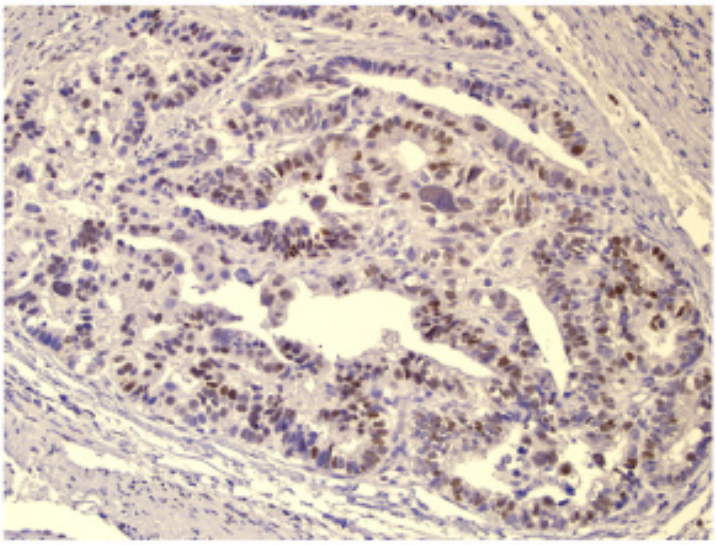

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The problem starts with increased oxidative stress. In response to GERD, interactions between the protein STAT3 and APE1 and isolevuglandins (IsoLGs) adducts (protein modifications) activate oncogenic transcription factors, increasing the risk of cancer progression.

These changes alter other proteins, including SOX9, STAT3 and SOX4, which play crucial roles in cellular transformation and growth. Usually, these proteins are tightly controlled; however, with the GERD-induced changes, they get turned on and stay on, increasing cancer risk.

Omaida C. Velazquez, M.D., F.A.C.S., chair of the DeWitt Daughtry Family Department of Surgery at the Miller School and surgeon-in-chief at UHealth – University of Miami Health System

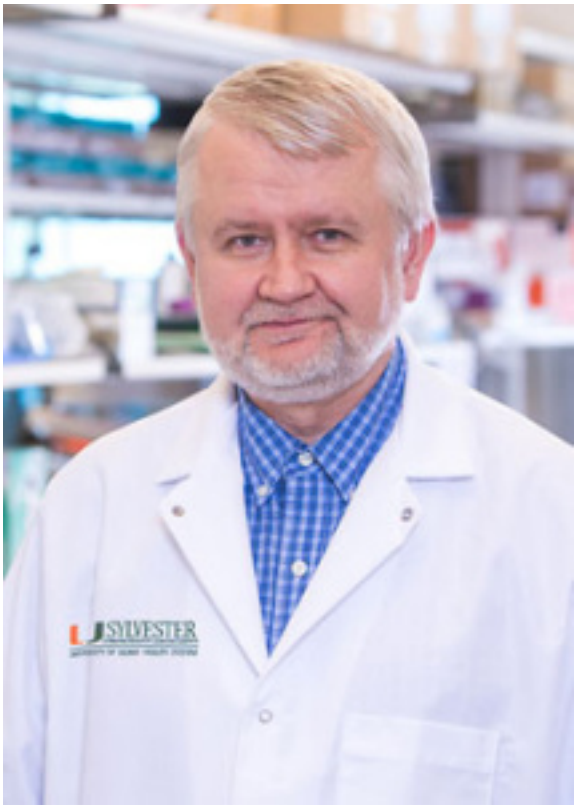
Exploring Prevention Strategies

In addition to interrogating the biology that drives Barrett's esophagus and EAC, the team will investigate compounds that can counteract these oncogenic processes.

"STAT3 plays a central role in the regulation of inflammation," said Professor of Surgery Alexander Zaika, M.D., a co-investigator on the grant. "Studying STAT3

regulation will allow us to better assess the contribution of inflammatory processes to esophageal cancer. Our studies have also revealed that certain natural compounds can prevent the emergence of isolevuglandins. Based on these findings, our group will explore novel strategies to prevent esophageal cancer."

