20.440 Analysis of Biological Networks
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March 9, 2021

20.440 Project Teams and Titles

Project Title: Characterizing Cellular Identities and Gene Expression in Axolotl Limb Regeneration
Dataset: https://www.nature.com/articles/s41467-018-07604-0#data-availability
https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE121737
The axolotl and other salamanders are unique among vertebrates in their ability to regenerate efficiently, especially limbs. Understanding how species-specific genes interact with those more conserved among vertebrates might help inform our understanding of regeneration. This is a single cell data set of axolotl limbs taken at different time points after injury. The data set includes 25,000 cells available in a fastq format and cell by gene matrices are also available. We aim to characterize the shifts in cellular population and gene expression profile across the span of regeneration especially seeking to find how species specific and conserved genes interact. To do so, we will use cellular markers as a proxy for cell types and counts to understand the changes in cellular heterogeneity at the site of injury, and look at differential gene expression to identify key genes in regeneration. We can augment the data with other publicly available information such as the axolotl genome with some identification of important genes and an alternative single cell data set available in gene count matrix form showing changes in cell identities at different time points during regeneration. The hypothesis would be that species specific genes drive cellular changes, offering one explanation for why regeneration is not conserved.
References:

1. Nowoshilow, S., Schloissnig, S., Fei, JF. *et al.* The axolotl genome and the evolution of key tissue formation regulators. *Nature* 554, 50–55 (2018). https://doi.org/10.1038/nature25458
2. Gerber, Tobias et al. “Single-cell analysis uncovers convergence of cell identities during axolotl limb regeneration.” *Science (New York, N.Y.)* vol. 362,6413 (2018): eaaq0681. doi:10.1126/science.aaq0681

Project Title: Profiling tissue-resident memory T cells across lung microenvironments
Dataset: https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE126030
https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE111898
Tissue-resident memory T cells (TRM) are long-lived T cells that reside in peripheral tissues. Their role is canonically described as immunosurveillance, particularly in response to developing tumors. TRM have been correlated to improved clinical outcomes in infections and cancers, however, mechanistic insight on their effective immune response still remains poorly understood. By studying the transcriptomic profile of TRM in healthy lung and lung cancer, we will interrogate their role in response to the tumor microevironment. This will allow us to profile

the TRM and understand their mechanism of action in facilitating an immune response. To do so, we will compare single-cell transcriptomic datasets of CD8+ TRM cells in homeostasis (2 donors), stimulated by T cells (2 donors) and in the tumor microenvironment of lung cancer (16 donors). We will cluster the TRM by their different subpopulations and cellular states - exhaustion, activation and proliferation - to identify the TRM population heterogeneity in response to environmental stimuli. We will also perform gene set enrichment analysis and gene ontology analysis to identify enriched gene sets and pathways key to facilitating an immune response and responsible for transitions in cell state.

References:

1. Szabo, P.A., Levitin, H.M., Miron, M. *et al.* Single-cell transcriptomics of human T cells reveals tissue and activation signatures in health and disease. *Nat Commun* 10, 4706 (2019). https://doi.org/10.1038/s41467-019-12464-3
2. Clarke, James et al. "Single-cell transcriptomic analysis of tissue-resident memory T cells in human lung cancer." *The Journal of experimental medicine* vol. 216,9 (2019): 2128-2149. doi:10.1084/jem.20190249

Project Title: Identifying Transcriptional Programs Associated with
Transcriptional Programs in Mouse Prefrontal Cortex During Addiction/Adolescence

Dataset: https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE124952
https://jeb.biologists.org/content/211/10/1623

The brain undergoes major transcriptional changes during development, especially under the influence of external stimuli. Varying neural activity can have long-term influences on the structure and function of a neuron by altering their transcriptional patterns. Using addiction as a model, we are interested in uncovering transcription dynamics associated with this challenge-induced neuroplasticity and discover conserved mechanisms across species. To do so, we will leverage data from young mice, adult mice, and adult mice subject to both cocaine self-administration and withdrawal as compared to zebrafish drug dependency data. Looking at how the brain's transcriptional programs are coordinated during major state changes will help us to understand the influence of addiction on neural development and tease out conserved pathways acted upon by addiction. The data for the mice is available pre-processed in a cell and gene counts matrix and the genes of interest involved in addiction in fish are available in a tabular format. Comparative analysis of the transcriptional dynamics can allow us to understand conserved mechanisms in challenged neural development across species. We would hypothesize that evolutionary conserved genes involved in addiction align in both zebrafish and mouse models, but are interested in examining which pathways they diverge.

Reference:

1. Bhattacherjee, A., Djekidel, M.N., Chen, R. *et al.* Cell type-specific transcriptional programs in mouse prefrontal cortex during adolescence and addiction. *Nat Commun*10, 4169 (2019). https://doi.org/10.1038/s41467-019-12054-3

2. Kily, Layla J M et al. “Gene expression changes in a zebrafish model of drug dependency suggest conservation of neuro-adaptation pathways.” *The Journal of experimental biology* vol. 211,Pt 10 (2008): 1623-34. doi:10.1242/jeb.014399