BIOGRAPHICAL SKETCH

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NAME: Orr Ashenberg

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

POSITION TITLE: Associate Director, Computational Biology at Broad Institute

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
Harvard College	A.B.	06/2006	Chemistry and Chemical Biology
Massachusetts Institute of Technology	Ph.D.	09/2012	Computational and Systems Biology
Fred Hutchinson Cancer Research Center	Postdoc	2013-2017	Molecular Evolution

A. Personal Statement

As the Associate Director of Computational Biology at the Klarman Cell Observatory (KCO), I initiate, lead, and manage novel computational biology projects that support the KCO mission to understand cells and their circuits in health and disease. I provide scientific expertise in genomics, computational biology, machine learning, and data management to a range of areas in biology (e.g. tissue homeostasis and disease) and technology development (e.g. single cell genomics and spatial genomics). Furthermore, I supervise and mentor a group of computational biologists doing research in diverse systems such as inflammatory diseases, immune responses in glioblastoma, and adipose tissue heterogeneity. As such, I have extensive experience in leading single cell and spatial data analysis and working closely with experimental biologists to develop and carry out the multi-omics analyses needed to profile cells, as well as to guide the next set of biological questions. This makes me ideally prepared to discover the pathways driving the immunosuppressive microenvironment in glioblastoma and the effects of immunotherapies on that environment.

Ongoing and recently completed projects that I would like to highlight include:

R01 AI167993-01A1
Kagan (PI), Role: Subcontract
09/19/22-07/31/27
Regulation of immunity by the cGAS-STING pathway.

RC2 DK116691-06
Ashenberg (PI)
05/24/23-03/31/28
RC2 Investigating Human Adipocyte Heterogeneity.

P01 CA236749
Chiocca (PI), Role: Core Lead
07/03/20-06/30/25
P01 Understanding and Overcoming T cell Immunosuppression in Glioblastoma.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2021-2025	Associate Director, Computational Biology, Broad Institute
2018-2021	Sr. Computational Biologist, Broad Institute
2017-2018	Computational Biologist, Broad Institute
2013-2016	Pacific Science Center Communication Fellow in Seattle, WA
2014	PhRMA (Pharmaceutical Research and Manufacturers of America) Postdoctoral Fellowship in Informatics
2007	National Science Foundation Graduate Research Fellowship

Honors

2015	Fred Hutchinson Conference Travel Award
2013	Scholarship to attend Summer Institute in Statistics and Modeling in Infectious Diseases
2010	1st Place Poster Prize, MIT Biology Department Retreat
2006	Graduated *summa cum laude*, Harvard College
2006	Elected to Phi Beta Kappa, Harvard College

C. Contributions to Science

1. My main research focus is the comprehensive characterization of cells in tumors. This area has been transformed by recent breakthroughs in single-cell profiling that allow identification of cell type and developmental state for hundreds of thousands of cells as well as technological advances allowing for multiomic profiing. I was the computational lead for the Human Tumor Atlas Pilot Program, where I led the efforts of the computational biologists carrying out single-cell transcriptomic and spatial genomics studies of seven different cancer types. In these publications, I carry out the computational analyses to show at the single-cell level how the tumor interacts with its microenvironment (immune cells, parenchyma), and in particular, how the immune response is evaded.
    a. Patel, A. G.*, **Ashenberg, O.***, Collins, N. B.*, Segerstolpe, Å., Jiang, S., Slyper, M., ... & Dyer, M. A. (2024). A spatial cell atlas of neuroblastoma reveals developmental, epigenetic and spatial axis of tumor heterogeneity. bioRxiv, 2024-01. *** These authors contributed equally to this work.**
    b. Mathewson, N. D.*, **Ashenberg, O.***, Tirosh, I.*, Gritsch, S.*, Perez, E. M.*, Marx, S.*, Jerby-Arnon, L., Chanoch-Myers, R., Hara, T., Richman, A. R., ..., Chiocca, E. A., Reardon, D. A., Regev, A., Suvà, M. L., Wucherpfennig, K. W. (2021). Inhibitory CD161 Receptor Identified in Glioma-infiltrating T cells by Single Cell Analysis. *Cell, 184*: 1281-1296. *** These authors contributed equally to this work.**
    c. Slyper, M. *, Porter, C. *, **Ashenberg, O. ***, Waldman, J., Drokhlyansky, E., Wakiro, I., Smillie, C., Smith-Rosario, G., Wu, J., Dionne, D., Vigneau, S., Jané-Valbuena, J., Tickle, T. L., Napolitano, S., Su, M. J., Patel, A. G., Karlstrom, A., Gritsch, S., Nomura, M., Waghray, A., … Regev, A. (2020). A single-cell and single-nucleus RNA-Seq toolbox for fresh and frozen human tumors. *Nature Medicine, 26(5)*: 792–802. *** These authors contributed equally to this work**.
    d. Rozenblatt-Rosen, O., Regev, A., Oberdoerffer, P., Nawy, T., Hupalowska, A., Rood, J. E., **Ashenberg, O.**, Cerami, E., Coffey, R. J., Demir, E., Ding, L., Esplin, E. D., Ford, J. M., Goecks, J., Ghosh, S., Gray, J. W., Guinney, J., Hanlon, S. E., Hughes, S. K., Hwang, E. S., … Human Tumor Atlas Network (2020). The Human Tumor Atlas Network: Charting Tumor Transitions across Space and Time at Single-Cell Resolution. *Cell, 181(2)*: 236–249.

