BIOGRAPHICAL SKETCH

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NAME: Ishwariya Venkatesh

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

POSITION TITLE: Research Assistant Professor

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	Completion Date	FIELD OF STUDY
Anna University, India	BS	2009	Biotechnology
University of Wisconsin- Milwaukee	PhD	2014	Neuroscience
Marquette University	Post-Doc	2014-18	Neuroscience

A. Personal Statement

I am motivated to identify molecular regulatory mechanisms that underlie successful axon growth and use that information to improve regenerative outcomes after CNS injuries. I have been thinking about and conducting research to uncover novel molecular regulatory codes underlying axon growth since the beginning of my graduate training. For my dissertation research, I used bioinformatics-based approaches to identify novel transcription factor combinations that drive successful optic nerve regeneration in zebrafish. During my PhD training, I gained foundational skills in molecular biology, including preparation of next-gen sequencing libraries (RNA-Seq, ChIP-Seq) and *in vivo* optic nerve surgeries. As a post-doc, I was instrumental in expanding the lab's discovery pipeline in two novel directions- *Bioinformatics-based approaches* to identify novel transcription factor (TF) combinations (1 manuscript, 1 review); *Epigenetic control of axon growth* (Post-doc fellowship from The Nielsen foundation, 2 manuscripts). During this time, I have gained extensive expertise in techniques to profile chromatin accessibility (ATAC-Seq, Histone ChIP-Seq) along with required bioinformatics skills (Gene regulatory networks, TF footprinting, ATAC-Seq data analysis). Following training at NIH-sponsored ANGUS-DIBSI, an intensive hands-on training workshop on NGS analysis, I received an NSF XSEDE allocation that covers costs towards cyber infrastructure required to power analyses proposed here. We are now generating the requisite datasets that will allow us to simultaneously address two critical *intrinsic* barriers to re-growth in CNS neurons – optimal pro-regenerative TF combinations/Pioneer TFs to achieve targeted chromatin remodeling. This two-pronged approach is completely novel in regenerative neuroscience and has the potential to identify novel molecular manipulations for therapeutic intervention.

B. Positions and Honors

Professional Experience

March 2018-Present Research Assistant Professor, Marquette University

Honors and Awards

2009	*Summa cum laude* – BS, India
2009-14	UWM Chancellor's graduate student award for excellence in merit
2012-14	Ruth Walker's graduate student research award for excellence in research
2013	Best graduate student research poster award – International Zebrafish meeting
2012-14	UWM Graduate student research travel grant
2014	Travel award – International society for Neuroregeneration

C. Contribution to Science

1. My graduate work was focused on the identification of a core set of transcription factors that are required for successful optic nerve regeneration in Zebrafish. Until then, individual transcription factors were identified as important for optic nerve regeneration in zebrafish, yet little was known about combinations/groups of interacting factors that interact to drive successful optic nerve regeneration. Using morpholino-based *in vivo* knockdown assays, I discovered a novel TF trifecta – cJUN, ATF3 and Ascl1a that was necessary for functional optic nerve regeneration in zebrafish. For one of those TFs, MASH1/Ascl1a, we showed that the capacity to drive growth is conserved across vertebrates and over-expression of Ascl1a improves regenerative outcomes after SCI.

    a. Williams RR*, **Venkatesh I*,** Pearse DD, Udvadia AJ, Bunge MB. MASH1/Ascl1a Leads to GAP43 Expression and Axon Regeneration in the Adult CNS. PLoS One. PMID: 25751153
    *- These two authors contributed equally

2. In my post-doc, I continued my research on identifying combinations of transcription factors that are required for successful axon growth. Although single TF treatments have proven effective in promoting regeneration following SCI, the effects are modest and it is critical to identify strategies to boost the effect. To this end, I developed multiple *in silico* frameworks targeted at identification of groups of TFs that synergize to drive axon growth, summarized in a review listed below. Using these workflows, we identified a novel TF combination KLF6/STAT3 that synergizes to drive axon growth in CNS neurons. Prior to this work, although it was acknowledged that combinations of TFs are critical for robust regeneration, rational *in silico* workflows to identify the same were lacking. One important outcome of this work is that we have now made the necessary *in silico* frameworks available to the regeneration community to identify groups of TFs relevant to their protein/Pathway of interest.

    a. Wang Z**,** Mehra V, Simpson M, Maunze B, Eastwood E, Holan L, Blackmore MG*, **Venkatesh I***. KLF6/STAT3 co-occupy regulatory DNA and functionally synergize to drive axon outgrowth in CNS neurons. bioarxiv. doi: https://doi.org/10.1101/257022
    *Co-corresponding authors.

    b. Venkatesh I, Blackmore MG. Neurosci Lett. 2016 Dec 23. doi: 10.1016/j.neulet.2016.12.032. Review. Selecting optimal combinations of transcription factors to promote axon regeneration: Why mechanisms matter.

    c. Simpson MT*, **Venkatesh I***, Callif BL, Thiel LK, Coley DM, Winsor KN, Wang Z, Kramer AA, Lerch JK, Blackmore MG. The tumor suppressor HHEX inhibits axon growth when prematurely expressed in developing central nervous system neurons. Mol Cell Neurosci. 2015 Sep;68:272-83. doi: 10.1016/j.mcn.2015.08.008.
    *- These two authors contributed equally

3. Another important research direction I have contributed to is the identification of chromatin restriction as a barrier to axon growth in adult CNS neurons. I have generated ATAC-Seq datasets and implemented bioinformatics workflows to detect developmental changes in chromatin accessibility in CNS neurons. Using these cutting-edge ATAC-Seq data analyses we have provided the first genome-wide evidence that adult CNS neurons undergo developmental chromatin restriction around pro-growth gene networks. A key finding of this work is the strong correlation between chromatin accessibility and *in vivo* efficacy of pro-regenerative TF treatments, identifying a strong epigenetic barrier to regrowth in adult CNS neurons. Proposed research will directly follow-up on these exciting findings and allow us to identify relevant pro-regenerative TFs/Pioneer TFs to reprogram adult CNS neurons back to a regeneration-competent state.

    a. Venkatesh I*, Simpson MT, Coley DM, Blackmore MG. Epigenetic profiling reveals a developmental decrease in promoter accessibility during cortical maturation *in vivo*. Neuroepigenetics. 2016 Dec;8:19-26.
    *Corresponding author

b. Venkatesh I*, Mehra V, Calliff B, Blackmore MG. Developmental chromatin restriction of pro-growth gene networks acts as an epigenetic barrier to axon regeneration in cortical neurons. doi: https://doi.org/10.1101/259408

*Corresponding author

D. Other Research Support

Ongoing Research Support

Craig H Nielsen post-doctoral fellowship- Venkatesh (PI) 09/2016-09/2018
Epigenetic manipulation of axon growth in mammalian CNS neurons
The goals of this grant are to identify strategies to relieve epigenetic constraints in mammalian CNS neurons. This grant enabled the production of pilot data for the present application but ends prior to this grant's start date, avoiding overlap.

NSF-XSEDE Venkatesh (PI) 08/2016-8/2019
***In silico* frameworks to identify novel transcription factor combinations that synergize to drive growth in CNS neurons**
This grant supports high-computing server costs to enable leading edge bioinformatics analyses, including the ATAC-seq analysis pipelines proposed here.