

NewYork-Presbyterian Advances Endocrinology

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NewYork-Presbyterian
Diabetes and Endocrinology
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Exploring Novel Treatments for Thyroid Cancer

“Endocrine surgery is a fascinating discipline that allows the integration of surgery and medicine in one field,” says **Thomas J. Fahey, III, MD**, Vice Chairman of the Department of Surgery, Chief of Endocrine Surgery, and Director of the Endocrine Oncology Program at Weill Cornell. “Most thyroid cancers are indolent and curable with standard treatments such as surgery, radioactive iodine therapy, and thyroid stimulating hormone suppression therapy for localized or regional disease. However, patients with thyroid cancer can have widely different clinical outcomes depending on the pathological subtype. Some 5 to 10 percent of patients develop progressive disease that is metastatic and refractory to current treatments.”

Dr. Fahey has long maintained a laboratory investigating the biology of endocrine tumors. “We have been at the forefront of the incorporation of molecular diagnostics into the diagnosis and management of patients with thyroid nodules and thyroid cancers,” he says. “Our lab was the first to identify the use of gene expression analysis



Dr. Thomas J. Fahey, III

to discriminate benign and malignant thyroid nodules. With the development of the precision medicine board here at Weill Cornell Medicine, we have the opportunity to completely sequence tumors that require additional treatment. More recently, our researchers have focused on novel treatments for advanced thyroid cancers.”

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Interventional Endocrinology: An Emerging Specialty

It is estimated that some 65 percent of people will have at least one thyroid nodule in their lifetime and within that number, only 5 percent are malignant. “That is a huge number of individuals with benign nodules,” says **Jennifer H. Kuo, MD, MS**, Director of the Interventional Endocrinology Program and Surgical Director of the Thyroid Biopsy Program at NewYork-Presbyterian/

“Interventional endocrinology has the potential to revolutionize the way we treat thyroid diseases.”

— Dr. Jennifer H. Kuo

Columbia University Irving Medical Center. “For some patients a benign nodule grows very slowly, but for others it can grow quite rapidly. The neck is a tight space and a large mass can exert pressure causing difficulty in breathing, swallowing, and sometimes changes in the voice. When patients start to have these compressive symptoms, even though the mass itself is benign, we have to think of what we can do to help relieve those symptoms. The only thing we have been able to offer until now has been surgery.”

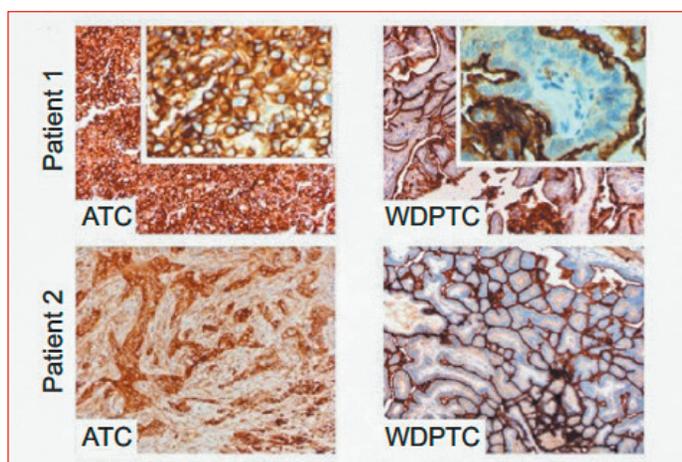
Thyroid lobectomy is an outpatient operation that offers patients overall good outcomes.

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Exploring Novel Treatments for Thyroid Cancer (continued from page 1)

CAR T Therapy Poorly differentiated thyroid cancer and anaplastic thyroid cancer (ATC) are rare yet lethal malignancies with limited treatment options. Dr. Fahey and **Irene M. Min, PhD**, Assistant Professor of Molecular Biology Research in Surgery at Weill Cornell Medicine, are pursuing investigations with **Moonsoo Jin, PhD**, in the Department of Radiology on the development of CAR T therapy for these cancers.

