BIOGRAPHICAL SKETCH

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NAME: Goff, Loyal Andrew

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

POSITION TITLE: Assistant Professor of Neuroscience

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
The College of New Jersey, Ewing, NJ	B.S	05/2001	Biology
Rutgers University, Piscataway, NJ	Ph.D.	04/2008	Cell & Developmental Biology
Massachusetts Institute of Technology, Cambridge, MA	Postdoctoral	01/2014	Computational Biology
Harvard University, Cambridge, MA	Postdoctoral	08/2014	ncRNA Biology / Neurodevelopment

A. Personal Statement

For this proposed project, I will be responsible for the coordination of all key investigators as part of our seed network. By leveraging the collective expertise of our group, we are poised to develop scalable search and annotation tools to enable rapid exploration of single cell RNA-Seq data for the Human Cell Atlas. Through several successful collaborations, my research group continues to develop and leverage linear and non-linear methods for dimensionality reduction and transfer learning for scRNA-Seq analysis, as well as single cell data generation and validation across a variety of cellular contexts.

The proposed project is well aligned with the current focus of my research group which seeks to characterize neural cell type specificication, key cell fate decisions during development, and the effects of disease-associated mutations on these choices. My lab uses bulk and single-cell RNA-Seq, as well as functional genomics tools, to characterize enriched populations of neuronal subtypes during development and identify functional relationships between transcriptional differences and physiological properties of distinct neuronal subtypes. I am interested in the mechanisms by which cells transition between states in the context of neuronal differentiation, synaptic plasticity, and degeneration. Currently, my focus is on the characterization of cell-type-specific trajectories in key developmental processes within the central nervous system, context-dependent (cell type) modulation of gene expression in response to sensory manipulation, and the reconstruction of continuous biological processes in neurodegenerative and developmental disorders, primarily familial Amyotrophic Lateral Sclerosis. By leveraging the power of high-throughput RNA-Sequencing, functional genomics, single-cell transcriptional analysis, and classical molecular biology techniques, we can dissect, with high resolution, the key cellular decisions that direct neural development and organization, and identify where and how these events are mis-regulated during disease.

In teaching, as in my research, I emphasize collaboration. Cooperative learning between peers provides an opportunity to discover novel concepts and viewpoints and fosters a collegial environment. I believe that the successful biologist of the modern era must be able to incorporate a diversity of high-dimensional data sources with practical experimental design, bench techniques, and validation strategies. Computational analyses provide insights into complex biological systems but this must be tempered with a solid grasp of fundamental biology and the ability to design and implement appropriately controlled experiments. I encourage inquiry-based learning

in both wet lab as well as computational facets of training, and expect trainees to be able to identify, propose solutions for, and address important outstanding questions in biology that are of particular interest to them.

1. Clark B, Stein-O'Brien G, Shiau F, Cannon GH, Davis E, Sherman T, Rajaii F, James-Esposito R, Gronostajski R, Fertig EJ, **Goff LA***, Blackshaw S*. Comprehensive analysis of retinal development at single cell resolution identifies NFI factors as essential for mitotic exit and specification of late-born cells. BioRxiv 378950 [Preprint]. July 30, 2018 [cited 2018 Sept 21]. Available from: https://doi.org/10.1101/378950 *Co-corresponding authors

2. Stein-O'Brien GL, Clark BS, Sherman T, Zibetti C, Hu Q, Sealfon R, Liu S, Qian J, Colantuoni C, Blackshaw S, **Goff LA***, Fertig EJ*. Decomposing cell identity for transfer learning across cellular measurements, platforms, tissues, and species. BioRxiv 395004 [Preprint]. August 20, 2018 [cited 2018 Sept 21]. Available from: https://doi.org/10.1101/395004 *Co-corresponding authors

B. Positions and Honors

Positions and Employment

2008–2008	Research Assistant, Rutgers University – Cell Biology and Neuroscience
2008–2014	Postdoctoral Fellow, MIT – Computer Science and Artificial Intelligence Lab
2009–2014	Postdoctoral Fellow, Harvard University – Stem Cells and Regenerative Biology
2014–	Assistant Professor, Johns Hopkins School of Medicine – Institute of Genetic Medicine
2015–	Associate Member, Kavli Neurodiscovery Institute – Johns Hopkins University SOM

Other Experience and Professional Memberships

2007–	Member, Society for Neuroscience
2015–	Member, American Society for Human Genetics

Honors

2009	NSF Postdoctoral Research Fellowship in Biology: Biological Informatics program
2009	NIH Ruth L. Kirschstein NRSA for Individual Postdoctoral Fellows (awarded but declined)
2018	Johns Hopkins University Catalyst Award