2. My other research focus areas are single-cell analyses of immune responses during homeostasis and disease (infection, autoimmunity, aging) and the development of new analysis tools and pipelines for single cell and single nucleus RNA-Seq. I also recently designed and ran a *Cancer Immunotherapy Data Science Grand Challenge*, which registered over 1000 individual participants and spurred the development of innovative algorithms for modeling single-cell perturbation responses in T cells.
    a. Chen, X., Hwang, H. S., Li, B., Zhao, Y., Ghosh, K., Deng, L., ... & **Ashenberg, O.**, Graham, D.B., Xavier, R. J. (2025). Nuclear receptor coregulator NRIP1 R448G modulates T cell gut homing to control intestinal inflammation. *Proceedings of the National Academy of Sciences*, *122*(38), e2508269122.

b. Dania Zhivaki, D., Kennedy, S. N.*, Park, J.*, … & **Ashenberg, O.**, Xavier, R. J., Kagan, J. C. (2024). Correction of age-associated defects in dendritic cell enables CD4 + T cells to eradicate tumors in the elderly. *Cell, 187(15)*, 3888-3903.
c. Emont, M. P…, **Ashenberg, O.**, Regev, A., Tsai, L. T., Rosen, E. D. (2022). A single-cell atlas of human and mouse white adipose tissue. Nature, 926-933.
d. Delorey, T. M..., **Ashenberg, O.***, Porter, C.*, Li, B.*, Shalek, A. K.*, Villani A.*, Rozenblatt-Rosen, O.*, Regev, A.* (2021). COVID-19 tissue atlases reveal SARS-CoV-2 pathology and cellular targets. Nature, 1-32. *** These authors jointly supervised this work.**
e. Li, B., Gould, J., Yang, Y., Sarkizova, S., Tabaka, M., **Ashenberg, O.**, Rosen, Y., Slyper, M., Kowalczyk, M.S., Villani, A.C., Tickle, T., Hacohen, N., Rozenblatt-Rosen, O., & Regev, A. (2020). Cumulus: a cloud-based data analysis framework for large-scale single-cell and single-nucleus RNA-seq. *Nature Methods*, *17*: 793–798.

3. In my postdoctoral research, I studied how the influenza virus could adapt to the immune system of a new host. This is a critical step in cross-species transmission of viruses, such as the introduction of avian influenza into humans. I developed a novel and massively parallel approach to map how all mutations to a viral protein affect recognition by antiviral host restriction factors. I used this approach to comprehensively understand the ways in which influenza virus could evolve to escape recognition by the human antiviral protein MxA, an important barrier to cross-species transmission.
    a. Phillips, A. M., Ponomarenko, A. I., Chen, K., **Ashenberg, O.**, Miao, J., McHugh, S. M., Butty, V. L., Whittaker, C. A., Moore, C. L., Bloom, J. D., Lin, Y. S., Shoulders, M. D. (2018). Destabilized adaptive influenza variants critical for innate immune system escape are potentiated by host chaperones. *PLoS Biol* 6(9), e3000008.
    b. **Ashenberg, O.**, Padmakumar, J., Doud, M. B., & Bloom, J. (2017). Deep mutational scanning identifies sites in influenza nucleoprotein that affect viral inhibition by MxA. *PLoS Path, 13*(3), e1006288.
    c. Doud, M. B. *, **Ashenberg, O.***, & Bloom, J. D. (2015). Site-specific amino-acid preferences are mostly conserved in two closely related protein homologs. *Molecular Biology and Evolution*, *32*(11): 2944-2960. *** These authors contributed equally to this work**.
    d. **Ashenberg, O.**, Gong, L. I., & Bloom, J. D. (2013). Mutational effects on stability are largely conserved during protein evolution. *Proceedings of the National Academy of Sciences*, *110*(52), 21071-21076.

4. In my graduate research, I studied the evolution of protein-protein interactions in both bacterial and eukaryotic signaling proteins. I found that sequence analyses of these proteins' evolutionary records could identify the molecular pathways by which new protein interactions evolve.
    a. Reinke, A. W., Baek, J., **Ashenberg, O.**, & Keating, A. E. (2013). Networks of bZIP protein-protein interactions diversified over a billion years of evolution. *Science*, *340*(6133), 730-734.
    b. **Ashenberg, O.**, Keating, A. E., & Laub, M. T. (2013). Helix bundle loops determine whether histidine kinases autophosphorylate in cis or in trans. *Journal of Molecular Biology*, *425*(7), 1198-1209.
    c. Capra, E. J., Perchuk, B. S., **Ashenberg, O.**, Seid, C. A., Snow, H. R., Skerker, J. M., & Laub, M. T. (2012). Spatial tethering of kinases to their substrates relaxes evolutionary constraints on specificity. *Molecular Microbiology*, *86*(6), 1393-1403.
    d. **Ashenberg, O.**, Rozen-Gagnon, K., Laub, M. T., & Keating, A. E. (2011). Determinants of homodimerization specificity in histidine kinases. *Journal of Molecular Biology*, *413*(1), 222-235.