ALFREDO M. VALENCIA, PH.D.

alfredo.m.valencia@gmail.com • LinkedIn • 714-673-1728 • Palo Alto, CA

SUMMARY

Scientist with 11.5 years of multidisciplinary research experience in cellular and molecular biology, functional genomics, biochemistry, and neurobiology.

- 3.5 years: pluripotent stem cell research, brain organoid disease modeling, and single-cell transcriptomics.
- 6 years: cancer and cell biology research using biochemistry and functional genomics.
- 2 years: molecular biology, molecular cloning, and bacterial protein expression and purification.

EDUCATION

Harvard University — Cambridge, MA
Ph.D. Chemical Biology — May 2020

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

Pitzer College — Claremont, CA
B.A. Biochemistry (Honors) — May 2014

RESEARCH EXPERIENCE

Stanford University and Stanford School of Medicine, Stanford, CA — **Postdoctoral Scholar**
Advisor: Sergiu P. Pașca, M.D. — August 2020-present

- **Primary Project:**
  - Seek to uncover the chromatin regulatory and neurodevelopmental mechanisms underlying the pathogenesis of neurodevelopmental disorders using human brain organoids and multiplexed single-cell transcriptomics..
- **Responsibilities:**
  - Independently planned, optimized, and executed CRISPR/Cas9 array screen using human brain organoids.
  - Established multiplexed gene editing validation procedure for 100+ individual targets at once.
  - Trained staff scientists, postdocs, and students in molecular biology (CRISPR/Cas9 gene editing, PCR, genotyping, western blotting) and project management. Supervise an undergraduate thesis project.
  - Generated dozens of knockout mutant iPSC clones for many gene targets.
  - Collaborate with a team to efficiently characterize organoids through biochemical, immunofluorescence microscopy, and functional genomics techniques.
- **Methodologies:** Human induced pluripotent stem cell culture, 3D-tissue culture of brain organoids, CRISPR/Cas9 genome-editing, single cell transcriptomics (10X & Parse Biosciences (SPLiT-seq) sc-RNA-seq), immunofluorescence microscopy.

Dana-Farber Cancer Institute, Harvard Medical School, & the Broad Institute, Boston, MA — **PhD Student**
Advisor: Cigall Kadoch, Ph.D. — August 2014-August 2020

- **Projects:**
  - Reported 85 novel neurodevelopmental disorder (NDD)-associated mSWI/SNF complex variants and characterized these and previously published variants through 3D structural mapping and a comparative analysis to cancer-associated variants (Valencia, Sankar et al., *Nature Genetics* 2023).
  - Discovered that the SMARCB1-CTD forms an alpha helix that binds to the nucleosome acidic patch and is conserved in yeast. SMARCB1-CTD mutations implicated in the neurodevelopmental disorder Coffin-Siris syndrome disrupt this interaction and attenuate mSWI/SNF activity genome-wide (Valencia et al., *Cell* 2019).
  - Uncovered that SMARCB1 rescue in *SMARCB1*-null cancer cells results in a genome-wide occupancy gain of BAF complexes, resulting in transcriptional activation via antagonism of Polycomb repressive complex (PRC2) (Nakayama, Pulice, Valencia et al., *Nature Genetics* 2017).
- **Responsibilities:**
  - Performed biochemical and functional genomics experiments to characterize the impact of full length and mutant SMARCB1 variants in *SMARCB1*-null cell lines.
  - Collaborated with computational, structural, and molecular biologists across institutions to characterize the BAF complex through molecular, functional genomics, and structural biology investigative methods.
- **Methodologies:** Cancer cell line tissue culture, functional genomics (ChIP-seq, ATAC-seq, Bulk-RNA-seq, MNase-seq), lentiviral production and transduction, Co-immunoprecipitation and Western blotting, protein complex purification from mammalian cell lines.

PUBLICATIONS

First-author* & selected publications. View all co-authored publications via Google Scholar.

1. Landscape of mSWI/SNF chromatin remodeling complex perturbations in neurodevelopmental disorders
   Valencia, A. M*., Sankar, A.*, van der Sluijs, P. J., Satterstrom, F. K., Fu, J., Talkowski, M. E., Vergano, S. A. S., Santen, G. W. E., & Kadoch, C.
   Nature Genetics — July 2023
2. Genome-wide CRISPR screens of T cell exhaustion identify chromatin remodeling factors that limit T cell persistence
   Belk, J.*, Yao, W., Ly, N., Freitas, K., Chen, Y-T., Shi, Q., **Valencia, A.M.**, Shifrut, E., Kale, N., Yost, K., Duffy, C., Hwee, M., Miao, Z., Ashworth, A., Mackall, C., Marson, A., Carnevale, J., Vardana, S., Satpathy, A.T.
   Cancer Cell — June 2022
3. Chromatin dynamics in human brain development and disease
   Valencia, A.M.* & Paşca, S.P.
   Trends in Cell Biology — February 2022
4. 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 — February 2022
5. Maturation of human cortical organoids matches key early postnatal transitions
   Gordon, A.*, Yoon, S-J., 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
6. 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
7. 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
8. Chromatin regulatory mechanisms and therapeutic opportunities in cancer
   Valencia, A. M.* & Kadoch, C.
   Nature Cell Biology — January 2019
9. 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., Zullow, 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
10. 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