Advanced, metastatic thyroid cancers have increased expression of ICAM-1, and so the researchers developed a CAR T therapy targeting ICAM-1 for the treatment of aggressive thyroid cancer. The results of their study, which were published in *Clinical Cancer Research*, demonstrated the significant and durable efficacy of ICAM-1 CAR T for targeting anaplastic thyroid cancer.



Representative ICAM-1-specific IHC images of anaplastic thyroid cancer (ATC) patient-derived tissue. Well-differentiated papillary thyroid cancer (WDPTC) or normal thyroid tissue images on the same slide are shown for comparison on the right.

“Furthermore, we showed that autologous ICAM-1 CAR T cells have significant therapeutic efficacy in animal models bearing ATC patient-specific tumors,” says Dr. Fahey. “Our CAR T-cell-based immunologic approach has potentially wide-ranging applications for the treatment of other solid cancers where there is a strong association between ICAM-1 expression and adverse prognosis. The process is always slower than you expect it to be, but we’re hoping to have FDA approval to start a phase 1 clinical trial in the near future to look at the efficacy of this very novel treatment.”

New Avenues of Research A small percentage of patients with metastatic differentiated thyroid cancer do not respond to radioactive iodine treatment and thyroid-stimulating hormone suppression. In these patients, there is still an option: targeted tyrosine kinase inhibitors. “Tyrosine kinase inhibitors now are being utilized in the treatment of previously treated refractory thyroid cancers and have certainly opened up new avenues for both treatment and further research,” notes Dr. Fahey. “The future will be to look at their ability to impact the redifferentiation of thyroid cancers to permit them to uptake radioactive iodine,

Clinical Trial for Advanced Thyroid Cancer

The Endocrine Oncology Program in the Department of Surgery at Weill Cornell Medicine will soon be opening a clinical trial testing a novel treatment for patients with advanced thyroid cancer. If you are interested in learning more about the trial, contact Dr. Fahey at tjfahey@med.cornell.edu.

a mainstay of adjuvant treatment for the routine thyroid cancer. We have been exploring potential ways to reestablish or reactivate that sodium iodine import mechanism in the lab. If we can reactivate the iodine uptake, then we can make a treatment, which as far as adjuvant treatments go is one of the safest in general, once again an option for these patients.”

“Our lab has evolved from looking at the differential expression of genes and proteins for differentiation of benign and malignant tumors to now also utilizing the information to identify therapeutic targets for more advanced thyroid cancers.”

— Dr. Thomas J. Fahey, III

Dr. Fahey and his colleagues are also interested in anticancer therapy-induced autophagy, which can trigger adaptive drug resistance in a variety of cancer types and treatments. In a multi-institutional collaborative study, the Weill Cornell investigators have explored if autophagy is activated in vemurafenib-treated BRAF-mutant thyroid cancer cells, and whether autophagy inhibition improves or impairs the treatment efficacy of vemurafenib, a cancer growth blocker. The combined effects of autophagy inhibitor and vemurafenib were assessed in terms of cell viability *in vitro* and tumor growth rate *in vivo*. The results of the study, published in the *Journal of Clinical Endocrinology Metabolism*, demonstrated that vemurafenib induces endoplasmic reticulum stress response-mediated autophagy in thyroid cancer and that autophagy inhibition may be a beneficial strategy to sensitize BRAF-mutant thyroid cancer to vemurafenib.

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For More Information

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Interventional Endocrinology: An Emerging Specialty (continued from page 1)

“The surgical complication risk is low, and patients tolerate it very well,” says Dr. Kuo. “With a lobectomy, ultimately most patients will not need any thyroid hormone supplementation because the other thyroid lobe remains functional. However, at least 25 percent of patients will need supplementation at some point after surgery.”

Interventional endocrinology is an emerging specialty that uses percutaneous, image-guided, less-invasive procedures to address endocrine disorders that offers an alternative to surgery. “This approach has the potential to revolutionize the way we treat these diseases,” says Dr. Kuo. “It’s not going to be the right treatment for everyone, but it is going to be a good treatment for a lot of people.”

