

Sunnybrook Health Sciences Centre

Auditory Development, Protection & Regeneration

Alain Dabdoub

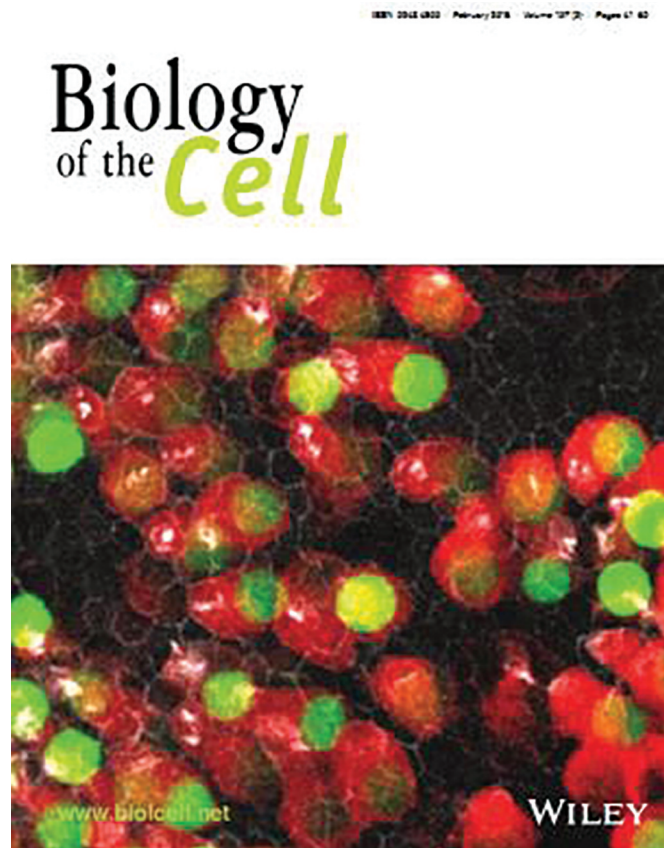
Hearing loss is mainly caused by damage to inner ear auditory hair cells – cells that detect sound, or auditory neurons – cells that connect the hair cells to the brain. Humans do not regenerate these cells, thus leading to permanent hearing loss. *The goal of our group is to understand how these cells are generated during development to guide their strategies for regeneration to ameliorate hearing impairment.* Hearing loss due to aging, noise, or ototoxic drugs is the fastest growing and one of the most prevalent chronic conditions facing millions of Canadians today. Our efforts are focused on discovery-driven and translational research to develop methodologies that could be used for the treatment of hearing loss.

Some of our accomplishments this year:

PUBLICATIONS:

Mulvaney, JF, Amemiya, Y, Freeman, S, Ladher, R, and **Dabdoub, A.** (2015). Molecular cloning and functional characterization of chicken Atonal homologue 1: a comparison with human Atoh1. *Biology of the Cell*. 107(2):41-60.

Journal Cover



Ectopic hair cells (marked with anti Myosin7a in red) induced by chicken Atoh1 (marked by a nuclear GFP reporter in green) displaying stereocilia (marked in white with phalloidin).

Mulvaney, JF, and **Dabdoub, A.** (2014). Long-term time lapse imaging of mouse cochlear explants. *Journal of Visualized Experiments*. 93:52101.

Link to instructional video: click [here](#)

Nishimura, K, Weichert, RM, Liu, W, Davis, RL, and **Dabdoub, A.** (2014). Generation of induced neurons by direct reprogramming in the mammalian cochlea. *Neuroscience*. 275:125-35.

Shi, F, Lingxiang, H, Jacques, B, Mulvaney J, **Dabdoub, A,** and Edge AS. (2014). β catenin is required for hair cell differentiation in the cochlea. *Journal of Neuroscience*. 34:6470-6479.

Books and Chapters

The Primary Auditory Neurons of the Mammalian Cochlea. (2015). Editors: **Dabdoub, A,** Fritzsich, B, Popper, AN, and Fay, R. Springer Handbook of Auditory Research, New York. *In press.*

The objective of this book is to provide a conceptual review on auditory neurons, elucidate and characterize their development, their environment, their electrophysiological characteristics, their connectivity to their targets in the inner ear and the brain, and discuss the potential for their regeneration.

Dabdoub, A, and Fritzsich, B. (2015). Connecting the inner ear to the central auditory system: molecular development and characteristics of the primary auditory neurons and their network. Chapter in: *The Primary Auditory Neurons of the Mammalian Cochlea.* Edited by: Dabdoub, A, Fritzsich, B, Popper, AN, and Fay, R. Springer, New York. *In press.*

Podium Presentations

Dabdoub, A. Wnt4 signaling inhibits hair cell formation in the developing mammalian cochlea through the non-canonical Wnt/calcium/PKC pathway. *Inner Ear Biology Meeting* 2014.

Mulvaney, JF, Amemiya, Y, Freeman, S, Ladher, R, and **Dabdoub, A.** Cloning and characterization of full-length chicken Atonal homologue 1. *Association for Research in Otolaryngology* 2015.

Nishimura, K. and **Dabdoub, A.** Induction of auditory neurons in cochlear endogenous cells in the mammalian cochlea. *Inner Ear Biology Meeting* 2014.

Funding

Hearing Health Foundation (USA). Expression of Wnt pathway molecules and potential to stimulate hair cell regeneration. Co-PI with Dr. Albert Edge, Harvard Medical School. \$121,000 USD.

