BIOGRAPHICAL SKETCH

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NAME: **Meharena, Hiruy Sibhatu**

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

POSITION TITLE: **Postdoctoral Fellow**

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 Asmara, Eritrea	BS	06/2005	Biology and Chemistry
University of California, San Diego	Ph.D.	09/2015	Biomedical Sciences
Massachusetts Institute of Technology	Postdoctoral	-	Brain and Cognitive Sciences

A. Personal Statement

Vision and Strategy - Structural variations of the genome, which includes aneuploidies and large copy number variations (CNVs) are implicated in neurological disorders associated with intellectual disability, such as Down syndrome (DS) and Autism Spectrum Disorder (ASD). These disabling and extremely prevalent disorders present a growing challenge for society. Disappointing clinical trial results demonstrate the unmet need in the treatment of these disorders and highlight the importance of elucidating the fundamental molecular principles governing these disorders. Additionally, studies have shown that gene expression dynamics, mediated by the epigenome and chromatin folding, play an integral role in neurodevelopment. Single Nucleotide Polymorphisms (SNPs) on genes involved in coordinating and maintaining the integrity of nuclear architecture have been linked to disorders characterized by intellectual disability. I am interested in a career path dedicated towards understanding how genomic imbalance, associated with DS and ASD, dysregulates the biophysical, biochemical, molecular and cellular properties governing the 3D-genome organization, epigenome and transcriptome disrupt brain morphogenesis and cognitive processing. My lab will take a multidimensional approach utilizing post-mortem human tissue samples, stem cell technology, mouse models, genome-editing tools, and experimental and computational genomics to elucidate the molecular-, cellular- and organ-level manifestations of genomic imbalance on brain development and cognition.

Expertise - For over a decade, my career has focused on attaining the expertise required to explore this vision. As a research assistant at the University of California, Irvine, and University of Colorado, Anschutz medical campus, I have acquired training in the field of protein biochemistry and pharmacology. My research during this time focused on understand the functional properties of neuronal nitric oxide synthase (nNOS) (*J Biol Chem 2008*) and pharmacologically disrupting the mechanisms utilized in quorum sensing (*PNAS 2010, Molecular microbiology 2012, Microbiology 2015*). As a National Science Foundation (NSF) graduate student fellow under the mentorship of Dr. Susan Taylor, I built a strong foundation in structural biophysics, molecular biology and computational biology to identify the atomic level organization required for the activation and inactivation of eukaryotic protein kinases (EPKs) and new approaches for rational drug discovery (P*LoS Biol. 2013, PLoS Biol. 2016, Cell 2013, Mol Cell Biol 2015*). My graduate work now serves as the fundamental framework for identifying and defining EPK functional states and mechanism of action of small molecule inhibitors. As a senior Alana fellow and UNCF/Merck postdoctoral fellow under the mentorship of Dr. Li-Huei Tsai, I expanded my expertise to include stem cell biology, mouse models and experimental and computational genomics to understand the consequences of genomic imbalance on the different cell types of the brain. My research identified that trisomy 21 (T21) induces a cell type specific molecular response, where NPCs are the most transcriptionally responsive to T21. Utilizing Hi-C, ATAC-seq, ChIP-seq and RNA-seq we find that NPCs harboring T21 uniquely exhibit global disruptions of the 3D-genome organization, epigenome and transcriptome consistent with the transcriptional and nuclear-architecture changes characteristic of cellular senescence, a hallmark of aging. Utilizing anti-senescence drugs (senolytics) we were able to ameliorate the DS-associated molecular and cellular phenotypes (*under-review in Cell Stem Cell)*. Additionally, in collaboration with a postdoctoral fellow in the Tsai lab, we utilized a mouse model that permanently tags activated neurons, Arc-TRAP mice, to decipher the nuclear architecture of memory encoding, consolidation and recall. We identified that the first phase of memory formation known as encoding, induces global epigenetic activation of enhancer regions of the genome without

altering the transcriptome. Next, during consolidation a subset of these primed enhancers form long-range chromatin interactions with their respective genes to induce transcriptional changes. Finally, during recall, an additional set of these primed enhancers form de novo promoter-enhancer interactions to further facilitate the transcriptional changes required for memory processing (Nat Neurosci 2020). My training in biophysics, biochemistry, pharmacology, genetics, epigenetics, stem cell biology and neurobiology uniquely equips me to tackle my vision from an interdisciplinary perspective.