Ultrasound-Guided Radiofrequency Ablation Ultrasound-guided radiofrequency ablation (RFA) treats specific types of benign thyroid nodules and lymph nodes with recurrent cancer. “RFA is best used in cases of cancers where surgery is not ideal or for symptomatic benign thyroid nodules,” says Dr. Kuo. “It involves ultrasound-guided placement of an electrode into the thyroid nodules. The electrode has an active tip that emits radiofrequency waves that allow us to burn the tissue we’re targeting in a very controlled manner. It’s similar to an ultrasound-guided fine needle biopsy. The procedure can be performed in an outpatient setting very safely. Patients are able to avoid general anesthesia and surgery, and there is no scar.”



Demonstrating ultrasound-guided radiofrequency ablation

According to Dr. Kuo, a key benefit is that thyroid hormone dependency after RFA is almost zero. “This is largely because we’ve targeted just the nodule and not any of the normal thyroid tissue that surrounds it,” she says. “With a good ablation, we are able to achieve an average of 80 to 90 percent volume reduction of these nodules without surgery and without a need for hormone supplementation in the future.”

Follow-up care involves using ultrasound to look at objective measures of volume reduction and patient symptoms. “Sometimes due to location we can’t ablate the whole nodule. For some very large nodules, multiple ablations may be needed,” explains Dr. Kuo. “For instance, if we achieve 50 percent volume reduction and the patient’s symptoms are gone, then the procedure is technically a success and the patient may not necessarily need



Dr. Jennifer H. Kuo

the whole nodule to be ablated. If the nodule grows back and the patient becomes symptomatic again, we can always repeat the procedure. In addition, having RFA does not preclude having surgery down the line if necessary.”

Dr. Kuo sees interventional approaches as a safe technique for patients with benign nodules seeking treatment other than surgery. “This is a good alternative for that population of patients,” she says. “However, if there’s a question of cancer or a question of our ability to make that diagnosis before surgery, that is not a patient population that we can treat right now with RFA.”

Ultrasound-Guided Ethanol Ablation This procedure uses high-resolution ultrasound to guide the injection of a small amount of ethanol into a thyroid nodule or lymph node. The ethanol causes an inflammatory response that leads to very targeted destruction of the nodule or node. “This approach has been very successful for treating cystic thyroid nodules, since simple cysts are almost never cancer and partially cystic nodules with no suspicious features have a less than 3 percent risk of malignancy,” says Dr. Kuo. “Treatment of thyroid cysts is considered when compressive symptoms are present or when the cyst is very large. Traditional options for treating thyroid cysts include needle aspiration or surgical removal. Unfortunately, needle aspiration has a 60 to 90 percent chance of the cyst recurring. Although surgery cures the problem, there is a low risk of complications and a very small group of patients may not be able to have surgery due to other medical problems. For these patients, ultrasound-guided ethanol ablation is a safe and effective option.”

As Dr. Kuo explains, while the overall survival for patients with thyroid cancer is excellent, up to 20 percent will have recurrent disease. Some 90 percent of recurrences are found in the lymph nodes. “Although surgery remains the preferred treatment for recurrent disease, the chance of complications increases because of scar tissue created in previous operations,” notes Dr. Kuo. “Both ultrasound-guided ethanol and radiofrequency ablation have proven to be safe and effective procedures for recurrent thyroid cancer.”

Enhancing Endocrinology Education for Physicians and Patients

Education is a major focus of **Aaron Schulman, MD**, an endocrinologist in the Division of Endocrinology, Diabetes, and Metabolism and Director of the Endocrinology Fellowship Program at NewYork-Presbyterian/Weill Cornell. “Education is a huge passion of mine and to be able to train the next generation of endocrinologists is very gratifying,” says Dr. Schulman, who is committed to ensuring that fellows have the best possible educational experience during the two-year intensive program.

