

ALFREDO M. VALENCIA, PH.D.

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EDUCATION

Ph.D. Chemical Biology

Harvard University, Cambridge, MA

May 2020

Dissertation Title: Biochemistry, Structure, and Function of SMARCB1-Mutant mSWI/SNF Chromatin Remodeling Complexes in Human Disease

Advisory committee: Cigall Kadoch (Advisor), David R. Liu (Chair), Robert E. Kingston, & Stephen J. Haggarty

B.A. Biochemistry, with Honors

Pitzer College, Claremont, CA

May 2014

RESEARCH EXPERIENCE

Postdoctoral Research, Stanford University and Stanford School of Medicine, Palo Alto, CA August 2020-present
Stanford Science Fellow, NASEM Ford Foundation Postdoctoral Fellow

Advisor: Sergiu P. Paşca, M.D.

- **Premise:** Intellectual disability (ID) affects approximately 1% of the population and often co-occurs with additional issues such as epilepsy and/or additional developmental abnormalities, yet the mechanisms underpinning these disorders remain incompletely understood. Although ID has heterogenous origins (i.e. environmental or genetic), genetic sequencing efforts have revealed high mutation rates in chromatin regulatory genes involved in these disorders.
- **Goal:** Using human brain organoids as a model system paired with single-cell transcriptional genomics and chromatin mapping investigative techniques, I aim to uncover the chromatin regulatory and neurodevelopmental mechanisms underlying the pathogenesis of neurodevelopmental disorders to better understand brain development and correlated brain disorders.
- **Significance:** By studying the most frequently mutated pathways and gene families implicated in these conditions, I am committed to making significant contributions in understanding the mechanisms underlying neurodevelopmental disorders and informing typical neurodevelopment.

Dissertation Research, Harvard Medical School, the Dana-Farber Cancer Institute, and the Broad Institute of MIT and Harvard, Boston, MA and Cambridge, MA August 2015-August 2020
HHMI Gilliam Fellow, NASEM Ford Foundation Predoctoral Fellow August 2017-August 2020

Advisor: Cigall Kadoch, Ph.D.

- **Premise:** Mutations to genes encoding for mSWI/SNF (BAF) chromatin remodeling complex proteins have been identified in ~20% of cancers, and more recently implicated in the development of a variety of intellectual disability syndromes, but the mechanisms by which these mutations result in these conditions is currently unclear.
- **Goal:** To gain mechanistic insight into the biochemical and functional consequences of SMARCB1 (BAF47) perturbations in the development of highly aggressive cancers and neurodevelopmental disorders.
- **Significance:** My research unmasked an evolutionarily conserved, structural role of the SMARCB1 protein that is perturbed in human disorders and disease. By combining human genetics, biochemistry, and structural biology, my research highlights the power of examining recurrent disease-associated mutations to advance our mechanistic understanding the function of the BAF complex, and other chromatin regulatory machinery, in healthy and disease states. (Valencia et al., *Cell* 2019; Nakayama, Pulice, Valencia, et al., *Nat. Gen.* 2017)

Undergraduate Research, W.M. Keck Science Department of the Claremont McKenna, Pitzer, and Scripps Colleges, Claremont, CA August 2012-May 2014
HHMI Summer Undergraduate Research Fellow June-August 2013

Advisor: Aaron M. Leconte, Ph.D.

- **Premise:** DNA polymerases synthesize the DNA of all living organisms. Several *Taq* DNA polymerases have been evolved in various laboratories to have an unnatural ability of synthesizing modified DNA. However, the origins of this unnatural activity are not fully characterized or understood.
- **Goal:** Use structural characterization of mutant *Taq* polymerases to elucidate conformational and biochemical differences between wild type and mutant enzymes to aid in future protein-engineering efforts.
- **Significance:** Modified DNA has many research, diagnostic, and potential therapeutic uses. In order to rationally design improved unnatural DNA polymerases, further characterization of their structure and function are needed.