Collaborations – I have forged collaborations with clinicians 1) Dr. Brian Skotko (Director of the Down Syndrome Program at Massachusetts General hospital (MGH)) who works with individuals with Down syndrome 2) Dr. Colleen Jackson-Cook (Director of Cytogenetics at Virginia Commonwealth University School of Medicine) who has curated a large library of biospecimens from individuals with aneuploidies, including individuals with DS and mosaic-DS, and 3) Dr. David Sweetser (Chief of Medical Genetics and Metabolism at MGH) who is interested in autism governed by copy number variants (CNVs) and other rare genetic abnormalities. Furthermore, I have forged a personal relationship with the mosaic down syndrome community (which only accounts for 2-3% of the down syndrome population) with my involvement with the International Mosaic Down syndrome Association (IMDSA). I was invited to attend a retreat for families organized by IMDSA. Here, I was able to connect with individuals with mosaic-DS and their families to have a deeper understanding of the most important scientific questions that would be most beneficial for individuals with DS. I was able to share my current and future research goals and received feedback which has significantly helped me craft a more impactful research program. I will continue to harness and expand my relationships with individuals with intellectual disabilities, their families and clinicians to guide my future research endeavors.

B. Positions and Honors

Positions and Employment

2004 – 2007	Teaching Assistant, Eritrean Institute of Technology, Eritrea
2007 - 2008	Research Assistant, University of California, Irvine, Irvine, CA
2008 - 2010	Professional Research Assistant, University of Colorado, Anschutz Medical Campus, Aurora, CO
2010 - 2015	Predoctoral Researcher, University of California, San Diego, La Jolla, MA
2015 -	Postdoctoral Fellow, Massachusetts Institute of Technology, Cambridge, MA

Other Experience and Professional Memberships

2012 - 2015	UCSD Black Graduate Student Association (BGSA) Founding Member
2016-	Trisomy 21 Research Society (T21RS) Member
2017	Massachusetts Institute of Technology (MIT) Impact Fellow
2018	Massachusetts Institute of Technology (MIT) Kaufman Teaching Certificate
2018-	Society for Neuroscience (SFN) Member
2018	Rising STAR in Biomedical Sciences Fellow
2019	Invited lecturer, Harvard Medical School, Cambridge, MA

C. Contribution to Science

1. **Early Career:** My early career contributions were focused on utilizing biochemistry, biophysics and structural biology to understand the functional properties of neuronal nitric oxide synthase (nNOS) and dissecting the principles governing the process of quorum sensing. My work during this time has yielded in 5 peer-reviewed publications which also includes a methods paper for isolating and characterizing the small molecules utilized in quorum sensing from tissue samples.
    a. Li H, Das A, **Sibhatu H**, Jamal J, Sligar SG, Poulos TL. Exploring the electron transfer properties of neuronal nitric-oxide synthase by reversal of the FMN redox potential. J Biol Chem. 2008 Dec 12;283(50):34762-72. doi: 10.1074/jbc.M806949200. Epub 2008 Oct 13. PMID: 18852262; PMCID: PMC2596388.
    b. Zan J, Cicirelli EM, Mohamed NM, **Sibhatu H**, Kroll S, Choi O, Uhlson CL, Wysoczynski CL, Murphy RC, Churchill ME, Hill RT, Fuqua C. A complex LuxR-LuxI type quorum sensing network in a roseobacterial marine sponge symbiont activates flagellar motility and inhibits biofilm formation. Mol Microbiol. 2012 Sep;85(5):916-33. doi: 10.1111/j.1365-2958.2012.08149.x. Epub 2012 Jul 18. PubMed PMID: 22742196; PubMed Central PMCID: PMC3429658.
    c. Churchill ME, **Sibhatu HM**, Uhlson CL. Defining the structure and function of acyl-homoserine lactone autoinducers. Methods Mol Biol. 2011;692:159-71. doi: 10.1007/978-1-60761-971-0_12. PubMed PMID: 21031311; PubMed Central PMCID: PMC3425365.

