

University Health Network

Guided Therapeutics (GTx) Research Jonathan Irish, David Goldstein, Michael Daly

The GTx Surgery Program, part of UHN's Techna Institute continues to accelerate the translation of novel image-guidance technology from pre-clinical laboratory work into the operating room, improving the use of image guided technologies in surgery. The multi-disciplinary GTx team developed a core technology platform which integrates three-dimensional imaging, surgical navigation, robotics and molecular imaging to provide precise intraoperative visualization of tumours and surrounding healthy tissue. The GTx program consists of two main physical resources: the GTx lab, located in the Princess Margaret Cancer Research Tower and a unique operating room, dedicated to research, the GTx Operating Room (GTx-OR), located within the clinical ORs at the Toronto General Hospital. The in-room computed tomography (CT) imaging capabilities of the GTx-OR, consisting of the Siemens Somatom Flash CT and the Siemens Artis Zeego Cone Beam CT, are under evaluation in a growing number of clinical studies which includes head & neck, skull base, orthopaedic, thoracic, vascular and cardiac patients.



The GTx Sarcoma Research and Surgery Team: a collaboration between UHN and Sinai Healthy System.

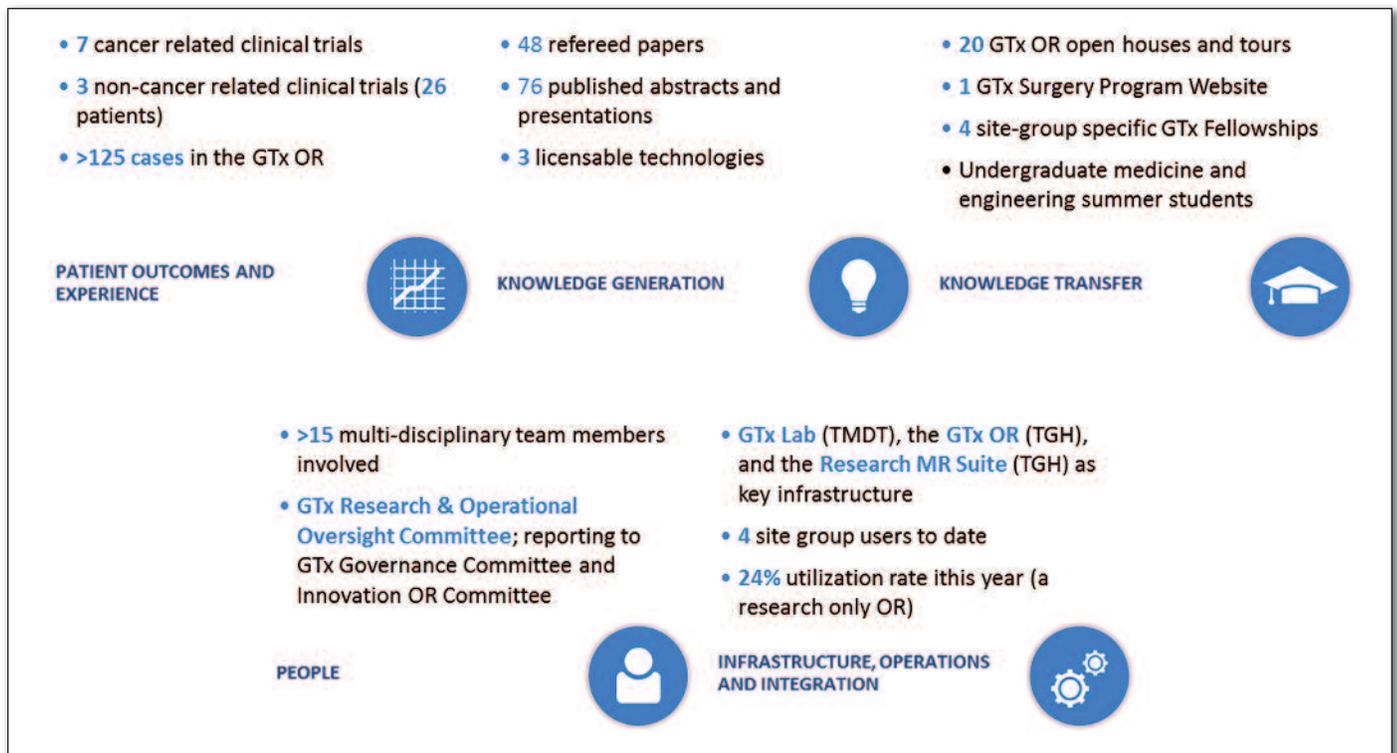
From benchtop to bedside, 2015 marked a successful year in translating the use of the GTx navigation and planning platform to the OR, with first-in-patient procedures for sarcoma surgery executed for a clinical trial lead by Dr. Jay Wunder. The GTx platform was further developed for patients with benign extremity bony tumors, a stepping stone toward more complex pelvi-sacral sarcoma surgeries. This work will also translate to head and neck clinical trial with guided osteotomies in maxillary and mandibular surgery. Lab work with phantom models and cadavers have already been initiated and first-in-human work is about to begin. Innovations developed and tested in the first clinical trials included: novel tool design and workflow to allow seamless automatic registration leveraging on the intra-operative robotic cone beam CT; a dynamic, real time intuitive color map that helps predict, visualize and control the distribution of Target Registration Errors; and a gesture control device called 'Leapy' which enables a gloved surgeon to manipulate, twist, turn and scroll through CT/MRI navigation images for best visualization while remaining sterile.