C. Contribution to Science

1. Throughout my career, I have been interested in the various mechanisms of RNA-mediated biological activity and regulation, and the potential roles for this class of macromolecule in the acquisition and maintenance of specific cellular identities. My early publications centered on both technology development and applications to address the question of how miRNAs direct the differentiation of multipotent stem cells towards a particular lineage. I was responsible for the design and development of one of the first multi-species microRNA microarray platforms, and utilized this technological advance to interrogate the differential regulation and functional contributions of microRNAs across a wide variety of stem cell differentiation contexts. By integrating microRNA and mRNA expression patterns, I was able to characterize the identity and differentiation potential of several neural stem cell clones with the ultimate goal of using microRNAs to direct differentiation towards cell fates with therapeutic transplantation potential in traumatic spinal cord injury.

    a. **Goff, L.A.**, Yang, M., Bowers, J., Getts, R.C., Padgett, R.W., and Hart, R.P. (2005). Rational probe optimization and enhanced detection strategy for microRNAs using microarrays. RNA Biol 2, 93–100.
    b. **Goff, L.A.**, Boucher, S., Ricupero, C.L., Fenstermacher, S., Swerdel, M., Chase, L.G., Adams, C.C., Chesnut, J., Lakshmipathy, U., and Hart, R.P. (2008). Differentiating human multipotent mesenchymal stromal cells regulate microRNAs: prediction of microRNA regulation by PDGF during osteogenesis. Exp. Hematol. 36, 1354–1369. PMCID: PMC2782644
    c. **Goff, L.A.***, Davila, J.*, Swerdel, M.R., Moore, J.C., Cohen, R.I., Wu, H., Sun, Y.E., and Hart, R.P. (2009). Ago2 immunoprecipitation identifies predicted microRNAs in human embryonic stem cells and neural precursors. PLoS ONE 4, e7192. *Authors contributed equally. PMCID: PMC2745660

d. Davila, J.L.*, **Goff, L.A.***, Ricupero, C.L.*, Camarillo, C., Oni, E.N., Swerdel, M.R., Toro-Ramos, A.J., Li, J., and Hart, R.P. (2014). A Positive Feedback Mechanism That Regulates Expression of miR-9 during Neurogenesis. PLoS ONE 9, e94348. *Authors contributed equally. PMCID: PMC3979806

2. Long non-coding RNAs (lncRNAs) are a recently described class of regulatory RNA genes with a high degree of cell-type specificity that are likely to contribute to specific cellular identities and functions. LncRNAs have demonstrated roles in differentiation, cell fate specification, apoptosis, body axis patterning, and a growing list of disorders including cancer. As part of my postdoctoral work I was responsible for the identification of thousands of human and mouse lncRNAs that are induced during various cellular differentiation programs or restricted to subpopulations of cells. As part of these studies I was able to demonstrate the physiological relevance of these genes as a class, and identify at least one novel mechanism by which lncRNAs contribute to nuclear organization. By establishing a cohort of neuronal lncRNA gene knockout mice, my research has determined that indeed several lncRNA loci are required for life, and many others have expression and developmental phenotypes within the mammalian brain.

   a. Cabili, M.N., Trapnell, C., **Goff, L.**, Koziol, M., Tazon-Vega, B., Regev, A., and Rinn, J.L. (2011). Integrative annotation of human large intergenic noncoding RNAs reveals global properties and specific subclasses. Genes & Development. PMCID: PMC3185964
   b. Sun, L.*, **Goff, L.A.***, Trapnell, C.*, Alexander, R., Lo, K.A., Hacisuleyman, E., Sauvageau, M., Tazon-Vega, B., Kelley, D.R., Hendrickson, D.G., et al. (2013). Long noncoding RNAs regulate adipogenesis. Proceedings of the National Academy of Sciences 110, 3387–3392. *Authors contributed equally. PMCID: PMC3587215
   c. Sauvageau, M.*, **Goff, L.A.***, Lodato, S.*, Bonev, B., Groff, A.F., Gerhardinger, C., Sanchez-Gomez, D.B., Hacisuleyman, E., Li, E., Spence, M., et al. (2013). Multiple knockout mouse models reveal lincRNAs are required for life and brain development. Elife 2, e01749. *Authors contributed equally. PMCID: PMC3874104
   d. **Goff, L.A.***, Groff, A.F.*, Sauvageau, M.*, Trayes-Gibson, Z., Sanchez-Gomez, D.b., Morse, M., Martin, R.D., Elcavage, L.E., Liapis, S.C., Gonzalez-Celeiro, M., Plana, Ol., Li, E., Gerhardinger, C., Tomassay, G.S., Arlotta, P., Rinn, J.L., (2015) Spatiotemporal expression and transcriptional perturbations by long noncoding RNAs in the mouse brain. PNAS 112(22): 6855-6862. * Authors Contributed Equally. PMCID: PMC4460505

