a selective pressure of interest, such as but not limited to drug treatment, genomic engineering, and engraftment into a host.

[05] In an example, a method for screening cells for a trait is provided. The method may include: (a) obtaining a plurality of barcoded cells, wherein each barcoded cell includes a single, unique barcode, or barcode combinations; (b) performing a first sequencing of RNA and/or DNA on a subset of the plurality of barcoded cells; (c) culturing the plurality of barcoded cells in the presence of a selection pressure for a first period of time, thereby forming a first plurality of cells; (d) performing a second sequencing of RNA and/or DNA on a subset of the first plurality of cells; (e) culturing the first plurality of cells in the presence of the selection pressure for a second period of time, thereby forming a second plurality of cells; and (f) performing a third sequencing of RNA and/or DNA on at least a subset of the second plurality of cells. The method may also include: (g) determining the relative abundance of a barcode sequenced in the first sequencing, second sequencing, and/or third sequencing. In one aspect, the present disclosure refers to a method for screening cells for a trait, the method comprising:

(a) obtaining a plurality of barcoded cells, wherein each barcoded cell comprises a single, unique barcode;

(b) performing a first sequencing of RNA and/or DNA on a subset of the plurality of barcoded cells;

(c) culturing the plurality of barcoded cells in the presence of a selection pressure for a first period of time, thereby forming a first plurality of cells;

(d) performing a second sequencing of RNA and/or DNA on a subset of the first plurality of cells;

(e) culturing the first plurality of cells in the presence of the selection pressure for a second period of time, thereby forming a second plurality of cells;

(f) performing a third sequencing of RNA and/or DNA on at least a subset of the second plurality of cells; and

(g) determining a level of a barcode sequenced in the first sequencing, second sequencing, and/or third sequencing,

wherein steps (e) and (f) are repeated for one or more iterations thereby forming one or more subsequent pluralities of cells and thereby performing one or more subsequent sequencing on a subset of said pluralities of cells,

wherein step (g) further comprises determining levels of barcodes sequenced in the one or more subsequent sequencings;

wherein step (g) further comprises:

(i) assigning cells with barcodes enriched in the second plurality of cells and/or the one or more subsequent pluralities of cells as resistant clones;

(ii) assigning cells with barcodes depleted in the second plurality of cells and/or the one or more subsequent pluralities of cells as sensitive clones; and

(iii) determining a genetic mutation and/or a transcription program associated with at least one resistant clone and at least one sensitive clone;

wherein the plurality of barcoded cells had been expanded in culture prior to step (a), step (b) or step (c);

wherein the plurality of barcoded cells comprises a plurality of clonal populations, wherein each cell within a single clonal population comprises the same single, unique barcode; and

wherein the relative abundance of cells in each clonal population is:

(i) approximately equal to the number of cells in each other clonal population in the plurality of barcoded cells; or

(ii) determined relative to the number of cells comprising each barcode as determined in the first sequencing step.

[06] In another example, a method for screening cells for a response trait to a therapeutic agent is provided. The method may include: (a) obtaining a plurality of barcoded cells, wherein each barcoded cell comprises a single, unique barcode; (b) performing a first sequencing of RNA and/or DNA on a subset of the plurality of barcoded cells; (c) culturing the plurality of barcoded cells in the presence of the therapeutic agent for a first period of time, thereby forming a first plurality of cells; (d) performing a second sequencing of RNA and/or DNA on a subset of the first plurality of cells; (e) culturing the first plurality of cells with the therapeutic agent for a second period of time, thereby forming a second plurality of cells; and (f) performing a third sequencing of RNA and/or DNA on a subset of the second plurality of cells. The method may also include: (g) determining the relative abundance of a barcode sequenced in the first sequencing, second sequencing, and/or third sequencing. In one aspect, the present disclosure refers to a method for screening cells for a response trait to a therapeutic agent, the method comprising:

(a) obtaining a plurality of barcoded cells, wherein each barcoded cell comprises a single, unique barcode;
(b) performing a first sequencing of RNA and/or DNA on a subset of the plurality of barcoded cells;
(c) culturing the plurality of barcoded cells in the presence of the therapeutic agent for a first period of time, thereby forming a first plurality of cells;
(d) performing a second sequencing of RNA and/or DNA on a subset of the first plurality of cells;
(e) culturing the first plurality of cells with the therapeutic agent for a second period of time, thereby forming a second plurality of cells;
(f) performing a third sequencing of RNA and/or DNA on a subset of the second plurality of cells; and
(g) determining a level of a barcode sequenced in the first sequencing, second sequencing, and/or third sequencing,

wherein steps (e) and (f) are repeated for one or more iterations thereby forming one or more subsequent pluralities of cells and thereby performing one or more subsequent sequencing on a subset of said pluralities of cells,

wherein step (g) further comprises determining levels of barcodes sequenced in the one or more subsequent sequencings;

wherein step (g) further comprises:

(i) assigning cells with barcodes enriched in the second plurality of cells and/or the one or more subsequent pluralities of cells as resistant clones;

(ii) assigning cells with barcodes depleted in the second plurality of cells and/or the one or more subsequent pluralities of cells as sensitive clones; and

(iii) determining a genetic mutation and/or a transcription program associated with at least one resistant clone and at least one sensitive clone;

wherein the plurality of barcoded cells had been expanded in culture prior to step (a), step (b) or step (c);

wherein the plurality of barcoded cells comprises a plurality of clonal populations, wherein each cell within a single clonal population comprises the same single, unique barcode; and

wherein the relative abundance of cells in each clonal population is:

(i) approximately equal to the number of cells in each other clonal population in the plurality of barcoded cells; or

(ii) determined relative to the number of cells comprising each barcode as determined in the first sequencing step.

[07] In another example is provided a method for comparing responses to selective pressures. The method may include: (a) obtaining a first plurality of barcoded cells, wherein each barcoded cell comprises a single, unique barcode; (b) obtaining a second plurality of barcoded cells that is substantially similar to the first plurality of barcoded cells; (c) performing a first sequencing of RNA and/or DNA from the first plurality of barcoded cells and/or the second plurality of barcoded cells; (d) culturing the first plurality of barcoded cells in the presence of a first selection pressure, thereby forming a first plurality of cells; (e) culturing the second plurality of barcoded cells in the presence of a second selection pressure,

thereby forming a second plurality of cells; (f) performing a second sequencing of RNA and/or DNA from the first plurality of cells and/or the second plurality of cells; (g) culturing the first plurality of cells in the presence of the first selection pressure, thereby forming a third plurality of cells; (h) culturing the second plurality of cells in the presence of the second selection pressure, thereby forming a fourth plurality of cells; and (i) performing a third sequencing of RNA and/or DNA from the third plurality of cells and/or the fourth plurality of cells. The method may also include: (j) determining the relative abundance of one or more barcodes sequenced in the first sequencing, second sequencing, and/or third sequencing. In one aspect, the present disclosure refers to a method for comparing responses to selective pressures, the method comprising:

(a) obtaining a first plurality of barcoded cells, wherein each barcoded cell comprises a single, unique barcode;

(b) obtaining a second plurality of barcoded cells that is substantially similar to the first plurality of barcoded cells;

(c) performing a first sequencing of RNA and/or DNA from the first plurality of barcoded cells and/or the second plurality of barcoded cells;

(d) culturing the first plurality of barcoded cells in the presence of a first selection pressure, thereby forming a first plurality of cells;

(e) culturing the second plurality of barcoded cells in the presence of a second selection pressure, thereby forming a second plurality of cells;

(f) performing a second sequencing of RNA and/or DNA from the first plurality of cells and/or the second plurality of cells;

(g) culturing the first plurality of cells in the presence of the first selection pressure, thereby forming a third plurality of cells;

(h) culturing the second plurality of cells in the presence of the second selection pressure, thereby forming a fourth plurality of cells;

(i) performing a third sequencing of RNA and/or DNA from the third plurality of cells and/or the fourth plurality of cells; and

(j) determining a level of one or more barcodes sequenced in the first sequencing, second sequencing, and/or third sequencing,

wherein steps (g) to (i) are repeated for one or more iterations, thereby forming one or more subsequent pluralities of cells and one or more subsequent sequencings,

wherein step (j) further comprises determining a level of one or more barcodes in the one or more subsequent sequencing steps;

wherein step (j) further comprises:

(i) assigning cells with barcodes enriched in the second plurality of cells, third plurality of cells and/or the one or more subsequent pluralities of cells as resistant clones;

(ii) assigning cells with barcodes depleted in the second plurality of cells, third plurality of cells and/or the one or more subsequent pluralities of cells as sensitive clones; and

(iii) determining a genetic mutation and/or a transcription program associated with at least one resistant clone and at least one sensitive clone;

wherein the first plurality of barcoded cells and the second plurality of barcoded cells comprise a plurality of clonal populations, wherein each cell within a single clonal population comprises the same single, unique barcode; and

wherein the relative abundance of cells in each clonal population is:

(i) approximately equal to the number of cells in each other clonal population in steps (a) and (b); or

(ii) determined relative to the number of cells comprising the barcode(s) as determined in the first sequencing step.

[08] In an example is provided method of screening cells for a trait in a cell. The method may include: (a) providing a mixture of cells comprising multiple clonal populations wherein each clonal population comprises an identifier that is unique to the respective clonal populations, and wherein initial genetic, transcriptomic, and/or proteomic information of at least one representative member of each clonal population is known; (b) culturing the mixture of cells in the presence of a first selective pressure for a first period of time, and at the end of the first period of time, obtaining second genetic, transcriptomic, and/or proteomic information for at least one member of a surviving clonal population from within the mixture of cells; (c) subjecting the mixture of cells that were subjected to the first selective pressure to a second selective pressure for a second period of time, and at the end of the second period of time, obtaining third genetic, transcriptomic, and/or proteomic information of at least one member of a surviving clonal population from within the mixture of cells; and (d) determining the relative abundance of each clonal population present in the final mixture of cells based upon the unique identifier for the clonal population. The method may also include (e) identifying an adaptive trait, wherein the adaptive trait is a genetic and/or proteomic trait present in or absent from a clonal population in the final mixture of cells. The method may also include (f) comparing information from the initial genetic, transcriptomic, and/or proteomic information, second genetic, transcriptomic, and/or proteomic information, and/or third genetic, transcriptomic, and/or proteomic information, and/or one or more subsequent genetic, transcriptomic, and/or proteomic information. The method may also include (g) comparing the initial genetic, transcriptomic, and/or proteomic information, second genetic, transcriptomic, and/or proteomic information, and/or third genetic, transcriptomic, and/or proteomic information, and/or one or more subsequent genetic, transcriptomic, and/or proteomic information to genetic, transcriptomic and/or proteomic

information of a different clonal population of cells having a different unique barcode that was subjected to the selective pressure.

[09] In another example, a method of identifying a cellular program that facilitates adaptation to a pressure is provided. The method may include: (a) transducing cells with a plurality of barcodes such that each cell contains a single, unique barcode, or barcode combinations; (b) expanding the cells in culture to create a starting cell pool of clones of cells containing each barcode; (c) obtaining first genetic, transcriptomic, and/or proteomic information from a first subset of the starting cell pool; (d) culturing a second subset of the starting cell pool in the presence of a selective pressure to expand the starting cell pool and form an intermediate cell pool; (e) obtaining second genetic, transcriptomic, and/or proteomic information from a first subset of the intermediate cell pool; (f) continuing to culture a second subset of the intermediate cell pool in the presence of the selective pressure to expand the intermediate cell pool and form a final cell pool; (g) obtaining third genetic, transcriptomic, and/or proteomic information from at least a subset of the final cell pool; and (h) quantifying a level of each barcode in the final cell pool, intermediate cell pool, and/or starting cell pool. The method may also include: (i) assigning cells with barcodes enriched in the final cell pool as winning clones and/or assigning cells with barcodes depleted in the final cell pool as losing clones. The method may also include: (j) determining a genetic mutation, transcription program, and/or protein expression associated with at least one winning clone and/or at least one losing clone. In one aspect, the present disclosure refers to a method of identifying a cellular program that facilitates adaptation to a pressure, comprising:

a. transducing cells with a plurality of barcodes such that each cell contains a single, unique barcode;
b. expanding the cells in culture to create a starting cell pool of clones of cells containing each barcode;
c. obtaining first genetic, transcriptomic, and/or proteomic information from a first subset of the starting cell pool;
d. culturing a second subset of the starting cell pool in the presence of a selective pressure to expand the starting cell pool and form an intermediate cell pool;
e. obtaining second genetic, transcriptomic, and/or proteomic information from a first subset of the intermediate cell pool;
f. continuing to culture a second subset of the intermediate cell pool in the presence of the selective pressure to expand the intermediate cell pool and form a final cell pool;
g. obtaining third genetic, transcriptomic, and/or proteomic information from at least a subset of the final cell pool;
h. quantifying a level of each barcode in the final cell pool, intermediate cell pool, and/or starting cell pool;
i. assigning cells with barcodes enriched in the final cell pool as resistant clones and/or assigning cells with barcodes depleted in the final cell pool as sensitive clones; and
j. determining a genetic mutation, transcription program, and/or protein expression associated with at least one resistant clone and/or at least one sensitive clone;

wherein approximately equal numbers of clones of cells containing each barcode are used to create the starting cell pool or the numbers of clones of cells are normalized relative to the numbers of cells comprising each barcode as obtained in step (c),

wherein steps (d) and (e) are repeated for one or more iterations thereby obtaining one or more additional intermediate cell pools and one or more additional intermediate genetic, transcriptomic, and/or proteomic information; and

wherein step (h) further comprises quantifying a level of each barcode in the one or more additional intermediate cell pools.

BRIEF DESCRIPTION OF THE DRAWINGS

[010] FIG. 1 is a schematic showing an example overview of longitudinal transcriptomics of barcoded cells (bottom), which combines traditional endpoint studies (top left) with clonal analysis (top right) to allow analysis of response and adaptation of individual cells/clones over time in response to a selective pressure.

[011] FIG. 2 is a schematic showing an example of expression-based high complexity barcoding coupled to single cell analysis for analysis of sensitivity and resistance to a drug treatment (or other selective pressure) over time.

[012] FIG. 3 illustrates an example scRNA-seq compatible barcoding construct with the barcode insertion site, T2A (self-cleaving peptide), and EGFP and puromycin selection genes

WHAT IS CLAIMED IS:

1. A method for screening cells for a trait, the method comprising:

(a) obtaining a plurality of barcoded cells, wherein each barcoded cell comprises a single, unique barcode;

(b) performing a first sequencing of RNA and/or DNA on a subset of the plurality of barcoded cells;

(c) culturing the plurality of barcoded cells in the presence of a selection pressure for a first period of time, thereby forming a first plurality of cells;

(d) performing a second sequencing of RNA and/or DNA on a subset of the first plurality of cells;

(e) culturing the first plurality of cells in the presence of the selection pressure for a second period of time, thereby forming a second plurality of cells;

(f) performing a third sequencing of RNA and/or DNA on at least a subset of the second plurality of cells; and

(g) determining a level of a barcode sequenced in the first sequencing, second sequencing, and/or third sequencing,

wherein steps (e) and (f) are repeated for one or more iterations thereby forming one or more subsequent pluralities of cells and thereby performing one or more subsequent sequencing on a subset of said pluralities of cells,

wherein step (g) further comprises determining levels of barcodes sequenced in the one or more subsequent sequencings;

wherein step (g) further comprises:

(i) assigning cells with barcodes enriched in the second plurality of cells and/or the one or more subsequent pluralities of cells as resistant clones;

(ii) assigning cells with barcodes depleted in the second plurality of cells and/or the one or more subsequent pluralities of cells as sensitive clones; and

(iii) determining a genetic mutation and/or a transcription program associated with at least one resistant clone and at least one sensitive clone;

wherein the plurality of barcoded cells had been expanded in culture prior to step (a), step (b) or step (c);

wherein the plurality of barcoded cells comprises a plurality of clonal populations, wherein each cell within a single clonal population comprises the same single, unique barcode; and

wherein the relative abundance of cells in each clonal population is:

(i) approximately equal to the number of cells in each other clonal population in the plurality of barcoded cells; or

(ii) determined relative to the number of cells comprising each barcode as determined in the first sequencing step.

2. The method of claim 1, wherein the selective pressure comprises treatment with a therapeutic agent, contact with a contaminant, genomic engineering, engraftment into a host, a culture condition, a growth condition, contact with a stimulus, or contact with other cells.

