

University Health Network

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

Established in 2006, the Guided Therapeutics Program (GTx) at the University Health Network is a collaboration of surgeons, medical imaging specialists, radiation oncologists, interventional radiologists, physicists, nanotechnology engineers and biomedical engineers all focused on the research,

development and clinical implementation of innovative technologies to enable novel head and neck cancer diagnostics and therapeutics. The current scope of the program includes research and development in pre-clinical and translational/clinical settings.

The physical resources available include the GTx-Lab in MaRS with 2 fully equipped operating rooms and the GTx-OR at the Toronto General Hospital/UHN.

GTx Lab



- Dedicated space and equipment for development, testing, pre-clinical evaluation of image guided technologies (computing, imaging, contrast agents, molecular imaging).
- Pre-GTx OR site for pre-clinical evaluation

GTx OR



- The largest research operating room in Canada
- First facility in the world that has a dual energy Siemens Definition FLASH CT scanner and a state-of-the-art robotic C-arm, the Siemens Artis Zeego, within the same OR
- Equipped with image-based surgical navigation technologies (x-ray and optical navigation; visualization)

The objectives of the GTx Program are to:

- Develop innovative imaging technologies for guiding therapies (e.g, 3D imaging, molecular imaging, computer-assisted surgery);
- Establish revolutionary treatments that combine the strengths of established therapies;
- Increasingly integrate robotic surgical and interventional radiology therapies into the treatment of cancers; and
- Evaluate the effectiveness of new imaging and ablative technologies when they are applied to both traditional and new treatments.

The GTx Program has had the following notable achievements in innovations within the past year:

- Navigational tools developed through augmented and virtual reality technologies that can allow an “Avatar” overlay on to the real image that is being visualized by the surgical team.
- An “early warning system” alert to surgeons when they approach critical structures such as nerves and arteries.
- A novel “surgical dashboard” that has been positioned on digital imaging screens in the recently developed GTx-OR.
- Use of augmented reality technology to develop aids in contouring tumours for radiation therapy

and for the display of radiation dose on an endoscopic image during surgery.

- Tests of UHN-developed novel contrast agents that identify tumours using both CT and fluorescence imaging.
- Improvements in the accuracy of complex mandibular and maxillary reconstruction through pre-operative 3D printing and modelling with intra-operative imaging confirmation.
- Conclusion of a study that examined the impact on procedure time and workflow: our group demonstrated the clinical feasibility of intraoperative cone-beam CT for head and neck surgery using our prototype mobile C-arm.
- Pre-clinical development of liposome and porphyrin-based contrast agents with multifunctionality capability including photoacoustic and photodynamic ablation.

The GTx Program is well positioned for further development of current studies. For example, the GTx Program in Sarcoma has actively been developing real time image guidance for complex osteotomies for the treatment of musculoskeletal malignancies. This research has demonstrated significant improvements in accuracy with and will be translated from the GTx-Lab to “first in human” clinical trials in the GTx-OR this year.

The GTx Program At-A-Glance:

- **7** cancer related clinical trials (**50** patients)
- **7** multi-disciplinary related clinical trials (**26** patients)
- **>50 cases** in the GTx OR
- **24** refereed papers
- **48** published abstracts and presentations
- **3** licensable technologies
- **15** GTx Rounds and **10** GTx OR open houses and tours
- **3** site-group specific GTx Fellowships
- Undergraduate medicine and engineering summer students

PATIENT OUTCOMES AND EXPERIENCE



KNOWLEDGE GENERATION



KNOWLEDGE TRANSFER



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. Our research team comprises of over 80 clinicians, scientists and research personnel, collectively working on several projects, including: tumour 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.

