Sunnybrook Health Sciences Centre

Auditory Development, Protection & Regeneration

Alain Dabdoub

Hearing loss is the most common sensory disability affecting 0.3% of newborns, 5% of people under age 45 and 50% by age 70; culminating in 400 million people worldwide according to the World Health Organization, 3.5 million here in Canada. Our fundamental research focuses on biological solutions for hearing loss and balance disorders.

Wnt Signaling in Hair Cell Development and Regeneration

Wnt signaling is intensively studied in many systems due to its key role and therapeutic implications in development, cancer, stem cells and tissue renewal. We have previously shown that canonical Wnt signaling is an essential pathway during development of the cochlea, and raised the possibility that Wnt signaling could be used to regenerate sensory hair cells. This year we published a study identifying all the Wnt pathway molecules expressed in the embryonic and adult cochlea and importantly, we continue to work on revealing the role of this important pathway in hair cell regeneration. Furthermore, I co-organized a symposium on Wnt signaling "Wnt Signaling in Development and Disease" for the Association for Research in Otolaryngology 2016 meeting.

Advances in Vestibular Research

In mammalian mouse studies, using manipulation of Wnt signaling as well as gene overexpression, we have been able to elicit regenerative abilities of the mature utricle, a vestibular organ responsible for balance. We want to determine whether this is translatable to humans. To do so, we are harvesting utricles from surgical patients and using the human tissue for experimentation. We are using this system to determine the effectiveness of potential new therapies, accelerating discovery, and reducing the costs of doing trials in patients. Ultimately this may provide us with the abiltiy to restore some balance function.

Regeneration of Auditory Neurons

Auditory neurons do not regenerate when they are lost or damaged due to noise exposure or aging; thus, their loss is prevalent and permanent and leads to hearing impairment. We are working to directly reprogram cochlear glial cells into neurons by overexpression of neurogenic and ear-specific transcription factors. This holds promise for regeneration of auditory neurons and amelioration of hearing loss. Outside the lab and as part of the CI2016 meeting, we organized a symposium on "Cochlear Implants Meet Regenerative Biology". In addition, in collaboration with colleagues published a book on auditory neurons, entitled "The Primary Auditory Neurons of the Mammalian Cochlea" (2016 – Springer Handbook of Auditory Research, New York).

Cochlear Implant Research

Vincent Lin, Julian Nedzelski, Joseph Chen

The Sunnybrook CI program played host to the international community in the largest CI meeting of its kind on May 11-14, 2016. The 14th International Conference on Cochlear Implantation (aka CI2016) drew 1700+ registrants with approximately 350 podium presentations and 500+ posters. This year's conference was focused on the research of auditory plasticity, adult aural rehabilitation and aging. Keynote speakers who addressed the audiences over three days included Michael Dorman, Steve Lomber, Charles Limb, Sandra Black, and Warren Estabrook. They received rave reviews for their expertise and passion demonstrated through their lectures. Special symposia on "Molecular Biology meets Technology"

chaired by Alain Dabdoub, and "Musicality" chaired by Lee Bartel were particularly well received. The Sunnybrook team presented 17 podium presentations and 6 posters; 6 members were interviewed and videos were made available to social media. The feedback from attendees were uniformly superb and most indicated that the CI2016 was the best in the history of this meeting that balanced high caliber science with relevant clinical presentations for everyone.

The meeting was co-chaired by Drs. Nedzelski and Chen; the scientific committee was organized by Drs. Lin and Dabdoub. The combined efforts from the Sunnybrook's and Hospital for Sick Children's cochlear implant teams were invaluable to the success of this meeting. The meeting also marked the finale of a stellar career of Dr. Julian Nedzelski and the end of an era in Canadian Cochlear Implantation.

To stay relevant and continue to maintain an international profile, the Sunnybrook program is entering into another phase in its growth in two strategic areas through recruitment.

1. Dr. Andrew Dimitrijevic, PhD, from the Cincinnati Children's Hospital has been recruited to come back to Toronto to help with research in electrophysiology and neuro-plasticity/imaging. He is a protégé of Professor Terry Picton and he will usher in a new era of auditory science that has been lacking in Toronto.
2. Dr. Trung Le, MD, PhD was recruited from the University of Manitoba/UBC to focus in molecular biology in the context of merging stem cell therapy through magnetic induction via a cochlear implant. He will work closely with Drs. Alain Dabdoub and Vincent Lin in the Sonja Koerner Inner Ear Regeneration Laboratory.