First-Author

1. **Chromatin dynamics in human brain development and disease.**
Valencia, A.M.* & Paşca, S.P. [Trends in Cell Biology](#) October 2021
2. **Recurrent SMARCB1 mutations reveal a nucleosome acidic patch interaction site that potentiates mSWI/SNF complex chromatin remodeling.**
Valencia, A. M.*, Collings, C.K., Dao, H. T., St. Pierre, R., Cheng, Y.C., Huang, J., Sun, ZY, Seo, HS, Mashtalir, N., Comstock, D.E., Bolonduro, O., Vangos, N.E., Yeoh, Z.C, Dornon, MK, Hermawan, C., Barrett, L., Dhe-Paganon, S., Woolf, C.J., Muir, T.W., & Kadoch, C. [Cell](#) November 2019
3. **Chromatin regulatory mechanisms and therapeutic opportunities in cancer.**
Valencia, A. M.* & Kadoch, C. [Nature Cell Biology](#) January 2019
4. **SMARCB1 is required for widespread BAF complex-mediated activation of enhancers and bivalent promoters.**
Nakayama, R.T.*, Pulice, J.L.*, Valencia, A.M.*, McBride, M.J., McKenzie, Z.M., Gillespie, M.A., Ku, W.L., Teng, M., Cui, K., Williams, R.T., Cassel, S.H., Qing, H., Widmer, C.J., Demetri, G.D., Irizarry, R.A., Zhao, K., Ranish, J.A., & Kadoch, C. [Nature Genetics](#) September 2017

Co-Author

5. **Molecular basis of human cortical interneuron migration in forebrain assembloids from Timothy Syndrome.**
Birey, F.*, Li, M-Y, Gordon, A., Thete, M.T., Valencia, A.M., Revah, O., Paşca, A.M., Geschwind, D.H., & Paşca, S.P. [Cell Stem Cell](#) January 2022
6. **Maturation of Human Cortical Organoids Matches Key Early Postnatal Transitions.**
Gordon, A.*, Yoon, S., Tran, S.S., Makinson, C.D., Park, J.Y., Anderson, J., Valencia, A.M., Horvath, S., Xiao, X., Huguenard, J.R., Paşca, S.P., & Geschwind, D.H. [Nature Neuroscience](#) February 2021
7. **BICRA, a SWI/SNF Complex Member, Is Associated with BAF-Disorder Related Phenotypes in Humans and Model Organisms.**
Barish, S.*, Barakat, T. S.*, Michel, B. C.*, Mashtalir, N.*, Phillips, J. B., Valencia, A. M., Ugur, B., Wegner, J., Scott, T. M., Bostwick, B., Undiagnosed Diseases Network, Murdock, D. R., Dai, H., Perenthaler, E., Nikoncuk, A., van Slegtenhorst, M., Brooks, A. S., Keren, B., Nava, C., Mignot, C., [...] Kadoch, C., & Bellen, H. J. [American Journal of Human Genetics](#) November 2020
8. **A structural model of the endogenous human BAF complex informs disease mechanisms.**
Mashtalir, N.*, Suzuki H.*, Farrell D. P.*, Sankar, A.*, Luo, J., D'Avino, A.R., Filipovski, M., St. Pierre, R., Valencia, A.M., Onikubo, T., Roeder, R.G., Han, Y., He, Y., Ranish, J.A., DiMaio, F., Walz, T., & Kadoch, C. [Cell](#) October 2020
9. **The nucleosome acidic patch and H2A ubiquitination underlie mSWI/SNF recruitment in synovial sarcoma.**
McBride, M.J.*, Mashtalir, N.*, Winter, E.B., Dao, H.T., Dao, H.T., Filipovski, M., D'Avino, A.R., Seo, H.S., Umbreit, N.T., St. Pierre, R., Valencia, A.M., Qian, K., Zullo, H.J., Jaffe, J.D., Dhe-Paganon, S., Muir T.W., & Kadoch, C. [Nature Structural & Molecular Biology](#) June 2020
10. **A non-canonical SWI/SNF complex is a synthetic lethal target in cancers driven by BAF complex perturbation.**
Michel, B. C.*, D'Avino, A.R.*, Cassel, S.H.*, Mashtalir, N., McKenzie, Z.M., McBride, M.J., Valencia, A.M., Zhou, Q., Bocker, M., Soares, L.M., Pan, J., Remillard, D. I., Lareau, C.A., Zullo, H.J., Fortoul, N., Gray, N.S., Bradner, J.E., Chan, H.M., & Kadoch, C. [Nature Cell Biology](#) November 2018
11. **Modular Organization and Assembly of SWI/SNF Family Chromatin Remodeling Complexes.**
Mashtalir, N.*, D'Avino, A.R., Michel, B.C., Luo, J., Pan, J., Otto, J.E., Zullo, H.J., McKenzie, Z.M., Kubiak, R.L., St. Pierre, R., Valencia, A.M., Poynter, S.J., Cassel, S.H., Ranish, J.A., & Kadoch, C. [Cell](#) October 2018