3. A method for screening cells for a response trait to a therapeutic agent, the method comprising:

(a) obtaining a plurality of barcoded cells, wherein each barcoded cell comprises a single, unique barcode;

(b) performing a first sequencing of RNA and/or DNA on a subset of the plurality of barcoded cells;

(c) culturing the plurality of barcoded cells in the presence of the therapeutic agent for a first period of time, thereby forming a first plurality of cells;

(d) performing a second sequencing of RNA and/or DNA on a subset of the first plurality of cells;

(e) culturing the first plurality of cells with the therapeutic agent for a second period of time, thereby forming a second plurality of cells;

(f) performing a third sequencing of RNA and/or DNA on a subset of the second plurality of cells; and

(g) determining a level of a barcode sequenced in the first sequencing, second sequencing, and/or third sequencing,

wherein steps (e) and (f) are repeated for one or more iterations thereby forming one or more subsequent pluralities of cells and thereby performing one or more subsequent sequencing on a subset of said pluralities of cells,

wherein step (g) further comprises determining levels of barcodes sequenced in the one or more subsequent sequencings;

wherein step (g) further comprises:

(i) assigning cells with barcodes enriched in the second plurality of cells and/or the one or more subsequent pluralities of cells as resistant clones;

(ii) assigning cells with barcodes depleted in the second plurality of cells and/or the one or more subsequent pluralities of cells as sensitive clones; and

(iii) determining a genetic mutation and/or a transcription program associated with at least one resistant clone and at least one sensitive clone;

wherein the plurality of barcoded cells had been expanded in culture prior to step (a), step (b) or step (c);

wherein the plurality of barcoded cells comprises a plurality of clonal populations, wherein each cell within a single clonal population comprises the same single, unique barcode; and

wherein the relative abundance of cells in each clonal population is:

(i) approximately equal to the number of cells in each other clonal population in the plurality of barcoded cells; or

(ii) determined relative to the number of cells comprising each barcode as determined in the first sequencing step.

4. The method of any one of claims 1 to 3, wherein a level of two or more barcodes sequenced in the first sequencing, second sequencing, and/or third sequencing are determined or a barcode(s) that is enriched or depleted in the first plurality of cells and/or the second plurality of cells and/or one or more subsequent pluralities of cells are identified.

5. The method of claim 4, wherein the barcode(s) is enriched or depleted compared to:

(i) one or more other barcodes in the first plurality of cells and/or the second plurality of cells and/or one or more subsequent pluralities of cells; or

(ii) the amount of the barcode(s) in the plurality of barcoded cells.

6. The method of any one of claims 1 to 5 further comprising identifying one or more genes having higher levels of expression in cells comprising the enriched barcode(s).

7. The method of claim 6, wherein the identifying the one or more genes comprises:

(i) determining that the level of expression of at least one gene is higher in the first sequencing, second sequencing, and/or the third sequencing and/or one or more subsequent sequencings in the cells comprising the enriched barcode(s) compared to cells comprising a different barcode(s) that had a different level of enrichment or no enrichment;

(ii) identifying an adaptive trait based upon higher expression of the at least one gene;

(iii) identifying that the gene is involved in adaptation of the cell to the selection pressure or therapeutic agent based upon higher expression of the at least one gene;

(iv) determining the level of expression of at least one gene is lower in the first sequencing, second sequencing, and/or the third sequencing and/or one or more subsequent sequencings in the cells comprising the enriched barcode(s) compared to cells comprising a different barcode(s) that had a different level of enrichment or no enrichment;

(v) identifying an adaptive trait based upon lower expression of the at least one gene; and/or

(vi) determining that the gene is involved in adaptation of the cell to the selection pressure or therapeutic agent based upon lower expression of the at least one gene.

8. The method of any one of claims 1 to 7 further comprising:

(a) identifying a barcode(s) that is enriched in the first plurality of cells and/or the second plurality of cells and/or one or more subsequent pluralities of cells; and

(b) identifying from the first sequencing a first gene; a second gene; and/or a third gene having a higher level of expression in cells comprising the enriched barcode(s) than in cells comprising a barcode(s) that is not enriched in the first plurality of cells and/or the second plurality of cells and/or one or more subsequent pluralities of cells, such that the higher expression of the first gene; the second gene; and/or the third indicates that the first gene; the second gene; and/or the third gene is a candidate pre-existing trait for resistance or sensitivity to the selective pressure or therapeutic agent.

