

CLAIMS

WHAT IS CLAIMED IS:

1. A method of multiomic single-cell analysis comprising:
 - a. isolating a single cell from a population of cells;
 - b. sequencing a cDNA library comprising polynucleotides amplified from mRNA transcripts from the single cell; and
 - c. sequencing a genome of the single cell, wherein sequencing the genome comprises:
 - i. contacting the genome with at least one amplification primer, at least one nucleic acid polymerase, and a mixture of nucleotides, wherein the mixture of nucleotides comprises at least one terminator nucleotide which terminates nucleic acid replication by the polymerase, and
 - ii. amplifying at least some of the genome to generate a plurality of terminated amplification products, wherein the replication proceeds by strand displacement replication;
 - iii. ligating the molecules obtained in step (ii) to adaptors, thereby generating a genomic DNA library; and
 - iv. sequencing the genomic DNA library.
2. The method of claim 1, wherein the mRNA transcripts comprise polyadenylated mRNA transcripts.
3. The method of claim 1, wherein the mRNA transcripts do not comprise polyadenylated mRNA transcripts.
4. The method of claim 1, wherein sequencing a cDNA library comprises amplification of mRNA transcripts with template-switching primers.
5. The method of claim 1, wherein at least some of the polynucleotides of the cDNA library comprise a barcode.
6. The method of claim 5, wherein the barcode comprises a cell barcode or a sample barcode.
7. The method of claim 1, wherein the cDNA library and the genomic DNA library are pooled prior to sequencing.
8. The method of claim 1, wherein the single cell is a primary cell.
9. The method of claim 1, wherein the single cells originate from liver, skin, kidney, blood, or lung.
10. The method of claim 1, wherein the single cell is a cancer cell, neuron, glial cell, or fetal cell.

11. The method of claim 1, wherein the single cell is isolated by flow cytometry.
12. The method of claim 1, wherein the method further comprises removing at least one terminator nucleotide from the terminated amplification products.
13. The method of claim 1, wherein the plurality of terminated amplification products comprise an average of 1000-2000 bases in length.
14. The method of claim 1, wherein the plurality of terminated amplification products are 250-1500 bases in length.
15. The method of claim 1, wherein the plurality of terminated amplification products comprise at least 97% of the single cell's genome.
16. The method of claim 1, wherein at least some of the amplification products comprise a cell barcode or a sample barcode.
17. The method of claim 1, wherein sequencing a cDNA library comprises cystolic lysis of the single cell, and reverse transcription.
18. The method of claim 1, wherein the mRNA transcripts are amplified via template-switching reverse transcription.
19. The method of claim 1, wherein the cDNA library comprises at least 10,000 genes.
20. The method of claim 1, wherein sequencing a genome of the single cell further comprises nuclear lysis of the single cell.
21. The method of claim 1, wherein the method further comprises an additional amplification step using PCR.
22. The method of claim 1, wherein at least one mutation is identified in the genome of the cell, wherein the mutation differs from a corresponding position in a reference sequence.
23. The method of claim 1, wherein the at least one mutation occurs in less than 1% of the population of cells.
24. The method of claim 1, wherein the at least one mutation occurs in no more than 0.1% of the population of cells.
25. The method of claim 1, wherein the at least one mutation occurs in no more than 0.001% of the population of cells.
26. The method of claim 1, wherein the at least one mutation occurs in no more than 1% of the amplification product sequences.
27. The method of claim 1, wherein the at least one mutation occurs in no more than 0.1% of the amplification product sequences.
28. The method of claim 1, wherein the at least one mutation occurs in no more than 0.001% of the amplification product sequences.

29. A method of multiomic single-cell analysis comprising:
- a. isolating a single cell from a population of cells;
 - b. identifying at least one protein on the surface of the single cell; and
 - c. sequencing a genome of the single cell, wherein sequencing the genome comprises:
 - i. contacting the genome with at least one amplification primer, at least one nucleic acid polymerase, and a mixture of nucleotides, wherein the mixture of nucleotides comprises at least one terminator nucleotide which terminates nucleic acid replication by the polymerase;
 - ii. amplifying at least some of the genome to generate a plurality of terminated amplification products, wherein the replication proceeds by strand displacement replication;
 - iii. ligating the molecules obtained in step (ii) to adaptors, thereby generating a genomic DNA library; and
 - iv. sequencing the genomic DNA library.
30. The method of claim 29, wherein identifying at least one protein on the cell surface comprises contacting the cell with a labeled antibody which binds to the at least one protein.
31. The method of claim 30, wherein the labeled antibody comprises at least one fluorescent label or mass-tag.
32. The method of claim 30, wherein the labeled antibody comprises at least one nucleic acid barcode.
33. A method of multiomic single-cell analysis comprising:
- a. isolating a single cell from a population of cells;
 - b. sequencing a genome of the single cell, wherein sequencing the genome of the cell comprises:
 - i. digesting the genome with a methylation-sensitive restriction enzyme to generate genomic fragments;
 - ii. contacting at least some of the genomic fragments with at least one amplification primer, at least one nucleic acid polymerase, and a mixture of nucleotides, wherein the mixture of nucleotides comprises at least one terminator nucleotide which terminates nucleic acid replication by the polymerase;
 - iii. amplifying at least some of the genome to generate a plurality of terminated amplification products, wherein the replication proceeds by strand displacement replication;

- iv. amplifying at least some of the genomic fragments with methylation-specific PCR;
- v. ligating the molecules obtained in steps (iii and iv) to adaptors, thereby generating a genomic DNA library and a methylome DNA library; and
- vi. sequencing the genomic DNA library and the methylome library.