HONORS AND AWARDS

- Ford Foundation Postdoctoral Fellow, National Academies of Sciences, Engineering, and Medicine 2021
- Stanford Science Fellow, Stanford University 2020
- Outstanding Research Presentation Award, 2020 SACNAS Virtual Conference 2020
- Top Presenter, 1st place (website), Graduate Division, Sigma Xi Student Research Showcase 2020
- Top Presenter, 2nd place (oral), Graduate Division, Sigma Xi Virtual Student Scholars Symposium 2020
- Howard Hughes Medical Institute (HHMI) Gilliam Fellow 2018-2020
- Diversity and Inclusion Fellow, Harvard Graduate School of Arts and Sciences 2018-2019
- Ford Foundation Predoctoral Fellow, National Academies of Sciences, Engineering, and Medicine 2017-2018
- Ruth L. Kirschstein National Research Service Award (F31 Individual NRSA) Award Recipient (*declined*) 2017
- Hispanic Scholarship Fund Scholarship Recipient 2017
- Harvard University Graduate Prize Fellowship Awardee 2014-2017
- Paul and Daisy Soros Fellowship Finalist 2015
- Sigma Xi Honor Society 2014
- John Stauffer Memorial Endowed Scholarship Recipient, Pitzer College 2014
- Departmental Honors, Biochemistry, Pitzer College 2014
- HHMI Summer Undergraduate Research Program Fellow 2013
- Ronald E. McNair Post-Baccalaureate Scholar, Claremont Graduate University 2012-2013
- Pritzker Scholarship Recipient, Pitzer College 2010
- A Better Chance Scholarship Alumnus & St. Margaret's Episcopal School Tartan Scholarship Recipient 2006-2010

