

2016 Annual Meeting

The 10th annual ITOG meeting was held at the University of Colorado School of Medicine. The meeting was organized and hosted by ITOG members Dr. Bryan Haugen, Dr. Rebecca Schweppe, Ms. Vicki Wright and Ms. Audrey Wen. This year, sixty attendees from sixteen medical institutions representing four countries - Australia, France, Italy, and United States - convened to learn and collaborate. More than thirty scientific and clinical research sessions were held, including the new ITOG Trials Updates and inaugural presentations for the Robert F. Gagel Discovery Award and the Rick Abrams Memorial Lecture.

The talks were grouped into six sessions, covering important topics in thyroid cancer research and treatment: Tumor Immunology, Kinase Signaling, Microenvironment, Preclinical Model Development, and Clinical Trials. Rounding out the Kinase Signaling session were presentations by three pharmaceutical representatives discussing new strategies for targeting cancers driven by the tyrosine kinase RET. These informative talks included “Targeting RET in Thyroid and Lung Cancer,” “Targeting Addicting Kinases in Thyroid Cancer,” and “Single-Agent: Precision Medicine Engineered to Simultaneously Target RET, RET Mutants, and Tumor Stroma.”

While the two-day meeting was packed with science and networking, the organizers did a fabulous job of introducing participants to the natural beauty of Colorado. The days were broken up by hikes in Red Rocks Park in the foothills west of Denver, with striking views of the world-famous natural outdoor amphitheater and the mountains. This meeting, enabling



Chair Dr. Lori Wirth and Secretary Dr. Manisha Shah

participants to develop new collaborations and clinical trials for thyroid cancer patients, could not happen without the camaraderie and cooperative spirit that is the heart of ITOG's existence. We are looking forward to our next Annual Meeting, hosted by Dr. Julie Ann Sosa at Duke University in the spring of 2017.

Targeting Tumor Associated Macrophages In Advanced Thyroid Cancers

The role of the tumor microenvironment in cancer progression has gained increased attention in recent years. Dr. Mabel Ryder of the Mayo Clinic in Rochester, Minnesota has focused on how the immune system is involved in thyroid cancer progression, in particular the participation of tumor-associated macrophages (TAMs), a kind of inflammatory cell, in facilitating tumor progression and metastases. In her talk at the 2016 ITOG meeting, Dr. Ryder reviewed previous findings in which she evaluated the presence of TAMs in a range of thyroid cancer samples and discovered a significant correlation between the abundance of TAM infiltration and the aggressiveness of the thyroid cancer. Tumors from anaplastic thyroid cancer (ATC) patients, an extremely aggressive cancer, are densely populated with TAMs and these patients have a very poor prognosis. In the hopes of finding more effective treatments for these aggressive tumors, Dr. Ryder developed cell-based experiments in which she tested the effectiveness of targeting the cancer cells with a traditional chemotherapy drug with or without a drug that blocks the TAMs. Surprisingly, she found that the TAMs block the efficacy of the chemotherapy, leading to the idea that targeting TAMs in models of thyroid cancer can reverse the aggressiveness of the disease. Dr. Ryder has more recently extended these findings to a mouse model of anaplastic thyroid cancer that was developed in Dr. Jim Fagin's laboratory. Although additional studies are needed, preliminary experiments suggest that combination therapies – targeting TAMs in addition to the cancer cells – might improve responses to chemotherapy, and represents a promising new approach for this advanced disease.

ITOG Develops A Clinical Trial For Combination Targeted Therapy Of Differentiated Thyroid Cancer

ITOG is soon to open a new clinical trial that will evaluate the effectiveness of a novel combinatorial treatment for differentiated thyroid cancer (DTC). This trial is spearheaded by Dr. Bryan Haugen of the University of Colorado School of Medicine and is being developed in concert with Dr. Lori Wirth of Massachusetts General Hospital and Dr. Jena French of the University of Colorado School of Medicine. This will be a multi-center Phase II trial of an immune checkpoint inhibitor in combination with a TKI in patients with progressive, radioiodine-refractive DTC.

Advanced thyroid cancers can be difficult to treat, especially if they do not respond to radioactive iodine (RAI). New immunotherapy treatments with the potential to unleash the immune system to eradicate cancer cells are being explored. Under normal conditions, immune 'checkpoint' proteins protect tissues from damage by the immune system. Unfortunately, these checkpoint proteins also keep T-cells from attacking cancer cells. Scientists have developed new immunotherapy drugs called 'checkpoint inhibitors' to help T-cells get back to work in protecting the body. The strategy proposed in this trial is a combination therapy designed to target both the tumor and the immune response, employing an oral multikinase inhibitor (MKI) that attacks cancer cells along with a checkpoint inhibitor designed to boost the immune system's ability to fight the tumor.

