BIOGRAPHICAL SKETCH

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NAME: Edmund Au

eRA COMMONS USER NAME (credential, e.g., agency login): aued03

POSITION TITLE: Associate Professor, Burke Neurological Institute

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of British Columbia	B.Sc.	05/1999	Biochemistry
University of British Columbia	Ph.D.	11/2005	Neuroscience
New York University	postdoc	8/2015	Neuroscience

A. Personal Statement

I have spent my entire scientific career working in developmental neurobiology. Over that time (24 years), I have published 18 peer-reviewed publications, and two others in review/ in preparation. My research experience has led me to explore the interface between neural regeneration and development and to then focus my efforts on the topic of cortical circuit formation – to understand the rules that govern cortical assembly and how, when these rules are compromised, it can lead to dysfunction. To do so, my research group (established in the fall of 2015) employs a number of approaches including, rodent surgery, primary culture, stem cell directed differentiation, in utero transplantation, genomics, and embryology. To the proposed work, I bring extensive experience with cortical interneuron development, having developed a novel ES cell-based model of MGE development (Au et al., 2013) to study the generation of Pv vs. Sst cells (McKenzie et al., 2019) and the delineation of projection neuron vs. interneuron lineages via the transcription factor St18 (Nunnelly et al., 2022). We have also applied tissue culture-based assays of developmental processes such as initiation of tangential migration (Genestine et al., 2021) and we have recently developed an image-based high throughput system to analyze cortical interneurons at a population level (Dummer et al., BioRxiv; funded by R21MH131947). This work has significantly expanded our team's expertise, now encompassing supervised and unsupervised AI/ML for computer vision, in-depth analysis of large, multidimensional data, and database design for linking complex experimental data across multiple levels. This unique combination of advanced skills makes us exceptionally well-qualified to develop novel tools that will build upon our existing methodology. Our efforts will focus on achieving a deeper understanding of cortical interneuron synaptic coverage across various contexts, directly enhancing our knowledge of interneuron function and dysfunction in disease states.

Ongoing and recently completed projects that I would like to highlight include:

R01 NS117695
Au (PI)
04/01/21-03/31/26
Studying the Molecular Regulation of MGE Projection Neuron Identity by St18

R21 MH131947
Au (PI)
12/01/22-11/30/24
Multilevel Analysis of Cortical Interneuron Dysfunction in Fragile X Syndrome

Irma T. Hirschl Foundation Grant
Au (PI)
01/01/18-01/01/23
Cortical Interneuron Arealization During Brain Development

Selected Citations:

1. Dummer, P. D., et al. (2024). *Multidimensional analysis of cortical interneuron synaptic features reveals underlying synaptic heterogeneity.* bioRxiv. https://www.biorxiv.org/content/10.1101/ 2024.03.22.586340v2
2. Au, E., Ahmed, T., Karayannis, T., Biswas, S., Gan, L., and Fishell, G. (2013). A modular gain-of function approach to generate cortical interneuron subtypes from ES cells. *Neuron 80*, 1145-1158. PMC5085060
3. McKenzie, M.G., Cobbs, L.V., Dummer, P.D., Petros, T.J., Halford, M.M., Stacker, S.A., Zou, Y., Fishell, G.J., and Au, E. (2019). Non-canonical Wnt Signaling through Ryk Regulates the Generation of Somatostatin- and Parvalbumin-Expressing Cortical Interneurons. *Neuron 103*, 853-864.e854. PMC6728181
4. Genestine, M., Ambriz, D., Crabtree, G.W., Dummer, P., Molotkova, A., Quintero, M., Mela, A., Biswas, S., Feng, H., Zhang, C.*, et al.* (2021). Vascular-derived SPARC and SerpinE1 regulate interneuron tangential migration and accelerate functional maturation of human stem cell-derived interneurons. *Elife 10*. PMC8099424
5. Nunnelly LF, Campbell M, Lee DI, Dummer P, Gu G, Menon V, Au E. St18 specifies globus pallidus projection neuron identity in MGE lineage. Nat Commun. 2022 Dec 14;13(1):7735. doi: 10.1038/s41467-022-35518-5. PMID: 36517477; PMCID: PMC9751150.