PRESENTATIONS

Conferences & Invited Research Presentations

- Exploring the chromatin biology of neurodevelopmental disorders through biochemical methods and human brain organoids
Oral: 2021 Ford Foundation Conference of Ford Fellows (virtual) October 2021
- Recurrent SMARCB1 mutations reveal a critical BAF complex-nucleosome interaction conserved for millennia.
Oral: Stanford University Center for Undiagnosed Diseases Weekly Curation & Science Meeting August 2021
Oral (Presentation Award: Life Sciences, Biochemistry): 2020 SACNAS Virtual Conference October 2020
Oral (Top Presenter): Sigma Xi Virtual Student Scholars Symposium, Sigma Xi Honor Society May 2020
Website (Top Presenter): Sigma Xi Student Research Showcase, Sigma Xi Honor Society (virtual) April 2020
- Recurrent SMARCB1 mutations reveal a nucleosome interaction that potentiates mSWI/SNF complex chromatin remodeling.
Oral: Cancer Chemical Biology & Metabolism Annual Retreat, Dana-Farber Cancer Institute September 2020
Oral: Fusion 2nd Epigenetics Conference: From Mechanisms to Disease, Nassau, Bahamas February 2020
Poster: 2019 HHMI Gilliam Fellows Conference, HHMI Headquarters, Chevy Chase, MD September 2019
- From human genetics to biochemistry, structure, and function: identifying a key protein interaction conserved for millennia.
Oral: Claremont Colleges SACNAS Chapter & Keck Science Chemistry Club, Claremont, CA November 2019
- Cancer and intellectual disability-associated mutations alter mSWI/SNF nucleosome interactions and transcriptional regulation.
Poster: 2019 Gordon Research Conference: Cancer Genetics and Epigenetics, Lucca (Barga) Italy April 2019
Poster: 2019 Keystone Conference: Epigenetics and Disease/3D Genome, Banff, Alberta, Canada March 2019
- SMARCB1 stabilizes BAF complexes on chromatin and drives a genome-wide occupancy gain of BAF complexes.
Oral: 2018 Konstanz Research School of Chemical Biology Annual Retreat, Blaubeuren, Germany August 2018
Poster: 2018 Ford Fellows Conference, National Academies of Sciences, Washington, DC May 2018
Poster: 2017 HHMI Gilliam Fellows Conference, HHMI Headquarters, Chevy Chase, MD September 2017
- Dissecting the oncogenic mechanisms of SMARCB1 deficient sarcomas through biochemical and bioinformatics investigations
Oral: Pitzer College MECHANISM Program (Invited Speaker), Pitzer College, Claremont, CA April 2018

PRESENTATIONS (continued)

Special Presentations & Events

- **Interview, Latinx Heritage Month Leaders of Tomorrow**, Invited by Assist. Principal of Rocketship Public Schools, Ms. Daysy Arellano (virtual) September 2021
- **Poster Presentation**, 2021 Stanford Science Fellows Retreat, Exploring the chromatin biology underlying neurodevelopmental disorders using human brain organoids: Progress on ARID1B (virtual) June 2021
- **Panelist**, Summit Public Schools Career Fair, Science Panel Career Session (virtual) March 2021
- **Panelist**, A Conversation with Latinx Professionals, Mississippi State University, MS (virtual) September 2020
- **Panelist**, Landry Cancer Biology Panel on Graduate Research, Harvard Medical School, Boston, MA October 2019
- **Panelist**, Broad Research and Technical Specialists (RATS) Career & Graduate School Discussion alongside Dr. Cigall Kadoch, The Broad Institute of MIT and Harvard, Cambridge, MA April 2019
- **Keynote Speaker**, St. Margaret's Episcopal School's 2018 Annual Tartan Tee-Off (Scholarship Fundraiser), Dana Point, CA October 2018
- **"Demystifying College as a FirstGen Student"**, Special event for St. Margaret's Episcopal School FirstGen Latinx high school students who received the same scholarship I did to attend St. Margaret's, San Juan Capistrano, CA October 2018
- **Featured Student Speaker**, Harvard Graduate School Incoming Student Orientation, Cambridge, MA September 2018
- **"Life as a Grad Student" Panelist**, Harvard's Summer Honors Undergraduate Research Program (SHURP), Harvard Medical School, Boston, MA June 2018
- **FirstGen in Academia Q&A Session**, Special event for Pitzer College FirstGen Program, Claremont, CA April 2018
- **Graduate Research Fellowship Seminar Presenter and Panelist**, Minority Biomedical Scientists of Harvard (MBSH) Student Organization, Harvard Medical School, Boston, MA October 2018
- **"Thriving in Graduate School" Student Panelist** for Minority Biomedical Scientists of Harvard (MBSH) Organization, Harvard Medical School, Boston, MA October 2017

TEACHING EXPERIENCE

Chemistry Coordinator, Dana-Farber Cancer Institute Science Enrichment Program Fall 2015-Spring 2016
John D. O'Bryant and Madison Park High Schools, Boston, MA

- Co-developed and led Experimental Chemistry Day for students in the program's inaugural year
- Advocate for students to pursue science and higher education

Teaching Fellow, Life Sciences 1a (An Integrative Chemistry and Biology Course) Fall 2015
Harvard University, Cambridge, MA

