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	11/2021	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 disabilities, such as Down syndrome (DS) and Autism Spectrum Disorder (ASD). These disabling and extremely prevalent disorders present a growing challenge for society, however, 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 also been linked to disorders characterized by intellectual disability. I am interested in understanding how genomic imbalance, associated with DS and ASD, dysregulate the biophysical, biochemical, molecular and cellular properties governing the 3D-genome organization, epigenome and transcriptome leading to abnormal brain morphogenesis and deficits in cognitive processing. My lab takes a multidimensional approach utilizing stem cell technology, mouse models, genome-editing tools, and experimental and computational genomics approaches to elucidate the molecular-, cellular- and organ-level manifestations of genomic imbalance on brain development and cognition.

Expertise - My career has focused on attaining the expertise required to successfully accomplish this vision. As a research assistant at the University of California, Irvine, and University of Colorado, Anschutz medical campus, I 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 an 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 (*Cell Stem Cell, in-press*). 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 dynamics 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).

Collaborations – We currently collaborate with clinicians at Massachusetts General hospital (MGH) and Virginia Commonwealth University to curate a large library of biospecimens from individuals with aneuploidies, and ASD associated with large copy number variants (CNVs) and other rare genetic abnormalities. Furthermore, we have partnered with the International Mosaic Down syndrome Association (IMDSA) to curate genetically controlled samples from individuals with trisomy 21. We also attend the yearly retreats organized by IMDSA and Massachusetts Down syndrome Congress (MDSC), which brings individuals with DS, their families, clinicians and scientists together to identify the most significant and impactful scientific questions that would benefit individuals with DS. We will continue to harness and expand our collaborative relationships with individuals with intellectual disabilities, their families and clinicians to guide our future research endeavors.

B. Positions and Honors

Positions and Employment

2021 -	Assistant Professor of Neurobiology and Molecular Biology, UC San Diego, La Jolla, CA
2015 - 2021	Postdoctoral Fellow, Massachusetts Institute of Technology, Cambridge, MA
2010 - 2015	Predoctoral Researcher, University of California, San Diego, La Jolla, CA
2008 - 2010	Professional Research Assistant, University of Colorado, Anschutz Medical Campus, Aurora, CO
2007 – 2008	Research Assistant, University of California, Irvine, Irvine, CA
2004 - 2007	Teaching Assistant, Eritrean Institute of Technology, Eritrea

Other Experience and Professional Memberships

2021 -	External Advisory Board (EAB), The Jackson Laboratory
2021 -	Trisomy 21 Research Society (T21RS) Pre clinical committee
2019	Invited lecturer, Harvard Medical School, Cambridge, MA
2018-	Society for Neuroscience (SFN) Member
2018	Massachusetts Institute of Technology (MIT) Kaufman Teaching Certificate
2016-	Trisomy 21 Research Society (T21RS) Member
2012 - 2015	UCSD Black Graduate Student Association (BGSA) Founding Member

Awards and Honors

2021	Intersections Science Fellow (ISFS)
2021	Massachusetts Institute of Technology (MIT) Infinite Expansion Award
2019	Alana Down syndrome Center (ADSC) Fellow
2018	Rising STAR in Biomedical Sciences Fellow
2017	T21RS Travel Award
2017	Massachusetts Institute of Technology (MIT) Impact Fellow
2016	Burroughs Wellcome Fund PDEP Fellow
2015	Merck/UNCF Postdoctoral Science Research Fellow
2012	National Institutes of Health (NIH) F31 Predoctoral Fellowship recipient
2012	National Science Foundation (NSF) Graduate Research Fellow (GRFP)

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). This work has been published in Nature Neuroscience.
    a. **Meharena HS***, Marco, A., Dileep, V., Lockshin, E.R., Akatsu, G.Y., Mullahoo, J., Watson, L.A., Ko, T., Guerin, L.N., Abdurrob, F., et al. (2022). Down-syndrome-induced senescence disrupts the nuclear architecture of neural progenitors. Cell Stem Cell 29, 116-130 e117. (*Corresponding author)
    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

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, H.S.,** Marco, A., Dileep, V., Lockshin, E.R., Akatsu, G.Y., Mullahoo, J., Watson, L.A., Ko, T., Guerin, L.N., Abdurrob, F., et al. (2022). Down-syndrome-induced senescence disrupts the nuclear architecture of neural progenitors. Cell Stem Cell 29, 116-130 e117
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, 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
4. 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.
5. 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.
6. 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.
7. **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.
8. 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.
9. 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.
10. 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.
11. 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.
12. 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.
13. 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 - Consequences of Down Syndrome on the Specific Cell-Types of the Brain. Massachusetts Down Syndrome Congress. March 2019.
10. Oral Presentation – Down Syndrome Induces Chromosomal Introversion in Neural Progenitor Cells. T21RS Conference Barcelona, June 2019.
11. Poster Presentation – Down Syndrome Induces Chromosomal Introversion in Neural Progenitor Cells. Society for Neuroscience (SFN), October 2019.
12. Oral Presentation - The Consequences of Down Syndrome on the 3D-Genome Architecture of the developing brain. Genetic Grand Rounds - Massachusetts General Hospital (MGH), October 2019.
13. Oral Presentation - Down syndrome Induces Cellular Aging During Neurodevelopment. Massachusetts Down Syndrome Congress. March 2020.
14. Oral Presentation - Cell-type Specific Interplay between Genomic Imbalance and 3D-Genome Organization in Down Syndrome. Intersections Science Fellows Symposium, January 2021.
15. Oral Presentation - Genomic Imbalance and 3D-Genome Organization in Intellectual Disability. Genetic Grand Rounds - Massachusetts General Hospital (MGH), January 2021.
16. Oral Presentation - Trisomy 21 Induces Cellular Aging of Neural Progenitors. Massachusetts Down Syndrome Congress. March 2021.

E. Outreach, Mentoring and Teaching

1.	MIT Undergraduate Research Opportunities Program (UROP)	2016 - 2020
2.	Harvard Medical School - Invited lecturer (Topic: Translational genetics and human disease)	2019
3.	MIT Undergraduate Summer Research Program in Biology and Neuroscience	2017 and 2018
4.	UCSD Initiative for Maximizing Student Diversity (IMSD)	2010 - 2015
5.	UCSD Summer Training Academy for Research in the Sciences (STARS)	2014
6.	UCSD Academic Connections – High school research scholars program	2012
7.	Eritrean Institute of Technology – Teaching assistant (Introduction to Biology and Genetics)	2004 – 2007

F. Research Support

Alana Foundation Fellowship Meharena (PI) 07/01/19-10/31/21
Decoding the Molecular and Cellular Consequences of Down Syndrome on Brain Cell Types. ($500,000)
Role: Postdoctoral Fellow

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