On the administrative side, in terms of provision of care, the adult program is growing due to increased awareness and referral. The surgical wait time has increased dramatically across Ontario, while this challenge is greatest in Toronto, approaching 2 years. In our leadership role, Sunnybrook has created a white paper to help the Ministry establish standards and quality metrics to achieve a sustainable future in CI funding in Ontario.

We look forward to another productive year in 2017.

Neurotology & Otology Research

Joseph Chen, Julian Nedzelski, Trung Le, Vincent Lin

Ageing: We have completed validation of the Hearing Impaired MoCA (HI-MoCA) for our group I and II patients (normal hearing, no cognitive loss & hearing impaired, no cognitive loss). This multi-year collaboration between our department and the Department of Neurology (Drs. Sandra Black and Mario Masellis) has worked tirelessly to develop this important screening test for the severely hearing impaired. Our results demonstrate no comparable differences between the standard MoCA and the HI-MoCA meaning that the cutoff score of 26 and greater as normal will be maintained for both versions of the test. This data was recently presented at the CI 2016 meeting held in Toronto. We are currently accruing patients in group III (confirmed cognitive impairment). We have also begun discussions to convert this test into an easier to administer app version which could be used on an iPad or Surface tablet.

Dementia: As a major adult implantation centre, we are expanding our research on the effects of hearing loss on the development and progression of dementia. We have now incorporated dementia screening in our at risk patients prior to cochlear implantation surgery. We have also begun to investigate the association between dementia and anesthesia in patients undergoing cochlear implant surgery and we continue to recruit patients for this longitudinal prospective study. Finally we recently published a major article that demonstrates a dramatic improvement in the quality of life in the partners of cochlear implant recipients. In the past, the main focus has always been on the recipient but caregiver burden is becoming a major health care issue so we will continue to investigate this link and the potential positive benefits from cochlear implant surgery.

Music: A new version of the MusicEAR (formerly MusicEAR) has been developed. This new software will now be freely available to clinics worldwide for auditory and music rehab in our cochlear implantation patients.

CI-CROS: We have finished our Phase 3 trial of our new CI-CROS prototype. This new prototype is now wireless and is based on the Phonak CROS technology. Our results demonstrate good situational improvement. Phase 4 would involve better microphone and sound processing algorithms to dynamically change the sound routing from side to side depending on the location of the sound source.

Outcomes Research: Acoustic Neuroma research continues in our department, with our current line of collaboration with Neurology and Radiology retrospectively examining whether irradiation effectively inhibits tumor growth over a minimum post-treatment interval of 5 years. We are also collaborating with the Division of Neuroradiology to examine the utility of MRI tractography to help predict intraoperative facial nerve location.

Head & Neck Research
Danny Enepekides, Kevin Higgins

ALT Perforator Flaps
Motor and Sensory Donor Site Morbidity Associated with the Anterolateral Thigh Perforator Flap: A Pilot Study

Anterolateral thigh (ALT) free flap remains one of the most commonly used flaps in head and neck construction. Understanding of the functional outcomes associated with donor site morbidity is limited by a lack of robust clinical data. The impact of the lateral femoral cutaneous nerve sacrifice, motor nerve sacrifice, and disruption of vastus lateralis is also unclear. Objective and subjective methods are implemented pre-operatively and post-operatively for patients over six-months and one-year time intervals for data accrual. Current data suggests minimal donor site morbidity, reduced sensation of the ALT, thigh strength not statistically different, and some impairment for patients undergoing musculocutaneous dissection. This study is still active and patient recruitment is currently ongoing to optimize the statistical power. A poster for this study was recently presented at the Canadian Society of Otolaryngology-Head & Neck Surgery 70th Annual General Meeting.