Cochlear Implant Research Vincent Lin, Julian Nedzelski, Joseph Chen

We have just published a paper in *Hearing Research* looking at the effects of corticosteroid responses in guinea pigs implanted with CI electrodes. Our data suggest that long pre-treatments with corticosteroids appear to have a protective effect in the spiral ganglion counts in the basal turn of our animals. Furthermore, fibrosis around the electrode as determined on H&E staining is less with the long pre-treatment arm and this may translate to lower impedences similar to our human findings. We are now well into the second phase of this study, examining the effectiveness of drug eluding electrodes in guinea pigs.

Another line of research we have begun recently involves attempting to elicit a dependable c-VEMP response in our guinea pigs in preparation for further studies looking at vestibular protection during cochlear implantation.

Neurotology & Otology Research Joseph Chen, Julian Nedzelski, Vincent Lin

Ageing

We continue to have multiple projects looking at the ageing auditory system. Our largest project is the MoCA study, a collaboration between our department and neurology. Our aim is to validate a

hearing impaired version of the MoCA (Montreal Cognitive Assessment) through 2 control arms (normal cognition +/- hearing loss) and 1 arm with confirmed mild cognitive impairment. Early results are showing significant correlations between our hearing impaired version and the original version, for both control groups. This project is ongoing; we have multiple international collaborations ongoing.

A second line of research that is in its early stages examines the effects that cochlear implantation has on the partners and spouses of cochlear implant recipients. We have a paper that has been provisionally accepted for publication in CI International, with our data indicating that partners of CI recipients experience significant improvements in quality of life post-CI implantation. We are currently expanding the testing groups to other family members, friends, and caregivers.

Vestibular

This line of research involves the characterization of novel clinical vestibular testing tools in patients undergoing cochlear implant to determine how this system changes with intervention. Subjective visual vertical, vHIT, and newer vestibular tests are being done longitudinally on our patients. We are finding some novel changes and ultimately these tests will become standard of care in our pre-implant patient test battery.

CI Programming Methodology

This relatively new line of research evaluates the speech perception outcomes of a program created using a remote controlled programming methodology versus a program created using the standard of care software. The outcomes of this research should lend us greater insight into ways to improve the speed and efficacy of the creation of programs for our patients.

Unilateral CI with CROS microphone study – Phase 3

Our collaboration with industry continues in this line of research, with an updated wireless prototype, examining the utility of a combined contralateral

microphone with a unilateral implant for improving speech perception in the presence of background noise.

Music

MusicEAR rehabilitation studies continue as our pilot data, presented at the CI International conference in Munich in June of 2014, demonstrated significant improvements in music and speech perception, as well as music appreciation, following 1 month of active rehabilitation. We continue to accrue patients for this project as we are in the early stages of a randomized controlled follow-up study, and are in collaboration with the faculty of music and auditory verbal therapists to develop a new paradigm of post-intervention therapy.

Structural Preservation

We have completed our clinical trial investigating different pre-operative and intraoperative dosing of corticosteroids to determine their effect on hearing preservation. Our 12 months of serial measurements are indicating that pre-operative treatment does reveal lower electrode impedances and eCAP slope differences which may be suggestive of improved structural preservation. We are also seeing improved hearing preservation rates and pure tone averages over time in our preliminary analyses. This data will be finalized and presented at the CI International conference in Toronto in 2016.

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 department of Neuroradiology to examine the utility of MRI tractography to help predict intraoperative facial nerve location.

Electrophysiological Research

Electrocochleographic measurements are continuing to show promise as predictors of outcome. Our current work uses a post-operative acoustically evoked cochlear microphonics measurement taken through the most apical cochlear implant electrode. Preliminary results are indicating significant correlations between magnitude of cochlear microphonic responses and speech perception.

Head & Neck Research Danny Enepekides, Kevin Higgins

Motor and Sensory Donor Site Morbidity Associated with the Anterolateral Thigh Perforator Flap: A pilot study.

Authors: Christopher Noel, BSc, Kevin Higgins MD, Danny Enepekides MD, Fayzullo Sultanov MD.
Current status: Manuscript will be submitted for publication in summer 2015.

Do Information Pamphlets Improve Post-operative Risk Recall.

Authors: Hussain Alsaffar MD, Kevin Higgins MD, Danny Enepekides MD, Fayzullo Sultanov MD.
Current status: Manuscript has been submitted for publication.

Management of Pulmonary Symptoms Following Laryngectomy and Tracheoectomy Using Provox® Heat and Moisture Exchangers (HMEs): A pilot study.

Authors: Robert De Santis Bsc, Kevin Higgins MD, Andrew Foreman MD, Danny Enepekides MD, Fayzullo Sultanov MD.
Current status: Manuscript will be submitted for publication in summer 2015.

Tissue Bioengineering of Cartilage Grafts.

Authors: Kevin Higgins MD, Stephen D. Waldman P.Eng, Stanley Liu MD.
Current status: Study is still in the data gathering stage.

Staging Nonmelanoma Skin Cancer Metastasis to the Parotid Gland Study.

Authors: Lukasz Czerwonka MD, Kevin Higgins MD, Danny Enepekides MD.
Current status: CAHNS collaborative project with UHN, data gathering is complete. Manuscript is planned during the summer 2015.

Surgeon Performed Ultrasound Guided FNAB with Report of Learning Curve.

Authors: Fernandes VT MD, Kevin Higgins MD, Danny Enepekides MD.
Current status: Manuscript is planned during the summer 2015.

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

Authors: Michael Chan MD, Kevin Higgins MD, Jabehtar Maralani Pejman MD.
Current status: Study is in the data gathering stage.

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

Authors: Kevin Higgins MD, Andrew Foreman MD, Danny Enepekides MD, Fayzullo Sultanov MD.
Current status: This is a pilot study. Data gathering will begin shortly.

Analysis of HAAH Expression as a Proteomic Marker of Thyroid Malignancy.

Authors: Danny Enepekides MD.
Current status: The study is currently underway and data analysis will begin shortly.