B. Positions, Scientific Appointments, and Honors

2023	Invited Short Talk, Gordon Conference, Inhibition in the CNS
2022	Invited Short Talk, Gordon Research Conference, Neural Development
2019	Invited Short Talk, Cold Spring Harbor Labs Meeting, Human Models of Cortical Development
2017	Irma T. Hirschl Foundation Awardee
2016	Whitehall Foundation Grant Awardee
2015-present	Assistant Professor, Columbia University, Department of Pathology and Cell Biology

2013	Travel Award and Short Talk Keystone Symposium (Neurogenesis) Santa Fe NM
2012	Short Talk, Christopher Reeves Hot Topics in Stem Cell Biology Symposium (Society for Neuroscience Annual Meeting)
2007-2010	Fellowship, Canadian Institutes of Health Research
2006-2014	Postdoctoral fellow, NYU Neuroscience Institute, NYU Langone Medical Center
2001-2005	Studentship, Multiple Sclerosis Society of Canada
1999-2005	PhD. graduate student, Neuroscience, University of British Columbia

C. Contributions to Science

1) From early on, I have been interested in applying reductionist approaches, such as tissue culture, to study the complex biology of disease in order to better understand its etiology and develop novel therapies. During my Ph.D. thesis work with Jane Roskams, I applied these principles to the study of cell based therapy for spinal cord injury. I developed a method to purify and expand olfactory ensheathing cells (OECs) and through quantitative proteomics, identified SPARC (secreted protein acidic rich in cysteine) as a critical component that accounted for much of the pro-regenerative properties of OECs. Collectively, publications stemming from my thesis work have been collectively cited more than 600 times.

1. **Au E**., Richter M.W., Vincent A.J., Tetzlaff W., Aebersold R., Sage E.H., Roskams A.J. (2007) SPARC from olfactory ensheathing cells stimulates Schwann cells to promote neurite outgrowth and enhances spinal cord repair. *The Journal of Neuroscience.* 27(27): 7208-21. PMC6794587
2. Steward O., Sharp K., Selvan G., Hadden A., Hofstadter M., **Au E**., Roskams J. (2006) A re-assessment of the consequences of delayed transplantation of olfactory lamina propria following complete spinal cord transection in rats. *Experimental Neurology.* 198(2): 483-99. (PMID: 16494866) PMC Journal – In Process.
3. Ramer L, Au E, Richter M, Liu J, Tetzlaff W, Roskams AJ. (2004) Peripheral olfactory ensheathing cells reduce scar formation and collaborate with host glia to induce regeneration in the lesioned spinal cord. *Journal of Comparative Neurology* 473(1): 1-15. (PMID: 15067714) PMC Journal – In Process.
4. Au E, Roskams AJ. (2003) Olfactory ensheathing cells of the lamina propria in vivo and in vitro. *Glia* 41(3): 224-36. (PMID: 12528178) PMC Journal – In Process.

2) As a postdoc in Gord Fishell's lab I wished to study the role of cINs in neuropsychiatric disorders. However, in order to do so, one would need a better understanding of how the different cortical interneuron (cIN) subtypes were generated, thereby allowing for each subtype to be studied in isolation for its contribution to disease: I established an ES cell-based gain-of-function strategy to study cIN development, with the aim of understanding the transcriptional regulation of interneuron diversity. In this study, I first developed a transcriptional approach to enrich for cIN differentiation. I then leveraged this general strategy in order to systematically test transcription factors expressed in the progenitor zones giving rise to cINs, but with unknown function. I was thus able to identify novel factors involved in cIN differentiation as well as PV+ subtype specification: *Pou3f4* and *Lmo3*.