The program had another banner year of innovation. We published over 15 peer-reviewed articles in leading scientific journals, and members of our team presented their findings at multiple venues, both locally and internationally, including USA, Japan, China, Turkey, Greece, and Germany. We also recruited new scientists and clinicians to the program, who are helping us expedite discoveries for personalized head and neck cancer therapy. Dr. Scott Bratman (MD PhD), a Radiation Oncologist with clinical practice in head and neck cancer, is leading a new research program focused on evaluation and characterization of circulating tumor DNA for identifying head and neck cancer patients at high risk of recurrence, in order to refine and individualize treatment for our patients. Drs. Benjamin Haibe-Kains and Trevor Pugh, both bio-informaticians, are also assisting our program in the analysis of these large genomic patient datasets.

One of the highlights of our program was the identification of 4 microRNAs whose abundance within primary nasopharyngeal carcinoma (NPC) tissues can predict an individual patient's risk of developing distant metastasis after initial treatment. In

a search for useful biomarkers for NPC, we measured the levels of hundreds of microRNAs in ~250 NPC patient samples. Using these data along with matched clinical follow-up data, we identified and validated a set of microRNAs whose abundance at the time of diagnosis was associated with the likelihood that a patient would develop distant metastases. 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.

Neurotology and Vestibular Research

David Pothier, Philip Gerretsen and John Rutka

Surgeon scientist, Dr. David Pothier continues to direct divisional research in otology/neurotology at the University Health Network in conjunction with staff at the Hertz Multidisciplinary Neurotology Clinic and the UHN Center for Advanced Hearing and Balance Testing.

We have continued with i) Investigation into the velocity and acceleration-specific measurement of the vestibular system; ii) Clinical research into the role for psychiatry and effects of catastrophization in chronic balance disorders in conjunction with the Department of Psychiatry; iii) Neural plasticity and biofeedback; iv) Worldwide collaboration in the measurement of sway from multilevel sensors. Collaborating institutions include Johns-Hopkins, University of Verona, Vanderbilt University, Harvard and UBC; v) Assessment and prevention of ototoxicity.

New research projects involving our Centre for Advanced Hearing and Balance Testing have included; i) Studies to compare the Vestibular Head Impulse Test (vHIT) to caloric and the head thrust testing for angular acceleration function; ii) Advanced tympanometry in the diagnosis of Meniere's disease; iii) the conceptual application of biofeedback to improve balance in those patients with dysequilibrium who wear hearing aids.

In partnership with The Toronto Rehabilitation Institute (TRI) we have entered into a collaboration to assess vestibular function in patients registered with the Falls Prevention Program. It is hoped that our input will add incrementally to the design of safety programs that will minimize injury to those elderly individuals prone to falls. The program will be led by Ms. Shaleen Sulway (PT) and Ms. Wanda Dillon (RN) who are part of the Hertz Multidisciplinary Neurotology Program.

Dr. Pothier continues to evaluate the role of endoscopic ear surgery (EES) in the field of minimally invasive ear surgery. The University of Toronto has continued to be a world leader in this field actively promoting this innovative surgery at international conferences, workshops and societal meetings. The culmination of years of work recently led to the publication of the first major and seminal text in EES with other members of the International Working Group on Endoscopic Ear Surgery (IWGEES). Clinical research projects include the retrospective analysis of results of EES in ear disease and the role of tenotomy surgery for intractable Meniere's Disease as an option to intratympanic aminoglycoside therapy.

We continue to promote a number of visiting professorships and are involved in expert panels and invited lectures. Members of our division continue to be involved in the process of setting up national and international courses in advanced vestibular assessment, advanced vestibular rehabilitation and the management of complex neurotological cases. We remain involved in developing innovative educational systems in both vestibular and oculomotor physiology.

We continue to draw clinical fellows and observers from all corners of the world who wish to advance their knowledge of vestibular disorders and to participate in ground breaking clinical based research. The addition of an international visiting scholar will further enhance our international reputation.

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 the four sites, with the majority of research occurring between the Toronto General Hospital and Princess Margaret Cancer Centre. 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 introduction 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 2014 to 2015 academic year there have been 60 peer reviewed publications published or accepted/in press and \$218,145 in new grant funding received.

