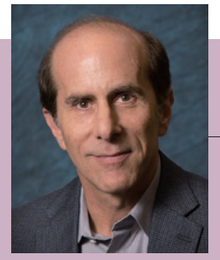

Kenneth S. ZARET

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Please replace [at sign] with @.

Research Interests

Transcription factor-chromatin interactions, heterochromatin, cell reprogramming,

Education

1982	PhD, Biophysics, University of Rochester Medical School, Rochester, NY
1982-1985	Postdoctoral fellowship, Biochemistry and Biophysics, University of California, San Francisco. CA

Professional Career

1986- 1999	Professor, Cell, Molecular, and Developmental Biology, Brown University, RI
1999 - 2009	Senior Member, Program Leader, Cell and Dev. Biology Program, Fox Chase Cancer Ctr., PA
2009 - present	Professor and Director, IRM, Perelman School of Medicine, University of Pennsylvania, PA

Scientific Activities

1986 - present	Signaling control of cell fate in embryonic development, cell reprogramming
1993 - present	Discovery and mechanism of action of pioneer transcription factors
2012 - present	Biophysical methods, proteomics to understand compacted heterochromatin chromatin
2017 - present	Single-molecule-tracking to understand how transcription factors scan genomic chromatin

Honors

2002	Hans Popper Basic Science Award, Amer. Assoc. for the Study of Liver Diseases, ALF
2007	Elected as a Fellow of the American Assoc. for the Adv. of Science
2017	Stanley N. Cohen Biomedical Research Award, Univ. Penn.

Publications

1. Zaret, K.S. (2020) Pioneer transcription factors initiating gene network changes. **Annual Review of Genetics**, (e-pub: https://doi.org/10.1146/annurev-genet-030220-015007).

2. Iwafuchi, M., Cuesta, I., Donahue, G, Takenaka, N. Osipovich, A.B., Magnuson, M. A., Roder, H., Seeholzer, S.H., Santisteban, P., and Zaret, K.S. (2020) Gene network transitions in embryos depend upon interactions between a pioneer transcription factor and core histones. **Nature Genetics 52**, 418-427. PMID:32203463

3. Lerner, J., Gomez-Garcia, P.A., McCarthy, R., Liu, Z., Lakadamyali, M., and Zaret, K.S. (2020) Two-parameter mobility assessments discriminate diverse regulatory factors behaviors in chromatin. **Molecular Cell 79**, 418-5427. PMID: 32574554

Two-Parameter, Single-Molecule-Tracking Assessments Discriminate Diverse Regulatory Factor Behaviors in Chromatin

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Our laboratory is interested in the ways that transcription factors initiate cell fate changes in embryonic development, cell reprogramming, and human diseases such as cancer. We discovered that a certain class of gene regulatory proteins, which we called "pioneer transcription factors," initiate cell fate changes by their ability to target DNA sequences that are wrapped on a nucleosome at silent genes in cellular chromatin [1]. The initial targeting of nucleosomal DNA by a pioneer factor causes an exposure of the underlying nucleosome [2], thus allowing cooperating transcription factors, co-regulators, and ATP-dependent nucleosome remodelers to access the DNA and activate the targeted gene. Yet recent studies have shown that silent genes can exist in various states of compaction in chromatin, and pioneer factors have differential access to different types of silenced chromatin. To better understand these issues, our laboratory employed HALO-tags on diverse chromosomal proteins and transcription factors, which enabled single-molecule-tracking (SMT) of the individual molecules in real time, as the molecules diffuse in, or bind to, different chromatin domains in the nucleus of living cells. We began by using SMT of core histone proteins and quantified two parameters of molecular movement tracks over millisecond time scales [3]. We plotted the radius of confinement, which estimates the area in which the molecule performs its confined motions, against the average displacement, representing the average distance between subsequent steps in a motion track, over time. The two parameters, though generally positively correlated, present deviations that resolve five mobility types for core histones with distinct subnuclear localizations. As expected, the mobility of diverse heterochromatin proteins correlates with lower mobility chromatin, with notable differences that relate to particular biochemical features of the proteins. Upon assessing the mobility of diverse transcription factors, we found that pioneer factors with nucleosome binding ability can access the lowest mobility chromatin domains. Using well-defined mutations of the pioneer factor FOXA1, we found that nonspecific DNA/nucleosome binding and histone interactions are essential for scanning compacted chromatin. Our two-parameter SMT approach reveals how gene regulatory proteins scan the genome during cell fate changes.

References

[1] Zaret, K.S. (2020) Pioneer transcription factors initiating gene network changes. **Annual Review of Genetics**, (e-pub: https://doi.org/10.1146/annurev-genet-030220-015007).

[2] Iwafuchi, M., et al. (2020) Gene network transitions in embryos depend upon interactions between a pioneer transcription factor and core histones. **Nature Genetics 52**, 418-427. PMID:32203463

[3] Lerner, J., Gomez-Garcia, P.A., McCarthy, R., Liu, Z., Lakadamyali, M., and Zaret, K.S. (2020) Two-parameter mobility assessments discriminate diverse regulatory factors behaviors in chromatin. **Molecular Cell 79**, 418-5427. PMID: 32574554