2. **Graduate Career:** My graduate research contributions focused on deciphering the atomic level biophysical and biochemical principles governing the function of eukaryotic protein kinases (EPKs). I utilized biochemical, biophysical, structural and computational approaches to classify the possible active and inactive structural conformations observed in more than 300 EPK family members. One of the great challenges of designing therapeutic drugs for EPKs is the lack of specificity, the objective of my studies was to discover new structural conformations that could be targeted for rational drug design to overcome the challenge of pharmacological specificity. This work yielded in 4 research articles and 2 review papers as well as a feature article of one of our articles. Furthermore, in graduate school I was able to design and execute a project that yielded in a first and co-corresponding authorship.
    a. **Meharena HS***, Fan X, Ahuja LG, Keshwani MM, McClendon CL, Chen AM, Adams JA, Taylor SS*. Decoding the Interactions Regulating the Active State Mechanics of Eukaryotic Protein Kinases. PLoS Biol. 2016 Nov;14(11):e2000127. doi: 10.1371/journal.pbio.2000127. eCollection 2016 Nov. PMID: 27902690; PMCID: PMC5130182. (*Corresponding author)
    b. **Meharena HS**, Chang P, Keshwani MM, Oruganty K, Nene AK, Kannan N, Taylor SS, Kornev AP. Deciphering the structural basis of eukaryotic protein kinase regulation. PLoS Biol. 2013 Oct;11(10):e1001680. doi: 10.1371/journal.pbio.1001680. Epub 2013 Oct 15. PMID: 24143133; PMCID: PMC3797032.
        - Robinson R. Confirming the importance of the R-spine: new insights into protein kinase regulation. PLoS Biol. 2013 Oct;11(10):e1001681. doi: 10.1371/journal.pbio.1001681. Epub 2013 Oct 15. PubMed PMID: 24143134; PubMed Central PMCID: PMC3797029.
    c. Hu J, Stites EC, Yu H, Germino EA, **Meharena HS**, Stork PJS, Kornev AP, Taylor SS, Shaw AS. Allosteric activation of functionally asymmetric RAF kinase dimers. Cell. 2013 Aug 29;154(5):1036-1046. doi: 10.1016/j.cell.2013.07.046. PubMed PMID: 23993095; PubMed Central PMCID: PMC3844432
3. **Postdoctoral Career:** As a postdoctoral fellow, I utilized human derived induced pluripotent stem cells (iPSCs) and the DS-mouse model to understand the consequences of genomic imbalance on the different cell types of the brain (neural progenitor cells (NPCs), neurons, astrocytes, and microglia). I find that trisomy 21 (T21) induces a cell type specific molecular response, where NPCs are the most transcriptionally responsive to T21. NPCs harboring T21 exhibit global 3D-genome architecture disruptions, altered heterochromatin distribution, and genome-wide chromatin accessibility changes in response to T21, consistent with the transcriptional and nuclear-architecture changes characteristic of senescent cells. This T21-induced genome-wide transcriptional disruption as well as the cellular hallmarks associated with DS, such as reduced cellular-migration and proliferation can be ameliorated utilizing senolytic drugs (dasatinib, an EPK inhibitor and quercetin, an antioxidant). This work is currently under-review in Cell Stem Cell.

    In collaboration with a postdoctoral fellow in the Tsai lab, we utilized a mouse model that permanently tags activated neurons to decipher the 3D-genome organization, epigenome and transcriptome during memory encoding, consolidation and recall. We identified that the first phase of memory formation known as encoding, induces global epigenetic activation of enhancer regions of the genome without altering the transcriptome. Next, during consolidation a subset of these primed enhancers form long-range chromatin interactions with their respective genes to induce transcriptional changes. Finally, during recall, an additional set of these primed enhancers form de novo promoter-enhancer interactions to further facilitate the transcriptional changes required for memory processing. My contributions to this project included designing and executing the computational pipelines required for the analysis of the 3D-genome organization (Hi-C and promoter capture Hi-C) and epigenome (ATAC-seq and ChIP-seq). This work has been published in Nature Neuroscience.
    a. **Meharena HS**, Marco A, Dileep V, Lockshin ER, Kuffner G, Mullahoo J, Watson LA, Ko T, Guerin L, Abdurob F, Rengarajan S, Papanastasiou M, Jaffe JD, Tsai L-H. Down Syndrome Induced Senescence Disrupts the Nuclear Architecture of Neural Progenitors. (*Under-revision in Cell Stem Cell*)
    b. Marco, A., **Meharena, H.S.**, Dileep, V. et al. Mapping the epigenomic and transcriptomic interplay during memory formation and recall in the hippocampal engram ensemble. Nat Neurosci (2020). https://doi.org/10.1038/s41593-020-00717-0
    c. **Meharena HS**, Lockshin E, Kuffner G, Dileep V, Marco, A., Guerin L, Tsai LH. Brain Cell-Type Specific Consequences of Down Syndrome. (In-preparation)
    d. Lin Y-T.[#], **Meharena HS[#]**, Woolf H, Yu CJ., Tsai LH. Single cell RNA-seq of Cerebral Organoids derived from individuals with Down syndrome reveals Oxidative Stress induced Senescence in Neural Progenitors. (In-preparation, # - equal contribution)