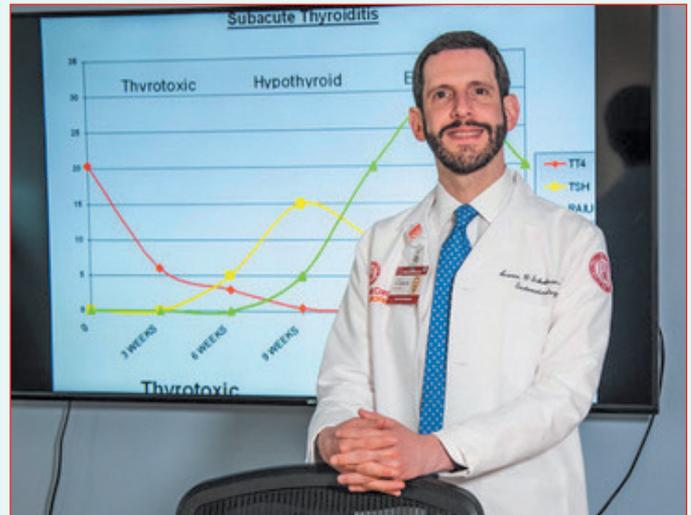
“Our program is unique in that our fellows are equally educated by faculty at Weill Cornell, Memorial Sloan Kettering Cancer Center, and Hospital for Special Surgery,” continues Dr. Schulman, who collaborates with the endocrinology faculty at all three institutions through conferences, grand rounds, case presentations, and the journal club. “I’m very involved and spend a lot of time listening to any concerns they have and tailoring the program to make it a great educational experience.”

Dr. Schulman also serves as Co-Director of the Endocrinology Program for Medical Students, and is involved in the residents’ endocrinology education, an interest borne out of his own educational training. “When I was a resident here at Weill Cornell, I recall that there wasn’t a lot of endocrinology education at the time, so I’ve made it a focus to try to bring that teaching to the residents as well,” says Dr. Schulman, who also completed his fellowship at Weill Cornell.

Dispelling Myths Surrounding Thyroid Disease

In addition to his academic teaching responsibilities, Dr. Schulman is interested in educating patients as well. “One of the frustrations of being a thyroidologist is that patients come in with a lot of preconceived notions about their thyroid and other glands based on what they’re reading online,” he says. “I address a lot of these claims with evidence-based research.”

Adrenal fatigue is one such example. “Adrenal fatigue has been used to explain a group of symptoms that are said to occur in people who are under long-term mental, emotional, or physical stress,” says Dr. Schulman. “Symptoms include tiredness, trouble falling asleep at night or waking in the morning, salt and sugar craving, and needing stimulants like caffeine to get through the day.” As Dr. Schulman points out, no scientific proof exists to support adrenal fatigue as a true



Dr. Aaron Schulman

medical condition and patients with these symptoms may have adrenal insufficiency or another health problem that requires an accurate diagnosis and treatment.

“Ultimately, the symptoms of thyroid disease are rather nonspecific,” says Dr. Schulman. “It’s easy for patients, and even providers, to suspect what the patient is experiencing may be related to the thyroid, and so they come in to see us. Sometimes their concerns are related to the thyroid and are very treatable. But oftentimes lab tests don’t bear out a thyroid connection, and in that case as endocrinologists we are unable to help the patient with fatigue, changes in weight, or those issues that people always assume are thyroid related, but are not necessarily.”

However, Dr. Schulman believes it’s important for primary care colleagues to have a degree of suspicion that a patient’s symptoms could result from a thyroid condition. “They should be looking at patients and listening to what they’re telling them and consider the possibility they could have thyroid pathology and test for it.”

For More Information

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Interventional Endocrinology: An Emerging Specialty (continued from page 3)

Dr. Kuo and interventional endocrinologists at several institutions are currently collaborating on establishing a multi-institutional case series to validate the efficacy of these procedures, which are regularly performed in Asia and Europe. “We’re looking at patients who choose to have surgery versus those who choose RFA and examining aspects of their quality of life,” says Dr. Kuo. “We are also conducting research on molecular profiling of thyroid nodules. Sometimes

it is very difficult to determine whether nodules are cancerous. Genetics work in this area is focused right now on diagnosing cancer and is moving towards better understanding the prognosis.”

