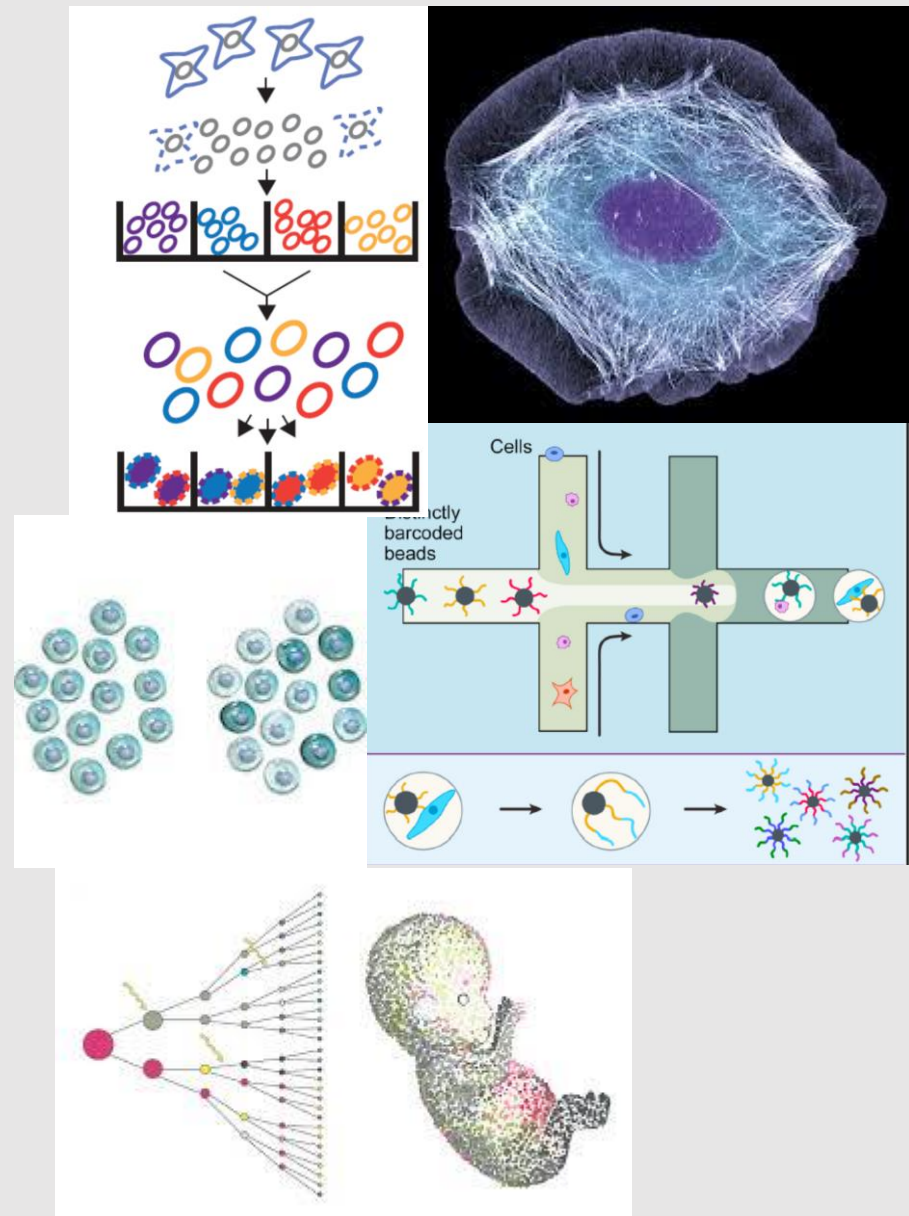




The Human Cell Atlas

Elizabeth Wilder, Ph.D.
Director, Office of Strategic Coordination

The Human Cell Atlas

- Concept encompasses ideas variably expressed by participants in Strategic Planning activities and through concepts provided by ICs
 - Single cell analysis to define populations within a tissue
 - In situ analyses to distinguish functions of cells that otherwise appear similar
 - Analyses to define intercellular interactions within a given tissue
 - Genomic analyses to define somatic mosaicism and its impact on cellular function
 - Technology development to enable these types of studies
- Our challenge: To determine whether the varied ideas are worth further planning and to envision the data that would have the highest impact



WHERE TO FOCUS?