- Designed and led an undergraduate discussion section reviewing weekly topics and problem sets
- Served as a lab manager; guided students through weekly laboratory experiments

Laboratory Assistant and Mentor, HHMI Summer Science Immersion Program Summer 2013-Spring 2014
W.M. Keck Science Department, Claremont, CA

- Mentored first-year students who had an interest in science, but minimal STEM experience
- Served as chemistry and biology laboratory teacher's assistant
- Met with students individually to plan their 4-year academic coursework

Laboratory Teacher's Assistant and Independent Tutor, Basic Principles of Chemistry Fall 2012
W.M. Keck Science Department, Claremont, CA

- Led students through weekly laboratory experiments and performed individual tutoring outside of the lab
- Organized weekly office hours to work through problems and discuss ideas and research proposals

Reviewer, 2021 SACNAS Conference Scholarship Awards and Presentation Abstracts

Fall 2021

- Volunteered as a reviewer for undergraduate scholarship applications and presentation abstracts

Mentor, Pitzer College Bloom Mentorship Program

Pitzer College, Claremont, CA

Fall 2020-Spring 2020

- Mentored Latinx Pitzer College seniors completing their bachelor's degrees

Executive Board Member & Co-President (2017-2018), Minority Biomedical Scientists of Harvard (MBSH)

Harvard Medical School, Boston, MA

Summer 2016-2020

- Organized and co-lead board meetings, managed budget, apply for grant funding
- Designed MBSH logo and maintained website
- Collaborated with Harvard's Director and Assistant Director of Diversity and Minority Affairs
- Organized annual MBSH Fellowship Seminar (~50 attendees)

Recruiter and Poster Judge at 2019 Annual Biomedical Research Conference for Minority Students (ABRCMS)

Anaheim, CA

November 2019

- Served as student representative for Harvard University's Chemical Biology Ph.D. Program
- Staffed booth and spoke with and provided information for undergraduate students applying to Ph.D. programs
- Served as poster judge for undergraduate student poster competition

Diversity and Inclusion Fellow, Harvard University Graduate School of Arts and Sciences

Harvard University, Cambridge, MA

Spring 2018-Spring 2019

- Aimed to foster a community of diverse scholars across the Harvard community
- Established and maintained student group contact information list and events calendar
- Served as a liaison between The Office of Diversity and Minority Affairs and student-led affinity organizations

Mentor, Native American High School Summer Program

Harvard Medical School, Boston, MA

Summer 2017, 2018

- Mentored two high school students from the Hopi (AZ) and Fort Peck (MT) tribes
- Discussed career goals, college plans, personal statements, and resumes with mentees

Mentor, Summer Honors Undergraduate Research Program (SHURP)

Summer 2017

Harvard Medical School, Boston, MA

- Mentored undergraduate student from UC Santa Cruz during his time in the laboratory of Prof. Fred Winston

Program Coordinator and Chemistry Director, Tutors for a Cause

Pitzer College, Claremont, CA

Fall 2010-Spring 2014

- Organized weekly tutoring/mentoring sessions for K-12 students (Pitzer maintenance and dining hall staff's children)
- Assisted with college planning and financial aid (FAFSA) workshops
- Designed kitchen chemistry experiments for students to perform in small groups

TECHNICAL SKILLS

Laboratory Techniques: Genome editing of mammalian cells, 2D and 3D tissue culture (brain organoids), RNA and DNA (genomic and plasmid) extraction and library preparation for sequencing (sc- and bulk-RNA-seq, sc- and bulk-ATAC-seq, CUT&RUN, ChIP-seq, and MNase-seq), protein quantification, immunoblotting, co-immunoprecipitation (co-IP), chromatin immunoprecipitation (ChIP), preparation of proteins for mass spectrometry (MS), bacterial and mammalian cell purification of proteins and protein complexes, chromatin remodeling complex nucleosome remodeling assays (restriction enzyme activity assay (REAA)) and ATPase activity determination, glycerol/sucrose based density sedimentation.