HONORS & AWARDS

- Howard Hughes Medical Institute (HHMI) Hanna Gray Fellowship Finalist — 2022
- 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
- Diversity and Inclusion Fellow, Harvard Graduate School of Arts and Sciences — 2018
- Howard Hughes Medical Institute (HHMI) Gilliam Fellow — 2017
- Ford Foundation Predoctoral Fellow, National Academies of Sciences, Engineering, and Medicine — 2017
- Ruth L. Kirschstein National Research Service Award (F31 Individual NRSA) Award Recipient *(declined)* — 2017
- Harvard University Graduate Prize Fellowship Awardee — 2014

PRESENTATIONS

- **Oral Presentation:** Exploring the chromatin biology of neurodevelopmental disorders through biochemical methods and human brain organoids
    - 2021 Ford Foundation Conference of Ford Fellows
- **Presentation:** Recurrent SMARCB1 mutations reveal a nucleosome interaction that potentiates mSWI/SNF complex chromatin remodeling

  Oral:
    - 2020 Cancer Chemical Biology & Metabolism Annual Retreat, Dana-Farber Cancer Institute
    - 2020 Fusion 2nd Epigenetics Conference: From Mechanisms to Disease, Nassau, Bahamas

  Poster:
    - 2019 HHMI Gilliam Fellows Conference, HHMI Headquarters, Chevy Chase, MD
    - 2019 Gordon Research Conference: Cancer Genetics and Epigenetics, Lucca (Barga) Italy
    - 2019 Keystone Conference: Epigenetics and Disease/3D Genome, Banff, Alberta, Canada
- **Oral Presentation:** Recurrent SMARCB1 mutations reveal a critical BAF complex-nucleosome interaction conserved for millennia
    - 2020 SACNAS Virtual Conference (Presentation Award: Life Sciences, Biochemistry)
    - 2020 Sigma Xi Virtual Student Scholars Symposium, Sigma Xi Honor Society (Top Presenter-2nd place)
    - 2020 Sigma Xi Student Research Showcase, Sigma Xi Honor Society (Top Presenter-1st place)
    - 2019 Claremont Colleges SACNAS Chapter & Keck Science Chemistry Club
- **Presentation:** 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

  Poster:
    - 2018 Ford Fellows Conference, National Academies of Sciences, Washington, DC
    - 2017 HHMI Gilliam Fellows Conference, HHMI Headquarters, Chevy Chase, MD
- **Oral Presentation:** Dissecting the oncogenic mechanisms of SMARCB1 deficient sarcomas through biochemical and bioinformatics investigations
    - Pitzer College MECHANISM Program, Pitzer College, Claremont, CA

TECHNICAL SKILLS

Laboratory Techniques:

- **Cell Biology:** 2D and 3D tissue culture (brain organoids, induced-pluripotent stem cells (iPSCs, cancer cell lines), CRISPR/Cas9 mutant cell line generation and genotyping (cancer cell lines and iPSCs), single-cell and single-nuclei dissociation of organoids for downstream genomics experiments, cryosectioning and immunofluorescence staining of tissue for downstream image analysis.
- **Molecular Biology and Biochemistry:** RNA and DNA extraction (genomic and plasmid), protein quantification (BCA and Bradford assay), immunoblotting, co-immunoprecipitation (co-IP), chromatin immunoprecipitation (ChIP), preparation of proteins for mass spectrometry (MS), bacterial and mammalian cell-based purification of proteins and protein complexes, molecular cloning, glycerol/sucrose based density sedimentation.
- **Genomics:** Proficient in library preparation for diverse sequencing applications, including single-cell and bulk RNA-seq, bulk ATAC-seq, ChIP-seq, and MNase-seq. Familiarity with functional genomics data processing using Terminal (command line, bash scripting) and R/RStudio.

Languages: English, Spanish

PATENT

Valencia AM, Kadoch C. Compositions Comprising Modified SMARCB1 and Uses Thereof. U.S. Pat. 20220396604A. 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.