Single-cell sequencing-based technologies will revolutionize whole-organism science

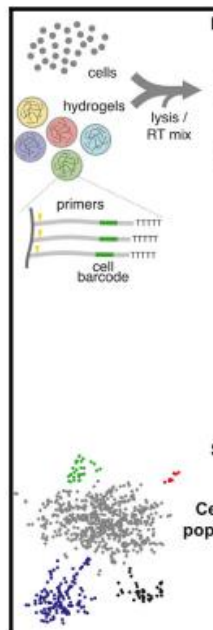
Ehud Shapiro^{1,2}, Tamir Biezuner^{1,2} and Sten Linnarsson³

Abstract | The unabated progress in next-generation sequencing technologies is fostering a wave of new genomics, epigenomics, transcriptomics and proteomics technologies. These sequencing-based technologies are increasingly being targeted to individual cells, which will allow many new and longstanding questions to be addressed. For example, single-cell genomics will help to uncover cell lineage relationships; single-cell transcriptomics will supplant the coarse notion of marker-based cell types; and single-cell epigenomics and proteomics will allow the functional states of individual cells to be analysed. These technologies will become integrated within a decade or so, enabling high-throughput, multi-dimensional analyses of individual cells that will produce detailed knowledge of the cell lineage trees of higher organisms, including humans. Such studies will have important implications for both basic biological research and medicine.

Cell

Droplet Based
Applied to

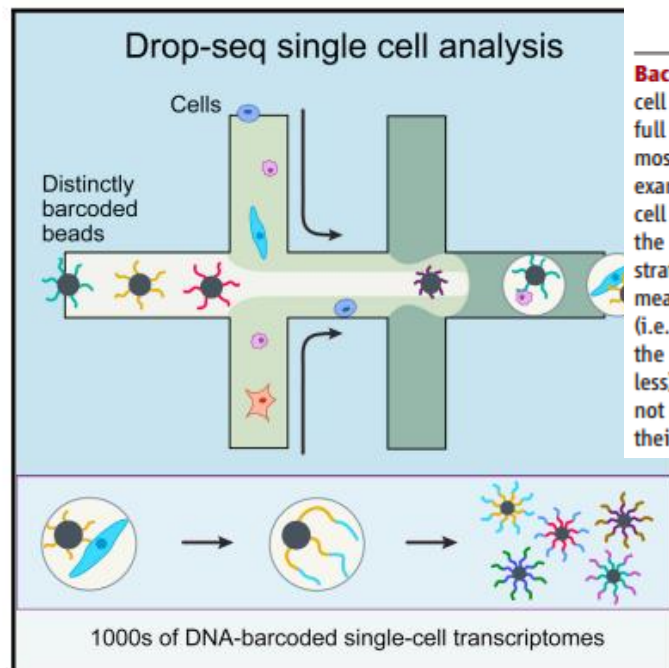
Graphical Abstract



Cell

Highly Parallel Genome-wide
Individual Cells Using Nanoliter

Graphical Abstract



Resource

Resource

REVIEW SUMMARY

Single-Cell Metabolomics: Analytical and Biological Perspectives

R. Zenobi

Background: In recent years, there has been a surge in cell genomics, transcriptomics, proteomics, and metabolomics. A full complement of small-molecule metabolites from most interesting potential application of single-cell metabolomics is expected to have an impact on the development of drug resistance; more general strategies for coping with chemical or environmental measurements, metabolomics provides a more immediate (i.e., of the phenotype) of a cell, but is arguably all the metabolome can dynamically react to the environment (i.e., because of the large structural diversity and it is not possible to amplify metabolites, and because of their normal function).

Applying this analysis to cells in mouse retinal tissue revealed transcriptionally distinct cell populations along with molecular markers of each type.

EPIGENETICS

Multiplex single-cell profiling of chromatin accessibility by combinatorial cellular indexing