HME Systems
Heat and Moisture Exchanger Use Reduces In-Hospital Complications Following Total Laryngectomy: A Case-Controlled Study

Total laryngectomy delivers excellent oncologic outcomes for patients with laryngeal cancer. Heat and Moisture Exchangers (HME) are used as a means to compensate for the lost functions in the upper respiratory tract due to TL. We hypothesized that improved compliance with humidification by way of HME usage could reduce the need for escalation of respiratory care and prevent significant adverse events such as return to the operating theatre for management of mucus plugging. This study is now accepted and published in the Journal of Otolaryngology-Head & Neck Surgery. We concluded that HME use does reduce in-hospital complications, in particular, episodes of mucus plugging and post-operative care requirements. Cost-benefit gains for using HME systems also warrants the wide spread introduction of these medical devices in head and neck surgery. A podium for this study was recently presented at the Canadian Society of Otolaryngology-Head & Neck Surgery 70th Annual General Meeting.

Parotid Metastases
Staging Cutaneous Squamous Cell Carcinoma Metastases to the Parotid Gland

The staging of cutaneous squamous cell cancers (cSCC) was revised by AJCC to incorporate known prognostic factors and expand the N category. The aim for this study was to validate this staging system using a North American cohort retrospectively collected from three separate institutions in Canada. This study focused on parotid cSCC metastasis and compared it to major salivary gland staging and the O'Brien P and N staging system, for the purpose of elucidating the most appropriate considerations for staging. Data accrual implies patients with cSCC metastasis to the parotid gland had good survival despite presentation with advanced disease, likely, due to adjuvant radiation therapy. cSCC staging in the setting of parotid metastasis is found to be, despite its limitations, the most reliable predictable staging system available. The study is complete and a final manuscript is generated. Currently, journal

submission and publication are pending. A podium for this study was recently presented at the Canadian Society of Otolaryngology-Head & Neck Surgery 70th Annual General Meeting.

LAFDA for Head and Neck Skin Flaps

Intraoperative Evaluation of Head and Neck Reconstruction Using Laser Assisted Fluorescent Dye Angiography, A Case Series

Laser assisted fluorescent dye angiography (LAFDA) is a novel technique utilizing the excitability of an injected dye (indocyanine green –ICG) to evaluate microvascular tissue in real time. LAFDA technology is proven to be extremely useful for objective evaluation of mastectomy skin flaps, perforator identification and post-anastomosis perfusion of free tissue transfers. In the setting of head and neck, our case study aims to evaluate LAFDA is assessing post-laryngectomy pharyngectomy pharyngeal mucosa and regional/free flap perfusion in head and neck cancer surgery/reconstruction and correlate with rates of postoperative wound complications. Clinical vignettes as recently presented via poster at the Canadian Society of Otolaryngology –Head and Neck Surgery 70th Annual General Meeting exemplify the continued use of LAFDA in select head and neck reconstructions, specifically, in situations where flap perfusion is questionable by standard techniques, surgeon suspicion of compromised perfusion is high, need for complex flap design, and/or in a post-radiation setting.

DEFINITY in Melanoma Head and Neck

A Single-Center, Nonrandomized, Single-Group Pilot Study of Feasibility of the Contrast-Enhanced Ultrasound for the Detection of Sentinel Lymph Nodes in Cutaneous Melanoma of the Head and Neck

Despite their proven efficacy, traditional sentinel lymph node biopsy (SLNB) techniques with blue dye injection and lymphoscintigraphy have limitations. Staining of second echelon nodes and shine through from the primary site may limit their utility. Microbubble-based ultrasound contrast agents (i.e. DEFINITY) injected around a primary melanoma have been demonstrated to concentrate in lymphatic channels and first echelon nodes for up to four hours and be detectable with contrast-enhanced ultrasound (CEUS). This pilot study investigated the technical feasibility of one such UCA for CEUS-assisted SLNB in head and neck melanomas. The plan is to move on to human subject clinical trials as soon as possible. We are currently collaborating with a radiation oncology and a medical imaging team to perform experiments via a model organism (i.e. rabbits) to further investigate any issues we encountered for protocol modification.

Thyroid US-FNAB

Surgeon-performed Ultrasound Guided Fine-Needle Aspirate Biopsy with Report of Learning Curve; A Consecutive Case-Series Study

Fine-needle aspiration biopsy became the standard of care for the evaluation of thyroid nodules. Recently, the use of ultrasound guided fine-needle aspiration biopsy (UG-FNAB) has improved adequacy of sampling. This biopsy is now increasingly more accessible with the advances of ultrasound technology. Adequacy rates and learning curves of a single surgeon at the adoption of UG-FNAB into surgical practice was investigated in this retrospective study. In respect of the retrospective data accrued within five years, we concluded that surgeons were capable of performing UG-FNABs with a learning curve noted to achieve standard adequacy rates. Cystic nodules were also shown to yield more non-diagnostic samples in the surgeon's office. The manuscript was submitted and accepted for publication via the Journal of Otolaryngology –Head & Neck Surgery.