Complete List of Published Work in My Bibliography:
www.ncbi.nlm.nih.gov/pubmed/?term=Hiruy+Meharena and www.ncbi.nlm.nih.gov/pubmed/?term=Hiruy+Sibhatu

D. Publications and Presentations

Publications

1. **Meharena HS**, Marco A, Dileep V, Lockshin ER, Kuffner G, Mullahoo J, Watson LA, Ko T, Guerin L, Abdurob F, Rengarajan S, Papanastasiou M, Jaffe JD, Tsai L-H. Down Syndrome Induced Senescence Disrupts the Nuclear Architecture of Neural Progenitors. (*Under-revision in Cell Stem Cell*)
2. Marco, A., **Meharena, H.S.**, Dileep, V. et al. Mapping the epigenomic and transcriptomic interplay during memory formation and recall in the hippocampal engram ensemble. Nat Neurosci (2020). https://doi.org/10.1038/s41593-020-00717-0
3. **Meharena HS**, Marco A, Kuffner G, Dileep V, Guerin L, Lockshin E, Tsai LH. Brain Cell-Type Specific Consequences of Down Syndrome. (In-progress)
4. Lin Y-T.[#], **Meharena HS[#]**, Woolf H, Yu CJ., Tsai LH. Single cell RNA-seq of Cerebral Organoids derived from individuals with Down syndrome reveals Oxidative Stress induced Senescence in Neural Progenitors. (In-progress, # - equal contribution)
5. **Meharena, H.S.**, Fan, X., Ahuja, L.G., Keshwani, M.M., McClendon, C.L., N., Adams, J.A., and Taylor, S.S. (2016). Decoding the Interactions Regulating the Active State Mechanics of Eukaryotic Protein Kinases. PLoS Biol. 2016 Nov 30;14(11):e2000127
6. Hu, J., Ahuja, L.G., **Meharena, H.S.**, Kannan, N., Kornev, A.P., Taylor, S.S., and Shaw, A.S. (2015). Kinase regulation by hydrophobic spine assembly in cancer. Mol Cell Biol 35, 264-276.
7. Pence, M.A., Haste, N.M., **Meharena, H.S.**, Olson, J., Gallo, R.L., Nizet, V., and Kristian, S.A. (2015). Beta-Lactamase Repressor BlaI Modulates Staphylococcus aureus Cathelicidin Antimicrobial Peptide Resistance and Virulence. PloS one 10, e0136605.
8. Zan, J., Choi, O., **Meharena, H.M.**, Uhlson, C.L., Churchill, M.E., Hill, R.T., and Fuqua, C. (2015). A solo luxI-type gene directs acylhomoserine lactone synthesis and contributes to motility control in the marine sponge symbiont Ruegeria sp. KLH11. Microbiology 161, 50-56.
9. **Meharena, H.S.**, Chang, P., Keshwani, M.M., Oruganty, K., Nene, A.K., Kannan, N., Taylor, S.S., and Kornev, A.P. (2013). Deciphering the structural basis of eukaryotic protein kinase regulation. PLoS Biol 11, e1001680.
    - Featured article Confirming the Importance of the R-Spine: New Insights into Protein Kinase Regulation. Richard Robinson. PLoS Biol 11(10): e1001681.
10. Hu, J., Stites, E.C., Yu, H., Germino, E.A., **Meharena, H.S.**, Stork, P.J., Kornev, A.P., Taylor, S.S., and Shaw, A.S. (2013). Allosteric activation of functionally asymmetric RAF kinase dimers. Cell 154, 1036-1046.
11. Taylor, S.S., Shaw, A., Hu, J., **Meharena, H.S.**, and Kornev, A. (2013). Pseudokinases from a structural perspective. Biochem Soc Trans 41, 981-986.
12. Zan, J., Cicirelli, E.M., Mohamed, N.M., **Sibhatu, H.M.**, Kroll, S., Choi, O., Uhlson, C.L., Wysoczynski, C.L., Murphy, R.C., Churchill, M.E., Hill, R.T., and Fuqua, C. (2012). A complex LuxR-LuxI type quorum sensing network in a roseobacterial marine sponge symbiont activates flagellar motility and inhibits biofilm formation. Molecular microbiology 85, 916-933.
13. Churchill, M.E., **Sibhatu, H.M.**, and Uhlson, C.L. (2011). Defining the structure and function of acyl-homoserine lactone autoinducers. Methods Mol Biol 692, 159-171.
14. Tizzano, M., Gulbransen, B.D., Vandenbeuch, A., Clapp, T.R., Herman, J.P., **Sibhatu, H.M.**, Churchill, M.E., Silver, W.L., Kinnamon, S.C., and Finger, T.E. (2010). Nasal chemosensory cells use bitter taste signaling to detect irritants and bacterial signals. Proc Natl Acad Sci USA 107, 3210-3215.
15. Li, H., Das, A., **Sibhatu, H.M.**, Jamal, J., Sligar, S.G., and Poulos, T.L. (2008). Exploring the electron transfer properties of neuronal nitric-oxide synthase by reversal of the FMN redox potential. J Biol Chem 283, 34762-34772.