Notable achievements for the GTx Surgery Program include further progress made in fluorescence-guided surgical studies. Heck & Neck and Thoracic are working on new clinical applications for existing multifunctional nanomedicines, setting the stage for first-in-human studies involving novel multi-modality contrast agents. When integrated with PET/computed tomography and fluorescence imaging, these particles accurately detect primary tumor and metastatic lymph nodes in head and neck cancer, and provide real-time visualization of lymphatic drainage to identify unknown primaries and recurrent tumors. The tumor-specific activation of fluorescence further enables image-guided surgery and increases the potential of localized ablation of disease while sparing the surrounding healthy tissue. Successful findings in 2015 on two such agents: porphyrins (collaboration with Dr. Gang Zheng)

and liposomes (Christine Allen, Jinzi Zheng, David Jaffray) showed promising translational potential of these nanoparticles to enhance both diagnosis and therapy of head and neck cancer, and were featured

as the cover stories in journals of Clinical Cancer Research (N. Muhanna, et al., 2015) and Advanced Healthcare Materials (N. Muhanna, et al., 2015).

The GTx Program At-A-Glance:



Head & Neck Translational Program Fei-Fei Liu

The Head and Neck Cancer (HNC) Translational Research Program at the Princess Margaret strives for a future where HNC can be cured without toxicity. This program has three main goals:

1. To understand HNC biology at the molecular, cellular, and tumour levels;
2. To elucidate the molecular and genetic bases of treatment toxicities in response to radiation, with or without chemotherapy; and,
3. To train young scientists and physicians in the scientific pursuits of understanding HNC.

The year 2015 marked the opening of the Joe Finley Centre for Head and Neck Cancer Research at the Princess Margaret. Our research team comprises of

over 80 clinicians, scientists and research personnel, collectively working on several projects, including: tumor initiating cells, genetic determinants of outcome, biomarkers & novel drug discovery, proteomic studies, treatment of human papilloma virus associated oropharynx cancer, and prognostic value of imaging-omic data.

This year has seen numerous advances in HNC research. In 2015, we published 13 peer-reviewed publications in leading scientific journals, with an additional 14 peer-reviewed publications in the first half of 2016 alone. Our team, in collaboration with The Cancer Genome Atlas, published a landmark article in one of the leading scientific journals, Nature. This article described the comprehensive genetic analysis of a large group of Head and Neck Squamous Cell Carcinomas (HNSCC), finding key genetic features related to tumour development, and importantly, identifying novel targets for personalized

treatment. Dr. Scott Bratman, who was recruited to the Princess Margaret in 2014, also led an investigation of the association between HPV genotype and survival in HNSCC, published in *JAMA Oncol* in early 2016. This study not only provides key insight into the biology of these tumours, but is also expected to significantly change clinical practice by informing trial development for patients with HPV-associated HNC. In addition, Dr. Fei-Fei Liu's group had published a study in *Oncotarget* that built upon previous research to identify and validate a 4-microRNA signature predictive of distant metastasis risk in Nasopharyngeal Carcinoma (NPC). Once this observation has been further confirmed clinically, this information could be used by oncologists to personalize the treatment of future NPC patients based on their risk (or lack thereof) of developing distant metastases; a major cause of death in patients with NPC.

One of the highlights of our program was the key study led by Dr. Brian O'Sullivan, published in *J Clin Oncol*, which detailed advancements in tumour stage and prognostic groups for Human Papillomavirus (HPV)-associated Oropharyngeal Carcinomas (OPC), refining the way we categorize and treat these tumours. This study, along with Dr. O'Sullivan's previous work to risk categorize OPC, which was published in the *J Clin Oncol* in 2013, aided in the development of a current NCI-US de-escalation clinical trial for HPV-associated OPC, whereby patients with these tumours are offered de-escalated treatments, in order to mitigate treatment toxicity (NCT02254278).

Neurotology and Vestibular Research

David Pothier, Philip Gerretsen and John Rutka

The neurotology/vestibular research program at UHN continues to be the flagship program in Canada for the assessment of the dizzy patient. Much of what has been accomplished is the result of a continued funding from Ms. Debbie Hertz to the Hertz Multidisciplinary Neurotology Clinic which has allowed for us to provide additional vestibular

rehabilitation therapy to those in need.