^{18}F-FDG-PET/CT in Oropharyngeal SCC Patients

Diagnostic Performance of Perfusion and Diffusion MR Imaging to Detect False Positive Rates of 18F FDG-PET-CT in Patients with Oropharyngeal Squamous Cell Carcinoma after Definitive Treatment

Functional imaging with ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG-PET/CT) is currently being utilized after definitive treatment in oropharyngeal squamous cell carcinoma (SCC) patients for evaluation of post-treatment response and detection of recurrence or residual disease. However, a relative low positive predictive value of ^{18}F-FDG-PET/CT has led to a diagnostic dilemma and necessitated the

development of more accurate diagnostic modalities in order to avoid further unnecessary invasive testing in those patients with positive PET scans. This prospective and pilot study investigates the role of advanced MR imaging techniques, specifically diffusion and perfusion weighted imaging, in improving the positive predictive value of post-PET-CT treatment for detecting locoregional tumour recurrence. This study is granted REB approval and will shortly begin data accrual.

HPV ± OPC

Radiologic Differences between Human Papillomavirus (HPV)-related Compared to HPV-Unrelated Oropharyngeal Carcinoma on Diffusion Weighted Imaging

Human papilloma virus-related oropharyngeal carcinoma (HPV+ OPC) is a unique entity with distinct epidemiological and clinical features compared to HPV-unrelated (HPV-) OPC. Previous studies have been inconsistent regarding the differences between HPV+ and HPV- OPCs on DWI. The purpose of this study is to evaluate the association between ADC values and HPV status in OPCs as an imaging biomarker. A retrospective review of OPC patients yielded higher ADC values in both primary tumour and lymph node metastases in HPV+ OPC compared to HPV –OPC. It was found that further studies are required in order to establish prognostic value of ADC and to verify any correlation, if any, between ADC and HPV status. The final manuscript is now submitted.

IRX-2 2015A

A Randomized Phase 2 Trial of Neoadjuvant and Adjuvant Therapy with the IRX-2 regimen in Patients with Newly Diagnosed Stage III or IVA Squamous Cell Carcinoma of the Oral Cavity

IRX-2 is a primary cell-derived biologic with multiple active cytokine components, produced under pharmaceutical standards from phytohemagglutinin (PHA) and ciprofloxacin stimulated donor mononuclear cells. This phase 2b study in head and neck squamous cell carcinoma (HN SCC) patients further investigates neoadjuvant therapy with IRX-2 regimen in a randomized trial. The objectives are to determine if event-free survival (EFS) of subjects treated with Regimen 1 is longer than for subjects treated with Regimen 2 and to compare the safety and feasibility of each regimen. The protocol is developed and the study is now successfully launched.

Other Studies Successfully Launched

1. Pilot Project to Assess the Feasibility, Acceptability and Impact of Cancer Care Ontario's Psycosocial Oncology & Palliative Care Pathway embedded into the outpatient care of patients with Head and Neck Cancer in the Odette Cancer Centre
2. A randomized phase II trial for patients with p16 positive, non-smoking associated, locoregionally advanced oropharyngeal cancer
3. A Phase III Randomized Trial of MK-3475 (Pembrolizumab) versus Standard Treatment in Subjects with Recurrent or Metastatic Head and Neck Cancer
4. A randomized phase II trial for patients with p16 positive, non-smoking associated, locoregionally advanced oropharyngeal cancer
5. Efficacy of Optically-Guided Surgery in the Management of Early-Staged Oral Cancer
6. A randomised, double-blind, placebo-controlled, phase III study to evaluate the efficacy and safety of afatinib (BIBW 2992) as adjuvant therapy after chemo-radiotherapy in primary unresected patients with stage III, IVa, or IVb loco-regionally advanced head and neck squamous cell carcinoma
7. A randomized, double-blind, multicenter, Phase III study of everolimus (RAD001) plus best supportive care versus placebo plus best supportive care in the treatment of patients with advanced NET of GI or lung origin