Presentations

1. Poster presentation - Architecture of the "Hydrophobic Spines" Controls Enzymatic Activity of Protein Kinases, Protein Kinases & Protein Phosphorylation, 2011 FASEB Summer Research Conferences Snowmass Village Conference Center. June 2011.
2. Oral Presentation – Molecular Anatomy of Eukaryotic Protein Kinase Activation. Pharmacology research discussion, UCSD. March 2012.

3. Oral Presentation – Deciphering the Structural Basis of Eukaryotic Protein Kinase Regulation. Pharmacology research discussion, UCSD. March 2013.
4. Oral Presentation – Deciphering the Structural Basis of Eukaryotic Protein Kinase Regulation. MCC Young Investigators Symposium, UCSD. August 2013.
5. Oral Presentation – The Functional Regulation of Eukaryotic Protein Kinases. Biomedical Sciences Recruitment, UCSD. March 2014.
6. Oral Presentation - How Does Trisomy 21 Induce the Brain Pathologies Observed in Down Syndrome? Massachusetts Down Syndrome Congress. March 2017.
7. Poster Presentation - Cell-type Specific Transcriptional and Epigenetic Aberrations Induced by Trisomy 21. T21RS Conference Chicago, June 2017.
8. Poster Presentation – Interplay between the Epigenome and Transcriptome in the Different Cell-Types of the Brain with Trisomy 21. Society for Neuroscience (SFN), 2018.
9. Oral Presentation – Down Syndrome Induces Chromosomal Introversion in Neural Progenitor Cells. T21RS Conference Barcelona, June 2019.
10. Poster Presentation – Down Syndrome Induces Chromosomal Introversion in Neural Progenitor Cells. Society for Neuroscience (SFN), October 2019.

E. Outreach, Mentoring and Teaching

1. MIT Undergraduate Research Opportunities Program (UROP)	2016 - current
2. MIT Undergraduate Summer Research Program in Biology and Neuroscience	2017 and 2018
3. UCSD Initiative for Maximizing Student Diversity (IMSD)	2010 - 2015
4. UCSD Summer Training Academy for Research in the Sciences (STARS)	2014
5. UCSD Academic Connections – High school research scholars program	2012
6. Eritrean Institute of Technology – Teaching assistant (Introduction to Biology and Genetics)	2004 – 2007

F. Research Support

Ongoing Research Support

Alana Foundation Fellowship — Meharena (PI) — 07/01/19-06/30/21
Decoding the Molecular and Cellular Consequences of Down Syndrome on Brain Cell Types. ($500,000)
Role: Postdoctoral Fellow

Completed Research Support

LuMind Foundation Research Grant — Meharena (PI) — 07/01/18-06/30/19
Identifying Novel Therapeutic Avenues for Treating Individuals with Down syndrome. ($220,000)
Role: Postdoctoral Fellow

BWF Postdoctoral Enrichment Program Fellowship — Meharena (PI) — 08/01/16-07/31/19
Deciphering the Role of Eukaryotic Protein Kinases in Down's Syndrome. ($60,000)
Role: Postdoctoral Fellow

Merck/UNCF Postdoctoral Science Research Fellowship — Meharena (PI) — 09/01/15-02/28/17
Deciphering the Role of Eukaryotic Protein Kinases in Down's Syndrome. ($92,000)
Role: Postdoctoral Fellow

National Science Foundation Graduate Research Fellowship — Meharena (PI) — 07/01/12-06/30/15
Deciphering the Architecture of Inactive Eukaryotic Protein Kinases. ($97,500)
Role: Graduate Student