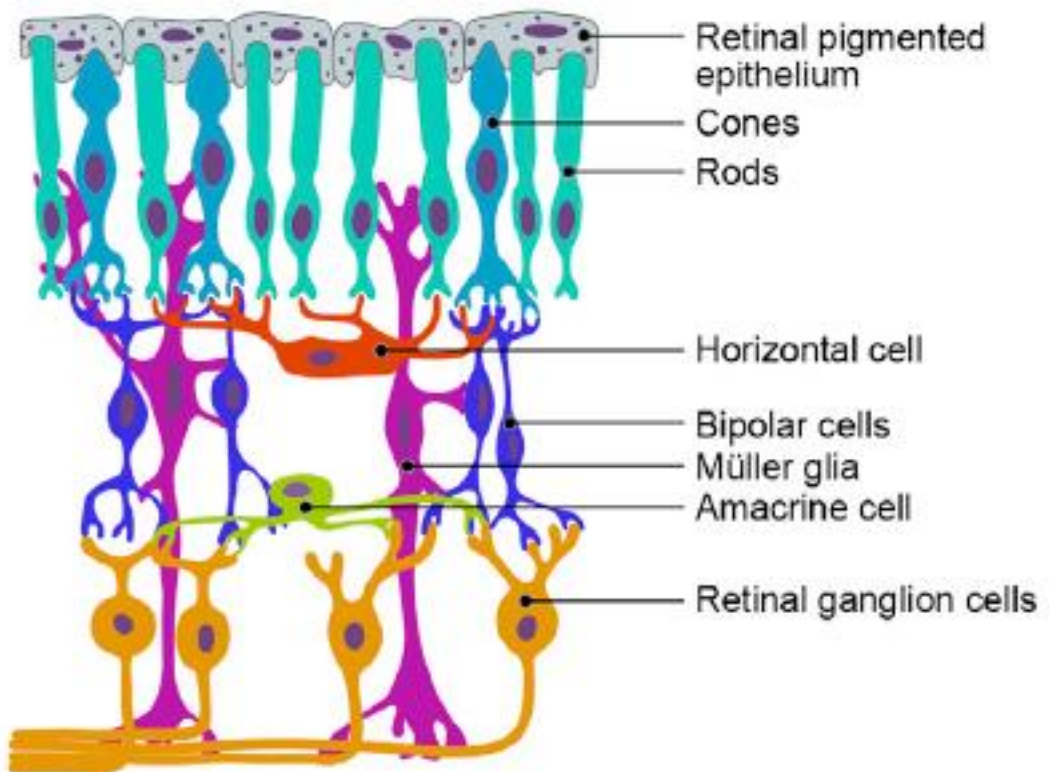
Darren A. Cusanovich,¹ Riza Daza,¹ Andrew Adey,² Hannah A. Pliner,¹ Lena Christiansen,³ Kevin L. Gunderson,³ Frank J. Steemers,³ Cole Trapnell,¹ Jay Shendure^{1,4}

Technical advances in data sets with single-cell epigenome has enabled methods scale to chromatin access for compartment profiles from microbasis of chromatin regulated chromatin within cell types human cell atlas

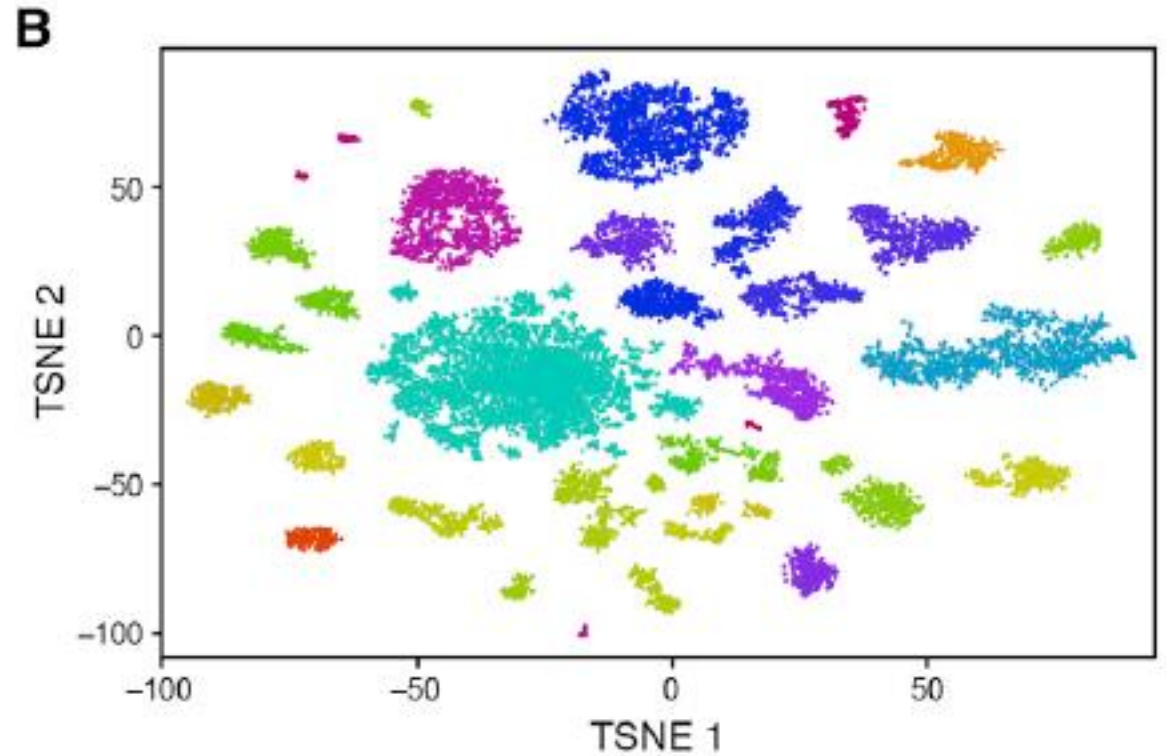
Highly Multiplexed Subcellular RNA Sequencing in Situ