3. As high-throughput sequencing technologies have evolved, so has the need for robust software and computational tools to enable exploration and analysis of these large datasets. As a result, I have been involved in the development of several key computational/informatic tools to facilitate increased adoption of, and access to RNA-Seq data. As part of this process, I am responsible for the development of several training programs aimed at encouraging molecular biologist to learn to analyze these complex data themselves. I am the principal author of the popular cummeRbund utility; an R/bioconductor package that facilitates exploration and visualization of differential RNA-Seq data. In addition, I have contributed to the development of several additional tools as part of the widely-used Tuxedo suite of utilities for bulk and single-cell RNA sequencing analysis.

   a. Trapnell, C., Roberts, A., **Goff, L.**, Pertea, G., Kim, D., Kelley, D.R., Pimentel, H., Salzberg, S.L., Rinn, J.L., and Pachter, L. (2012). Differential gene and transcript expression analysis of RNA-seq experiments with TopHat and Cufflinks. Nat Protoc 7, 562–578. PMCID: PMC3334321
   b. Trapnell, C., Hendrickson, D.G., Sauvageau, M., **Goff, L.**, Rinn, J.L., and Pachter, L. (2013). Differential analysis of gene regulation at transcript resolution with RNA-seq. Nat. Biotechnol. 31, 46–53. PMCID: PMC3869392
   c. Stein-O'Brien GL, Arora R, Culhane AC, Favorov A, Greene C, **Goff LA**, Li Y, Ngom A, Ochs MF, Xu Y, Fertig EJ. (2018) Enter the matrix: Factorization Uncovers Knowledge from Omics. Trends In Genetics. 34(10), 790-805.
   d. Stein-O'Brien GL, Clark BS, Sherman T, Zibetti C, Hu Q, Sealfon R, Liu S, Qian J, Colantuoni C, Blackshaw S, Goff LA*, Fertig EJ*. Decomposing cell identity for transfer learning across cellular measurements, platforms, tissues, and species. BioRxiv 395004 [Preprint]. August 20, 2018 [cited 2018 Sept

21]. Available from: https://doi.org/10.1101/395004 *Co-corresponding authors

4. Through various collaborative and independent projects, I have contributed to the identification of novel mechanisms for RNA-mediated regulation and to the development of transcriptome-wide technologies to elucidate functional RNA elements. In each case, my contributions included data acquisition and analysis, as well as experimental design, wet-bench experiments, and technology development.

    a. Di Ruscio, A., Ebralidze, A.K., Benoukraf, T., Amabile, G., **Goff, L.A.**, Terragni, J., Figueroa, M.E., De Figueiredo Pontes, L.L., Alberich-Jorda, M., Zhang, P., et al. (2013). DNMT1-interacting RNAs block gene-specific DNA methylation. Nature 503, 371–376. PMCID: PMC3870304
    b. Gregory, B.D., Rinn, J., Li, F., Trapnell, C., and **Goff, L.A.** (2015). High-throughput methodology for identifying RNA-protein interactions transcriptome-wide. US Patent Office. US9097708 B2.
    c. Silverman, I.M., Li, F., Alexander, A., **Goff, L.,** Trapnell, C., Rinn, J.L., and Gregory, B.D. (2014). RNase-mediated protein footprint sequencing reveals protein-binding sites throughout the human transcriptome. Genome Biol 15, R3. PMCID: PMC4053792
    d. Hacisuleyman, E.*, **Goff, L.A.***, Trapnell, C., Williams, A., Henao-Mejia, J., Sun, L., McClanahan, P., Hendrickson, D.G., Sauvageau, M., Kelley, D.R., et al. (2014). Topological organization of multichromosomal regions by the long intergenic noncoding RNA Firre. Nat. Struct. Mol. Biol. 21, 198–206. *Authors contributed equally. PMCID: PMC3950333

5. Recent work has focused on transcriptional characterization of subpopulations of neuronal cell types during development using combinations of enrichment and single cell RNA-Seq analysis. A major obstacle to our understanding of the organization and development of the mammalian brain has been the inherent complexity and cellular heterogeneity of this important tissue. To address this, I contributed to the development of both computational and experimental techniques for enrichment and functional characterization of specific neuronal subtypes that have enabled comprehensive transcriptional profiling neuronal subtypes. Beyond simply classifying these enriched cell types, recent work has delved deeper to identify and define the sources of variation (basis vectors) that independently contribute to the transcriptional state of a cell. I have used this approach to explore the cell type biased transcriptional programs evoked during experience dependent plasticity in discrete subtypes of cortical projection neurons. Furthermore, I have demonstrated that context-specific gene expression can be used in conjunction with GWAS results to refine the genetic architecture of disease, and adapted this method to identify novel candidate genes in Parkinson's disease. These achievements demonstrate the power of single cell analysis to enhance our understanding of specific classes of neural cells, and illustrate how single cell RNA-Seq can be used in conjunction with a variety of classical approaches to examine the relationships between cellular identity, phenotype, and disease.