For More Information

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Dr. Laura Alonso New Chief of Endocrinology at Weill Cornell

Laura C. Alonso, MD, a noted physician-scientist, has been appointed Chief of the Division of Endocrinology, Diabetes and Metabolism at NewYork-Presbyterian/Weill Cornell Medical Center and Director of the newly established Joan and Sanford I. Weill Center for Metabolic Health at Weill Cornell Medicine. Dr. Alonso succeeds **Julianne Imperato-McGinley, MD**, who has led the division for the past 25 years.

Dr. Alonso comes to Weill Cornell Medicine and NewYork-Presbyterian/Weill Cornell from the University of Massachusetts Medical School in Worcester, MA. There she served as George F. and Sybil H. Fuller Foundation Term Chair in Diabetes, as well as the Director of Beta Cell Biological Studies in the Diabetes Center of Excellence.

In her new roles at Weill Cornell, Dr. Alonso will seek to advance the division's already distinguished reputation for clinical excellence. A champion of collaboration, Dr. Alonso will encourage faculty to establish and strengthen interdisciplinary relationships with physicians and scientists at Weill Cornell Medicine and NewYork-Presbyterian, as well as with Cornell University in Ithaca. This commitment extends to the Weill Center for Metabolic Health, which Dr. Alonso will work to develop from its infancy into a world-class diabetes center encompassing basic, translational, and clinical research in diabetes and related metabolic syndromes. The close integration between the division and the Weill Center for Metabolic Health will help prepare the division's trainees to be well informed with both basic science and clinical care and help create a pipeline of physician-scientists.

As Director of the Weill Center for Metabolic Health, Dr. Alonso will launch new initiatives in research that will accelerate breakthroughs in the scientific understanding of metabolic health and disease with the goal of advancing cutting edge treatments for diabetes and related metabolic syndromes. Her dual role as the inaugural leader of the Weill Center for Metabolic Health will enable her team to more rapidly translate research into care.

"We are thrilled to welcome Dr. Alonso to Weill Cornell Medicine and NewYork-Presbyterian/Weill Cornell," says **Anthony N. Hollenberg, MD**, Physician-in-Chief at NewYork-Presbyterian/Weill Cornell. "She is a distinguished physician-scientist whose work in understanding pancreatic beta cell function and regeneration has the potential to transform the paradigm for diabetes care for patients around the world. We couldn't think of anyone better suited to lead the division than Dr. Alonso."



Dr. Laura C. Alonso

About Dr. Alonso

Dr. Alonso is a leading investigator in pancreatic beta cell regeneration with a particular focus on understanding how the pancreas in healthy people is able to produce enough beta cells to meet their need for insulin and approaches to leveraging these discoveries to improve patient care. Her research, which is supported by major grants from the National Institutes of Health and the American Diabetes Association, is published in the top journals in her field. Dr. Alonso also serves on the editorial boards of *The Journal of Biological Chemistry*, *Diabetes*, and *The FASEB Journal*, and is an associate editor for *Physiological Reports*.

Dr. Alonso is an elected member of the American Society for Clinical Investigation, a standing member and former Co-Chair of the NIH's Molecular and Cellular Endocrinology Study Section, and she serves on the organizing panel for the Scientific Sessions of the American Diabetes Association.

Dr. Alonso received her medical degree in 1998 from the Perelman School of Medicine at the University of Pennsylvania in Philadelphia. She completed her residency training in internal medicine at the Pritzker School of Medicine at the University of Chicago and fellowships in endocrinology and metabolism at the University of Chicago and New York University. She completed postdoctoral fellowship training in stem cell biology with Dr. Elaine Fuchs at the University of Chicago and The Rockefeller University, and in pancreatic islet biology with Dr. Andrew Stewart at the University of Pittsburgh. She directed Beta Cell Biological Studies at the University of Massachusetts and served as an associate professor there.



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