Laboratory Equipment: Microscopy (for cell culture, confocal immunofluorescence), NextSeq500 (for Next Gen Sequencing), ultrasonicator (for chromatin shearing, tissue homogenization), Automated electrophoresis for DNA/RNA qc (Tapestation, Bioanalyzer), fast-protein and high-performance liquid chromatography systems (FPLC and HPLC), thermal cycler for PCR, q-PCR, UV-Vis spectrophotometer, micropipettes.

Software: Chimera, PyMol, Geneious, Gene Conservation Analysis, Microsoft Office Suite, Adobe Creative Suite.

Languages: Bilingual in Spanish and English

Valencia AM, Kadoch C. Compositions Comprising Modified SMARCB1 and Uses Thereof. U.S. Pat. Appl. No. 62/926,139. Filed: 10-25-19. Summary: This patent describes a novel interface between the mammalian SWI/SNF complex and the nucleosome acidic patch that is required for mSWI/SNF complex-mediated chromatin remodeling in vitro and in cells. The invention details strategies for therapeutic inhibition of mSWI/SNF complexes via disruption of this specific interface with utility in specific cancer types.

MEDIA COVERAGE ON RESEARCH, AWARDS, & SERVICE

1. [“Pitzer Students and Alumni Recognized for Academic Excellence and Innovation”](#) by Laurie Babcock, Pitzer College Office of Communications, April 27, 2021. Announcement of Pitzer College student awards including my 2021 Ford Foundation Postdoctoral Fellowship.
2. [“Stanford Science Fellows program announces first cohort”](#) by Ker Than, Stanford University, May 28, 2020. Program announcement for the inaugural Stanford Science Fellows Cohort.
3. [“A Critical Understanding”](#) by Deborah Halber. Harvard University Graduate School of Arts and Sciences News, February 14, 2020. Covers the inspiration, broad results, and implications of my first-author research article investigating intellectual disability associated mutations of the SMARCB1 protein (Valencia et al., *Cell* 2019).
4. [“Pitzer College Alumnus Alfredo Valencia ’14 Explores Groundbreaking Cancer Research in New Article”](#) by Laurie Babcock, Pitzer College Office of Communications. January 23, 2019. College alumni highlight summarizing my review on chromatin regulatory mechanisms in cancer (Valencia & Kadoch, *Nature Cell Biology* 2019).
5. [“Freddy Valencia ’10 Paving the Way”](#) by Ryan Wood, St. Margaret’s Episcopal School Highlander Magazine, Winter 2019. March 9, 2019. A high school alumni profile describing my scientific interests and commitment to mentoring the next generation of students of color from underrepresented backgrounds.
6. [“From Santa Ana to Cambridge: Freddy Valencia returns to SMES to share his story”](#) by Breakthrough San Juan Capistrano. October 24, 2018. Summarizes the visit to my high school alma mater, St. Margaret’s Episcopal School, where I spoke to students with the same scholarship I received about college, and my experience as a first-generation, low-income Latinx college student.
7. [“Emboldening Student Voices”](#) by Anna Fisher-Pinkert. The Harvard GSAS Bulletin. March 23, 2018. Story on me and my colleague Alyssa Hernandez describing our roles as Harvard’s inaugural Diversity and Inclusion Fellows.
8. [“Pitzer Alumnus Alfredo Valencia ’14 Wins HHMI Gilliam Fellowship for Exceptional Graduate Students”](#) by Susan Warmbrunn, Pitzer College Office of Communications. August 22, 2017. Press release for my HHMI Gilliam Fellowship award.
9. [“HHMI Awards 39 Gilliam Fellowships to Support Diversity in Science”](#) by Meghan Rosen. Howard Hughes Medical Institute News. August 15, 2017. Press release for the HHMI Gilliam Fellowship awards.
10. [“Pitzer College Student and Alumnus Win 2017 Ford Foundation Predoctoral Fellowships”](#) by Laurie Babcock, Pitzer College Office of Communications. April 14, 2017. Press release on my Ford Foundation Fellowship award.