There is a great deal of enthusiasm over ITOG's third clinical trial, which is being coordinated by the Academic and Community Cancer Research United (ACCRU). In the spirit of international collaboration, the trial will include six sites in the US and four sites in Europe. The study plans to enroll patients with DTC whose tumors are refractory to RAI. Patients will be grouped into two categories: those who are naïve to both drugs and those whose cancers have progressed on the MKI. Tissue samples will be analyzed for markers to elucidate how this combination therapy acts on the tumors and the immune response.

This trial is under active development and is expected to open in early 2017. Be sure to check the ITOG Clinical Trials page (<http://www.itog.org/clinical-trials>) for more information.



Dr. Bryan Haugen

Harnessing The Immune System To Target Advanced Thyroid Cancer

The majority of patients with differentiated thyroid cancers respond well to standard therapies, yet for those patients who develop more invasive disease, current treatment strategies are limited. Patients with progressive thyroid cancer could benefit from novel immune-targeted approaches. Dr. Jena French of the University of Colorado School of Medicine studies how to harness the immune system to help eliminate thyroid cancer. Her lab has characterized T-cells, immune cells that naturally fight infection, in a range of thyroid cancers with a focus on more aggressive forms of anaplastic thyroid cancer (ATC). Dr. French has investigated whether T-cells are present in tumors, both non-aggressive tumors and regional metastases, and has observed striking correlations between numbers of T-cells and degrees of lymph node metastases. In her talk at this year's ITOG meeting, she presented data examining the presence of T-cells as well as immune checkpoint proteins, which have been shown in other cancer types to be associated with T-cell exhaustion and poor prognosis. Interestingly, she found that a high number of ATCs express immune checkpoint proteins, suggesting that these cancers could be candidates for checkpoint blockade therapy. These data form the basis for ITOG's third clinical trial, described above, developed in collaboration with ITOG members Dr. Bryan Haugen and Dr. Lori Wirth.

Therapeutic Opportunities Arising From Genomic Analysis of Thyroid Cancers

Examining the genomic landscape of tumors can provide insights into the genetic changes driving cancer growth. Dr. Jim Fagin's laboratory at Memorial Sloan Kettering Cancer Center in New York has been instrumental in characterizing the genomic changes associated with advanced thyroid cancers with a goal towards identifying new molecular-based therapies. At the 2016 ITOG meeting, Dr. Fagin presented exciting data on the genomics of poorly differentiated thyroid carcinoma (PDTC) and ATC, both rare and aggressive diseases. Virtually all cases are refractory to RAI and chemotherapy, and radiotherapy is of marginal benefit. Efforts to treat these cancers have been thwarted by the paucity of information on the genomics of these tumors. Dr. Fagin performed deep sequencing and expression profiling of PDTCs and ATCs, revealing novel insight into their molecular footprints. For instance, mutations in the telomerase (TERT) gene promoter were far more prevalent in PDTCs and ATCs relative to DTCs, representing a pivotal event in tumor microevolution. Dr. Fagin also found insightful differences between PDTC and ATC gene signatures sharing key functional properties, providing tools that can be leveraged to improve the molecular diagnosis of these cancer types, as well as a basis for developing more effective therapeutics.



Dr. Jim Fagin

ITOG Announces The Robert F. Gagel Discovery Award

Dr. Robert F. Gagel is a principal founder of ITOG. After treating patients with rare thyroid cancers at MD Anderson Cancer Center in Texas, he had the foresight to design a better approach to utilize the limited funding resources available and envisioned a new organization to bring experts together to share research, debate ideas and to develop a logical approach for prioritizing new treatments. In 2004, he and Dr. Barry Nelkin selected a "Dream Team" of physicians and scientists to attend the first ITOG meeting in Bethesda, MD. He worked tirelessly to get the organization off the ground and was elected to become the first Chair and was then reelected to serve a second term. One of Dr. Gagel's greatest contributions to ITOG was his focus on establishing a culture of trust in order to foster collaboration. His professional accomplishments, including his research in familial medullary thyroid cancer (MTC), speak for themselves.



Dr. Robert Gagel

In honor of Dr. Gagel's tremendous contributions to ITOG, the Board of Directors established a grant of \$100,000 for the ITOG member with the best scientific proposal that would have direct translational implications toward developing novel treatments for thyroid cancer. After a competitive scientific peer review process, ITOG awarded the inaugural Robert F. Gagel Discovery Award to Dr. Yariv Houvras, Assistant Professor of Medicine at Weill Cornell Medical College.