1. **Au E**., Ahmed T, Karayannis T., Biswas S., Gan L., Fishell G. (2013) A modular gain-of-function approach to generate cortical interneuron subtypes from ES cells. *Neuron.* 80(5): 1145-58. PMC5085060

3) I observed *in silico* that the developing thalamus is a source of Wnt that creates a gradient across the ventral eminences, thus establishing heterogeneity in cIN progenitor zones. Subsequent experiments revealed that Wnt responsiveness delineates the two main classes of cINs (parvalbumin- (PV) and somatostatin-expressing (SST) subpopulations). Making use of the ES-cell system I developed, I have determined that this process involves a non-canonical Wnt pathway, acting in a gradient through Ryk signaling.

a. Melissa G. McKenzie, Lucy V. Cobbs, Patrick D. Dummer, Timothy J. Petros, Michael M. Halford, Steven Stacker, Yimin Zou, Gord J. Fishell, **Edmund Au*.** (2019) Non-Canonical Wnt-Signaling through *Ryk* Regulates the Generation of Somatostatin- and Parvalbumin- Expressing Cortical Interneurons. *Neuron.* 103(5): 853-64. PMC6728181

4) In an effort to more directly address the question of cINs in psychiatric disease, I studied a synaptic scaffolding protein (closely related to the ASD risk gene *CNTNAP2*), *Cntnap4*, whose expression we discovered is largely confined to (PV+) fast-spiking basket cells within the neocortex as well as midbrain dopaminergic projection neurons. We determined that *CNTNAP4* is a novel susceptibility gene for autism, schizophrenia and ADHD. Examination of the Cntnap4 null mouse revealed excessive grooming as well as abnormal pre-pulse inhibition to auditory startle, both of which are endophenotypes of affective disorders. We demonstrated that *Cntnap4* functions pre-synaptically and is required for proper neurotransmission at basket cell GABAergic as well as midbrain dopaminergic synapses. Aberrant synaptic transmission accounted for the abnormal endophenotypes observed in the null mouse and they could be rescued by specifically impinging on these two systems pharmacologically.

The Au lab is interested in answering two interrelated questions: **i)** *How do diverse interneuron populations 'wire' into the developing cortex and form functional microcircuits?* **ii)** *How do these different interneuron subtypes coordinately function in cortical circuitry in health and disease?* The principal approaches to address both questions are mouse genetics and stem cell-directed differentiation.These allow for various genetic in vivo and in vitro manipulations in order to elucidate the molecular logic for how diverse interneuron populations are specified, migrate and form synaptic connections and function in health and disease; They also allow for the production of highly specific interneuron subtypes from human stem cells that can be embedded in functional host cortical circuitry. Along this line of inquiry, we initiated a project to address a long-standing limitation in model human neuronal disease: the inefficient and lengthy process of functional neuronal maturation. To do so, we studied the molecular basis for how mouse interneurons mature as quickly as they do and successfully reverse-engineered our findings to accelerate human stem cell-derived interneurons. These cells exhibit rapid migration in xenografts into mouse cortex and importantly, exhibit mature electrophysiological properties as early as 2-months post transplantation (Genestine et al., 2021). Our lab is also interested in studying how cortical interneurons synaptically integrate during perinatal development. Here, we are developing a number of tools that enable us to interrogate synaptic connectivity through high resolution imaging and machine learning.

1. Karayannis* T, **Au* E**, Patel J., Kruglikov I., Markx S., Delorme R., Heron D, Glessner J., Restituito S., Gordon A., Roy N.C., Gogos J., Rudy B., Rice M.E., Karyiorgou M., Hakonarson H., Bourgeron T., Hoeffer C., Tsien R.W., Peles E., Fishell G. (2014) *Cntnap4* differentially contributes to GABAergic and Dopaminergic Synaptic Transmission. *Nature.* 511(7508): 236-40. PMC4281262

6. Genestine M, Ambriz D, Crabtree GW, Dummer P, Molotkova A, Quintero M, Mela A, Biswas S, Feng H, Zhang C, Canoll P, Hargus G, Agalliu D, Gogos JA, **Au E***. Vascular-derived SPARC and SerpinE1 regulate interneuron tangential migration and accelerate functional maturation of human stem cell-derived interneurons. *Elife*. 2021 Apr 27;10. doi: 10.7554/eLife.56063. PMC8099424

For all publications: https://www.ncbi.nlm.nih.gov/myncbi/1xCtnkCwzcaQp/bibliography/public/