Working in conjunction with the UHN Center for Advanced Hearing and Balance Testing we have continued our clinical research in i) High velocity/acceleration VOR activity, ii) the effects of catastrophization in chronic balance disorders in conjunction with the Department of Psychiatry, iii) neuroplasticity for vestibular loss and iv) the assessment and prevention of ototoxicity in a structured multidisciplinary program.

Dr. David Pothier continues his pioneering work in endoscopic ear surgery and continues to be a highly sought after speaker promoting this exciting technology internationally. He is a founding member of the International Working Group in Endoscopic Ear Surgery (IWGEES). He is continuing his study of endoscopic tenotomy surgery for the treatment of incapacitating Meniere's disease.

David Pothier and his co-editor Jane Lea have put the finishing touches on a Vestibular Disorders Book that is nearing completion for publication. Chapters have been written by world experts and it is anticipated that this book will be a seminal achievement in our understanding and appreciation of the vestibular system. Chapters have been written on Vestibulotoxicity and Vestibular Rehabilitation Therapy for the book by UHN authors.

We have also continued our research looking into i) comparing and defining the role of the vestibular head impulse test (vHIT) to caloric and scleral coil testing for VOR activity, ii) Advanced tympanometry in the diagnosis of Meniere's Disease, iii) the role of the otolithic organs in the development of positional vertigo not arising from the posterior semicircular canal.

The academic year 2015-2016 saw a seismic number of publications from our unit through the industry of our fellows (specifically Drs. Ilan and Syed).

Despite our formal retirement as mentors for the TWJ Foundation we continue to have a full complement of clinical fellows and observers who wish to advance their knowledge of the vestibular system.

Head & Neck Surgical Research

David Goldstein, Ralph Gilbert, Patrick Gullane, Dale Brown, Jonathan Irish and John de Almeida

Research at the University Health Network takes place across three sites, with the majority of research occurring between the Toronto General Hospital and Princess Margaret Cancer Center. The two major research programs are the head and neck oncology program and the otology/neurotology program. The surgeon investigators for the head and neck oncology program have affiliations with both the Ontario Cancer Institute and the Toronto General Research Institute. The research program is a multidisciplinary program with local, national and international collaborations. This academic year has seen the continuation of weekly future directions meeting with representation from surgical oncology, medical oncology and radiation oncology. The goal of these meetings is to develop trials for novel treatment approaches to head and neck cancer.

The research program has 4 major themes:

1. Guided therapeutics program whose work is covered in a separate report;
2. Clinical outcomes research in head and neck oncology and reconstructive surgery. Outcomes research includes clinical trials, and prospective and retrospective observational studies in mucosal, salivary gland, endocrine and skull base neoplasms. In addition, there is a major focus on evaluation of outcomes with microsurgical reconstruction and functional outcomes including quality of life assessment;
3. Basic science and translational research program is a multidisciplinary program that involves radiation and medical oncology, pathology, and basic science labs. Research includes proteomics, genomics, stem cell research, and molecular epidemiology. A large focus of the program is on the identification and assessment of biomarkers in the treatment of head and neck cancer;
4. Health services research with a focus on patterns of practice and volume outcome studies in head and neck oncology.

Resident and fellow research is a major component of the research program. There have been a number of residents and fellows who have been mentored and supported by members of the head and neck surgery research program. In the 2015-2016 academic year there have been approximately 53 peer-reviewed publications and book chapters published. The head and neck research program has had the following notable research within the past year:

- Recruitment to the ORATOR clinical trial comparing transoral robotic surgery (with or without adjuvant radiation) to chemoradiation or radiation for HPV related oropharynx cancer
- Development of a radiolucent mouth retractor and evaluation for use in image guidance during transoral robotic surgery
- Evaluation of endoscopic versus open surgical techniques for nasopharyngectomy and evaluation of a novel approach to reconstructing nasopharyngectomy defects with free tissue transfer
- Evaluation of the impact of post-operative infection and inflammation on recurrence and survival in patients with oral cavity cancer and larynx cancer
- Development of a run-in/window of opportunity trial of immunotherapy in head and neck cancer patients
- Completion of building a fully annotated oral cavity cancer tissue microarray on over 400 patients
- Evaluation of the invasive front in oral cavity cancer and development of digital research pathology slide viewing system
- Cost-utility studies on nerve monitoring for thyroidectomy and banning of tanning beds in youth
- Development of a clinical trial aimed to increase detection of occult malignancies in oropharynx cancer using a transoral robotic approach with the goal to reduce radiotherapy volumes
- Development and recruitment for a study investigating active surveillance in patients with low risk papillary thyroid cancer

- Evaluation in changes in incidence in head and neck cancer in Ontario using population based (ICES) data
- Various reconstructive surgery projects evaluating outcomes with different reconstructive techniques
- Development of a clinical and translational assessment of neck fibrosis in patients undergoing head and neck cancer treatment
- Development of an online research project development and tracking database