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Jonathan Weissman, Ph.D., studies how cells ensure that proteins fold into their correct shape, as well as the role of protein misfolding in disease and normal physiology. He is also widely recognized for building innovative tools for broadly exploring organizational principles of biological systems. These include ribosome profiling, which globally monitors protein translation, and CRISPRi/a for controlling the expression of human genes and rewiring the epigenome.

Dr. Weissman is a professor at the University of California San Francisco and an Investigator at the Howard Hughes Medical Institute. He is a member of the National Academy of Sciences, a member of the Scientific Advisory Board for Amgen, co-director of the Innovative Genome Initiative of Berkeley and UCSF, and a member of the President's Advisory Group for the Chan-Zuckerberg Biohub.

Dr. Weissman has received numerous awards including the Beverly and Raymond Sackler International Prize in Biophysics (2008), The Keith Porter Award Lecture from the American Society of Cell Biology (2015) and the National Academy Science Award for Scientific Discovery (2015).

Abstract: Manifold Destiny: Exploring Genetic Interactions in High Dimensions Through Massively Parallel Single Cell RNA-seq

A major principle that has emerged from modern genomic and gene expression studies is that the complexity of cell types in multicellular organisms is driven not by a large increase in gene number but instead by the combinatorial expression of a surprisingly small number of components. This is possible because specific combinations of genes exhibit emergent properties when functioning together, enabling the generation of many diverse cell types and behaviors. Understanding such genetic interactions has important practical and theoretical applications. For example, they can reveal synthetic lethal vulnerabilities in tumors, identify suppressors of inherited and acquired disorders, guide the design of cocktails of genes to drive trans-differentiation between cell types, inform the search for missing inheritance in genetic studies of complex traits, and enable systematic approaches to define gene function in an objective and principled manner. Defining how genes interact is thus a central challenge of the post-genomic era.

The combinatorial explosion of possible genetic interactions (GIs), however, has necessitated the use of scalar interaction readouts (e.g. growth) that conflate diverse outcomes. I will present our work developing an analytical framework for interpreting manifolds constructed from high-dimensional interaction phenotypes. We applied this framework to rich phenotypes obtained by Perturb-seq (single-cell RNA-seq pooled CRISPR screens) profiling of strong GIs mined from a growth-based, gain-of-function GI map. Exploration of this manifold enabled ordering of regulatory pathways, classification of GIs in a principled manner (e.g. identifying true suppressors), and mechanistic elucidation of synthetic lethal GIs, including an unexpected synergy between CBL and CNN1 driving erythroid differentiation. Finally, we applied recommender system machine learning to predict interactions, facilitating exploration of vastly larger GI manifolds. We expect the conceptual and computational frameworks presented here will be broadly applicable to genetic interactions obtained via other rich phenotyping approaches (e.g. proteomics, imaging) and methods of perturbation (e.g. knockdown, knockout, mutagenesis).