The head and neck research program has had the following notable research within the past year:

- Assessment of a novel reconstructive surgical approach for patients with subglottic stenosis and patients requiring cricoid and tracheal resections for cancer using a vascularized composite allograft
- Evaluation of chromatin remodeling genes and outcomes in head and neck cancer
- Biomarkers predictive of matted nodes and outcome in patients with oropharynx cancer
- Biomarkers predictive of outcomes in oral cavity cancer
- Cost-effectiveness evaluation of nerve monitoring during thyroidectomy
- Cost-effectiveness in melanoma prevention through the banning of tanning bed use in minors
- A prospective evaluation of functional outcomes of elderly patients undergoing head and neck surgery
- Assessment of variations in adherence to guideline recommended processes of care in head and neck cancer patients in Ontario
- Prospective evaluation of quality of life following open and endoscopic skull base surgery
- Assessment of the impact of diabetes and metformin on head and neck cancer related outcomes
- Development of radiolucent mouth retractor and creation of an image guidance system for transoral robotic surgery

In addition to the above mentioned work in the past year the Head and neck site group at the Princess Margaret Cancer Center, has had great research output. The following are selected highlights:

- Proposal for significant modification of the traditional TNM stage classification and prognostic grouping for oropharyngeal cancer (OPC), if it is caused by HPV (J Clin Oncol 33:836-845, 2015). It offers a more personalized approach to predict outcomes and guide treatment. This work has been immediately noticed by oncology community.
- Prognostic value of pretreatment circulating neutrophils, monocytes, and lymphocytes in oropharyngeal cancer stratified by HPV status” (published in Cancer. 121:545-55, 2015) provided an insight on complicated interaction between the host immune system, HPV-related OPC, and treatment outcomes.
- Differential impact of Cisplatin dose intensity on HPV-related and HPV-unrelated locally advanced head and neck cancer. We found that cisplatin dose intensity ≤ 200 mg/m² had a detrimental impact on overall survival in HPV–LAHNSCC pts. The impact of CDDP dose intensity on HPV+ pts was not significant.
- Analysis of the pattern of failure and natural course following failure after definitive (chemo–) radiotherapy in HPV-related [HPV(+)] and HPV-unrelated [HPV(–)] oropharyngeal cancer (OPC). We found that there is a differing natural course following disease failure in HPV(+) and HPV(–) OPC. A longer survival in HPV(+) pts is observed in almost all subsets compared to their HPV(–) counterparts. In HPV(+) pts, delayed distant failures are a feature with 22% distant metastasis presenting after 2 years of follow up.
- Assessment of survival in HPV-related head and neck cancer patients following positive post-radiation planned neck dissection (Head Neck 37:946-52, 2015). We found that HPV related HNC patients with residual neck disease represent a less favorable biologic subset of the HPV related HNC population and have poor survival. However, they generally still live longer than their HPV unrelated counterparts.

- Evaluation of outcomes of surgical salvage for recurrent oropharyngeal cancer. We found that surgical salvage for oropharyngeal SCC after failure of radiotherapy (+/- chemotherapy) is feasible. Patients who may benefit from surgery include those without regional recurrence and/or those in whom negative margins can be obtained. The p16 status did not seem to have prognostic impact in the salvage setting (Head Neck. In-press, 2015).
- Our site group has been involved in international collaboration of clinical trials. There are 2 trials recently open in our centre: NRG-HN002 and EORTC 1219 trial. The NRG-HN002 is targeting low-risk p16-positive, non-smoking associated HPV-related oropharyngeal cancer which seeks to define new, less-intensive treatment options for this patient population. EORTC1219 will test whether the hypoxic radiosensitizer nomorazole in combination with radiation could improve outcome of HPV/p16 negative head and neck squamous cell carcinoma. Our group is also in the process to be involved in the ORATOR trial testing the role of trans-oral robotic surgery (TORS) in management of T1-T2 oropharyngeal cancer. Currently we are designing a trial on identifying primary origin using TORS and exploring reduction of radiotherapy volume for unknown primary cancers of the head and neck.