Je Hyuk Lee,^{1,2,4,†} Evan R. Daugherty,^{1,2,4,*} Jonathan Scheiman,^{1,2} Reza Kalhor,² Joyce L. Yang,² Thomas C. Ferrante,¹ Richard Terry,¹ Sauveur S. F. Jeanty,¹ Chao Li,¹ Ryoji Amamoto,³ Derek T. Peters,³ Brian M. Turczyk,¹ Adam H. Marblestone,^{1,2} Samuel A. Inverso,¹ Amy Bernard,⁵ Prashant Mali,² Xavier Rios,² John Aach,² George M. Church^{1,2,†}

Understanding the spatial organization of gene expression with single-nucleotide resolution requires localizing the sequences of expressed RNA transcripts within a cell in situ. Here, we describe fluorescent in situ RNA sequencing (FISSEQ), in which stably cross-linked complementary DNA (cDNA) amplicons are sequenced within a biological sample. Using 30-base reads from 8102 genes in situ, we examined RNA expression and localization in human primary fibroblasts with a simulated wound-healing assay. FISSEQ is compatible with tissue sections and whole-mount embryos and reduces the limitations of optical resolution and noisy signals on single-molecule detection. Our platform enables massively parallel detection of genetic elements, including gene transcripts and molecular barcodes, and can be used to investigate cellular phenotype, gene regulation, and environment in situ.