The team will also be looking for molecular biomarkers that could help identify which Barrett's esophagus patients have the highest risk of developing EAC. Currently, all Barrett's esophagus patients undergo regular endoscopies to see if they are progressing. New biomarkers could help clinicians only monitor the patients most likely to progress, reducing the need for endoscopies.



Professor of Surgery Alexander Zaika, M.D., a co-investigator on the grant

“In the lab, we investigate experimental biomarkers that assess a patient’s risk of developing cancer, as well as how patients with cancer might respond to various therapies,” said co-investigator and Associate

Professor Oliver McDonald, M.D., Ph.D., who directs both the gastrointestinal translational pathology research and the molecular pathology core. “Any promising biomarkers discovered in the lab can then be rigorously validated across patient tissue samples and refined into new tools that can change how cancer is diagnosed and treated.”

‘Incredible Opportunity’

This large and complex research program also includes Steven Chen, Ph.D., professor and director of the bioinformatics and biostatistics core on the grant, and Jianwen Que, M.D., Ph.D., associate professor of medicine at Columbia University.

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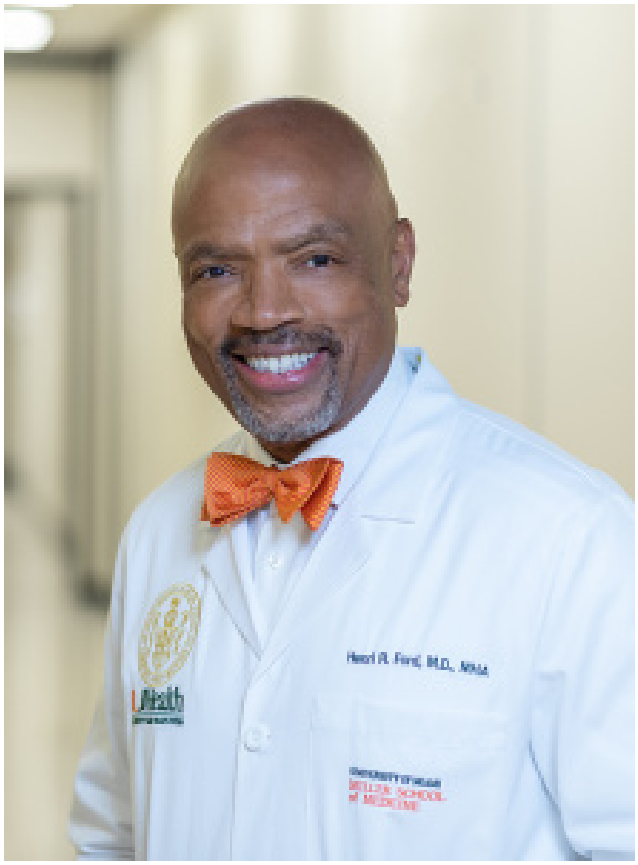

Henri R. Ford, M.D., M.H.A., dean and chief academic officer of the Miller School of Medicine

“We’re at the forefront of prevention. Our physician-scientists are highly skilled and equipped to undertake this important work and abate the growth and prevalence of EAC,” said Henri R. Ford, M.D., M.H.A., dean and chief academic officer of the Miller School of Medicine.

“When they talk about bench-to-bedside research, this is exactly what they are describing,” said Craig Moskowitz, M.D., interim deputy director, physician-in-chief for the oncology service line, and professor in the Department of Medicine. “This is an incredible opportunity to pursue impactful,

translational research that has great potential to change how we provide care."

"This grant underscores why Sylvester is a world leader in both fundamental discovery research and patient care," said Dorothy Graves, Ph.D., assistant vice president and associate director for administration at Sylvester. "We are proud of Dr. El-Rifai's team and what they will accomplish."

Dorothy Graves, Ph.D., assistant vice president and associate director for administration at Sylvester

The NCI grant will give the team the necessary resources to investigate esophageal cancer and hopefully learn how to stop it.

“We are beginning to understand how esophageal cells adapt to GERD’s acidic environment and how those changes can lead to Barrett’s esophagus and eventually cancer,” said Dr. El-Rifai. “Now, we have to find better ways to intervene. More than 18,000 people in the U.S. die from EAC each year – we need to do better.”

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