Dr. Yariv Houvras

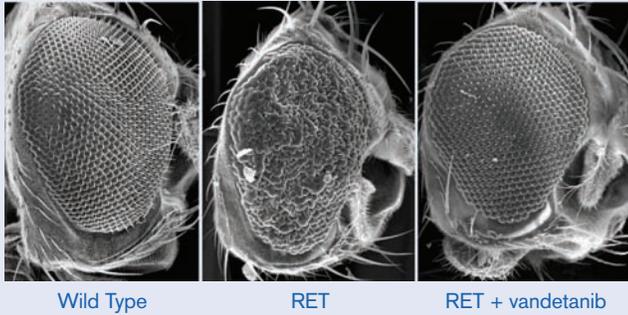
Dr. Houvras leads a laboratory that has pioneered the use of zebrafish to study thyroid cancer. Zebrafish are a small transparent fish that can be used to study the genetic basis of cancer.

In his proposal, Dissecting the Mechanism of Kinase Inhibition in Thyroid Cancer, Dr. Houvras and colleagues will perform experiments to understand how thyroid cancer drugs work. These studies will hopefully lead to specific insights that can benefit patients treated for advanced thyroid cancer.

"I am thrilled to have the support of ITOG to perform these studies in my laboratory. The idea for these experiments comes directly from my experiences treating patients with thyroid cancer. I believe our zebrafish models can illuminate new biology that will lead to improved care for patients. It is a tremendous honor to be the inaugural recipient of this award, particularly since I hold Dr. Robert Gagel in the highest regard as a scientist and physician."

Fly-To-Bedside: Developing Targeted Therapies For Cancer Treatments

Dr. Ross Cagan's laboratory at Mount Sinai Hospital in New York focuses on the fruit fly, *Drosophila melanogaster*, to better understand thyroid cancers and to develop new treatments. Early models from his laboratory helped identify the mechanisms by which the tyrosine kinase RET drives medullary thyroid cancer (MTC); this work also helped validate vandetanib as a candidate therapeutic (Figure: Suppression of "tumors" in fly eye). In his talk at the 2016 ITOG meeting, Dr. Cagan discussed how expressing the abnormal proteins responsible for papillary thyroid cancer (PTC)—fusions that also activate RET—in the fly can similarly promote tumors. He showed evidence that these "fusion" forms of RET act differently than the mutated RET that results in MTC, both in how they signal in the cell and the drugs to which they respond. These findings suggest new drug combinations that could be tailored to PTC. Finally, Dr. Cagan discussed the ongoing clinical trials in the Center for Personalized Cancer Therapeutics at the Icahn School of Medicine at Mount Sinai, an experimental fly-to-bedside trial that seeks to use fly models to predict personalized drug cocktails for cancer patients, including MTC patients.



The Rick Abrams Memorial Lecture

ITOG lost beloved member Richard D. "Rick" Abrams in June, 2014 after a long and courageous battle with thyroid cancer. He was 59. Rick's engagement with ITOG was merely one example of his boundless enthusiasm and energy for making the world a better place. Rick spread the word about ITOG through online initiatives and by bringing his unique patient perspective to the annual ITOG meeting and THYCA (Thyroid Cancer Survivors) conference. Beyond ITOG, Rick had a successful professional career as an innovator in education and technology, and he was devoted to several other philanthropic and research organizations.

Rick's dedication to ITOG was deep. He was instrumental in developing plans to raise money for research, building awareness of advanced thyroid cancer, and organizing and hosting the 2014 ITOG Annual Meeting in Boston. Rick made crucial contributions to our ITOG website design. He also reached out to other patient advocates to share his enthusiasm for ITOG's mission.

Those who knew Rick experienced his unending curiosity, generosity and kindness. ITOG is fortunate to count amongst its membership patients like Rick Abrams. His dedication inspires us all to work a little harder to catalyze a cure for thyroid cancer.

In honor of Rick's contributions, ITOG named the guest lecture at the Annual Meeting dinner the "Rick Abrams Memorial Lecture." Rick's wife, Susan Kenyon, also an ITOG volunteer, and their three children, Archie, Stan, and Sydney, joined the Annual Meeting this year to celebrate this recognition. In accepting the honor Susan said, "Rick was drawn to ITOG because he believed strongly in its mission and was impressed with the camaraderie and cooperative spirit that is fundamental to ITOG; your dedication to patients, your resolve to come together at ITOG to improve the outcomes for your patients and your constant kindness and humbleness. Without the tireless work of all of you, and in particular his personal caregivers, we would never have had Rick in our lives for ten years after his diagnosis. Most patients want a guarantee, a new treatment from their doctors. As Rick said in the video on the ITOG website, you have to get over the concept of a guarantee, to be happy and to live with hope. You all gave him that hope, and he lived a full and productive life - right up to a couple of weeks before he died."

Dr. Peter Buttrick, Professor of Medicine, Head of the Division of Cardiology, and Senior Associate Dean for Academic Affairs for the University of Colorado School of Medicine was invited to give the inaugural Rick Abrams Memorial Lecture. He gave an enlightening talk enjoyed by all, entitled "Cardiac Care In Colorado In The 1950s And How It Affected A President."



The Abrams Family

Would you like to help? Please visit our website www.itog.org or contact Dwight Vicks at dwight@itog.org.