Major cell types of retina



39 distinct retinal cell populations

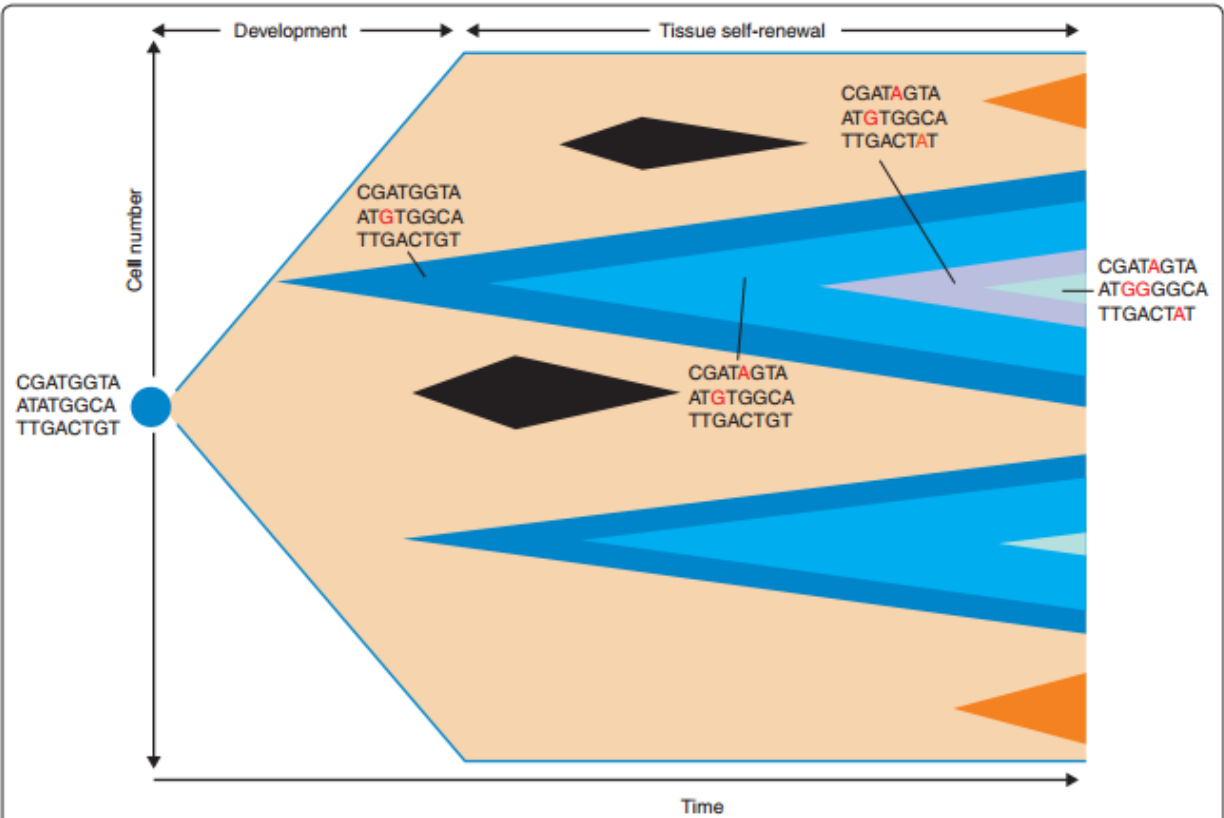


Figure 1. A schematic representation of the effects of somatic mutations at different phases of development and tissue renewal. Life starts from a single cell, a fertilized egg (blue circle). A complete organism, that is a human, is formed from this cell by many cell divisions. Novel somatic mutations can occur with each cell division. The diagram shows how such mutations are passed on to daughter cells as the organism develops: a mutation may undergo clonal expansion during tissue renewal. If the somatic mutation occurs late (brown clones), the mutation will be found in only a small compartment of the body, that is, it is likely to be confined to one organ. If the mutation occurs very early in development - for example, during embryogenesis (dark blue clones) - it is likely to occur in different organs. Successive mutations, which can then establish organismal cell lineage trees, can occur in cells derived from those that underwent an early mutation (clones in lighter blue color within the dark blue clone). The serial acquisition of novel mutations is shown as an example for the first series of blue clones (red bases). Some mutations may be disadvantageous and go extinct (black clones). (Image adapted in part from [6].)

Single-Cell, Genome-wide Sequencing Identifies Clonal Somatic Copy-Number Variation in the Human Brain

Xuyu Cai,^{1,2,3,4,6} Gilad D. Evrony,^{1,2,3,4} Hillel S. Lehmann,^{1,2,3} Princess C. Elhosary,^{1,2,3} Bhaven K. Mehta,^{1,2,3} Annapurna Poduri,^{1,2,3,5} and Christopher A. Walsh^{1,2,3,4,*}
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<http://dx.doi.org/10.1016/j.celrep.2014.07.043>
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REVIEW

Somatic mutation in cancer and normal cells

Iñigo Martincorena¹ and Peter J. Campbell^{1,2*}

Spontaneously occurring mutations accumulate in somatic cells throughout a person's lifetime. The majority of these mutations do not have a noticeable effect, but some can alter key cellular functions. Early somatic mutations can cause developmental disorders, whereas the progressive accumulation of mutations throughout life can lead to cancer and contribute to aging. Genome sequencing has revolutionized our understanding of somatic mutation in cancer, providing a detailed view of the mutational processes and genes that drive cancer. Yet, fundamental gaps remain in our knowledge of how normal cells evolve into cancer cells. We briefly summarize a number of the lessons learned over 5 years of cancer genome sequencing and discuss their implications for our understanding of cancer progression and aging.

“... Systematic sequencing studies of normal tissues are needed to clarify this debate. Unfortunately, such studies are still technically challenging, as the error rate of single-cell sequencing remains too high for accurate detection of de novo mutations, and only clonally expanded mutations can be reliably detected with current technologies. Despite these limitations, sequencing ...”

Goals for a Human Cell Atlas Program:

- Catalog human cell types
 - Transcriptional profiling for many tissues; use of in situ methods, epigenomics and metabolomics for subsets?
 - Characterize somatic mosaicism?
 - Compare samples over lifespan, compare healthy versus disease versus treated/exposed?
 - SPECIFIC GOALS AND BOUNDARIES TO BE DEFINED BY FURTHER PLANNING
- Data coordination
 - Data to be rapidly and publicly available
- Technology development
 - To enhance capacity for analysis as the program moves forward

Expected Deliverables and Impact:

- New paradigms for tissue structure and function
 - Changing cell populations over the lifespan
 - Definition of cellular impact of exposures
 - Cellular function in health and disease
 - New, more specific drug targets
- Hypothesis generating
 - Data to be mined for continued analysis via investigator-initiated research
- Technology development
 - New technologies expected to be broadly enabling