    a. Molyneaux, B.J.*, **Goff, L.A.***, Brettler, A.C., Chen, H.-H., Brown, J.R., Hrvatin, S., Rinn, J.L., and Arlotta, P. (2015). DeCoN: genome-wide analysis of in vivo transcriptional dynamics during pyramidal neuron fate selection in neocortex. Neuron 85, 275–288. *Authors Contributed Equally PMCID: PMC4430475
    b. Hook P, McClymont SA, Cannon GH, Law WD, Morton JA, **Goff LA***, McCallion AS* (2017) Single-cell RNA-seq of dopaminergic neurons informs candidate gene selection for sporadic Parkinson's disease. Am J Hum Genet. 2018 Mar 1;102(3):427-446. doi: 10.1016/j.ajhg.2018.02.001. *Co-corresponding authors
    c. Cheveé M, Robertson JJ, Cannon GH, Brown SP, **Goff LA** (2018) Variation in activity state, axonal projection and position define the transcriptional identity of individual neocortical projection neurons. Cell Reports. Jan9; 22(2):441-455. PMID: 29320739
    d. Clark B, Stein-O'Brien G, Shiau F, Cannon GH, Davis E, Sherman T, Rajaii F, James-Esposito R, Gronostajski R, Fertig EJ, **Goff LA***, Blackshaw S*. Comprehensive analysis of retinal development at single cell resolution identifies NFI factors as essential for mitotic exit and specification of late-born cells. BioRxiv 378950 [Preprint]. July 30, 2018 [cited 2018 Sept 21]. Available from: https://doi.org/10.1101/378950 *Co-corresponding authors

Complete List of Published Work in MyBibliography:

https://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40255272/?sort=date&direction=descending

D. Research Support

Ongoing Research Support

2016-MSCRFI-2805 Goff 06/01/16–05/31/19
Single cell analysis of hippocampal neurogenesis defects in Kabuki Syndrome 1
The goal of this project is to characterize the molecular mechanisms responsible for learning and memory dysfunction as a result of defective neurogenesis associated with Kabuki Syndrome 1 patient mutations.
Role: PI

IOS-1665692activity NSF Brown/Goff 03/01/17–02/28/21
Cell type specific gene expression differences induced by experience-dependent plasticity
This proposal aims to examine the transcriptional profiles of distinct neuronal types within mouse sensory cortex to identify common and cell type-specific molecular changes induced by well-established paradigms of experience-dependent plasticity.
Role: Co-PI

TargetALS Foundation Goff 05/01/17–4/30/19
Cellular Mechanisms of Cortical Hyperexcitability
This project will explore the cell-type-specific effects of familial ALS mutations on hyperexcitability of cortical neurons, and the common and distinct gene expression changes that evoke this phenotype in ALS mouse models.
Role: PI

Chan Zuckerberg Institute Award Goff 04/01/18–3/31/19
Rapid exploration, interpretation, and comparison of discrete basis vectors contributing to transcriptional Signatures of single cells at the scale of the Human Cell Atlas with ProjectoR
The major goals of this project are to develop computational tools and workflows for transfer learning methods in single cell analysis.
Role: PI

1R21AI139358-01 NIAID Potter/McMeniman/Goff 05/01/18–4/30/2020
Identification and characterization of mosquito sensory neurons detecting human-related cues
The major goals of this project are to 1) To develop a genetic method in Aedes aegypti mosquitoes for labeling sensory neurons activated by human-related odorants and 2) To identify candidate molecular receptors from activated mosquito sensory neurons that may be targeted for novel mosquito behavioral disruption strategies.
Role: Co-Investigator

Completed Research Support

JHU Science of Learning Institute Brown/Goff 06/01/16–05/31/18
Cell-type specific heterogeneity in experience-induced gene expression
The major goals of this project are to generate preliminary data on common and variable transcriptional signatures of plasticity across distinct populations of neuronal cell types and sensory inputs.
Role: Co-PI

JHU Synergy Award Goff/Fertig 07/01/17–6/30/18
Systematic characterization of transcriptional variation in retinal development at single cell resolution
The major goals of this project are to establish the transcriptional landscape of the developing mouse retina to identify key factors governing fate specification and changes in progenitor cell competency.
Role: Co-PI