9. The method of claim 8, wherein the expression of the third gene is not higher in cells comprising a barcode(s) that is not enriched in the first plurality of cells and/or the second plurality of cells and/or one more subsequent pluralities of cells.

10. The method of any one of claims 1 to 9, further comprising:

(a) identifying a barcode(s) that is enriched in the first plurality of cells and/or the second plurality of cells and/or one more subsequent pluralities of cells; and

(b) identifying from the second sequencing and/or the third sequencing a fourth gene having a lower level of expression in cells comprising the enriched barcode(s) than in cells comprising a barcode(s) that is not enriched in the first plurality of cells and/or the second

plurality of cells and/or one or more subsequent pluralities of cells, such that the lower expression of the fourth gene indicates that the first gene is a candidate adaptive trait for resistance or sensitivity to the selective pressure or therapeutic agent.

11. The method of claim 10, wherein the expression of the fourth gene is not lower in cells comprising a barcode(s) that is not enriched in the first plurality of cells and/or the second plurality of cells.

12. The method of any one of claims 6 to 11, wherein the one or more genes comprises a gene set.

13. The method of any one of claims 1 to 12, wherein the unique barcode is integrated into the genome of the barcoded cell or is not integrated into the genome of the barcoded cell.

14. The method of any one of claims 1 to 13, wherein the first sequencing, second sequencing, and/or the third sequencing and/or one or more subsequent sequencings is performed using RNA-seq, DNA sequencing or epigenetic sequencing.

15. A method for comparing responses to selective pressures, the method comprising:

(a) obtaining a first plurality of barcoded cells, wherein each barcoded cell comprises a single, unique barcode;

(b) obtaining a second plurality of barcoded cells that is substantially similar to the first plurality of barcoded cells;

(c) performing a first sequencing of RNA and/or DNA from the first plurality of barcoded cells and/or the second plurality of barcoded cells;

(d) culturing the first plurality of barcoded cells in the presence of a first selection pressure, thereby forming a first plurality of cells;

(e) culturing the second plurality of barcoded cells in the presence of a second selection pressure, thereby forming a second plurality of cells;

(f) performing a second sequencing of RNA and/or DNA from the first plurality of cells and/or the second plurality of cells;

(g) culturing the first plurality of cells in the presence of the first selection pressure, thereby forming a third plurality of cells;

(h) culturing the second plurality of cells in the presence of the second selection pressure, thereby forming a fourth plurality of cells;

(i) performing a third sequencing of RNA and/or DNA from the third plurality of cells and/or the fourth plurality of cells; and

(j) determining a level of one or more barcodes sequenced in the first sequencing, second sequencing, and/or third sequencing,

wherein steps (g) to (i) are repeated for one or more iterations, thereby forming one or more subsequent pluralities of cells and one or more subsequent sequencings,

wherein step (j) further comprises determining a level of one or more barcodes in the one or more subsequent sequencing steps;

wherein step (j) further comprises:

(i) assigning cells with barcodes enriched in the second plurality of cells, third plurality of cells and/or the one or more subsequent pluralities of cells as resistant clones;

(ii) assigning cells with barcodes depleted in the second plurality of cells, third plurality of cells and/or the one or more subsequent pluralities of cells as sensitive clones; and

(iii) determining a genetic mutation and/or a transcription program associated with at least one resistant clone and at least one sensitive clone;

wherein the first plurality of barcoded cells and the second plurality of barcoded cells comprise a plurality of clonal populations, wherein each cell within a single clonal population comprises the same single, unique barcode; and

wherein the relative abundance of cells in each clonal population is:

(i) approximately equal to the number of cells in each other clonal population in steps (a) and (b); or

(ii) determined relative to the number of cells comprising the barcode(s) as determined in the first sequencing step.

16. The method of claim 15, wherein the single, unique barcode is a unique combination of barcodes.

17. The method of claim 15 or 16, further comprising identifying one or more genes having higher levels of expression in cells comprising the enriched barcode(s).

18. The method of any one of claims 15 to 17, further comprising determining a first level of expression of a gene in cells having a barcode(s) enriched or depleted in the first plurality of cells and/or third plurality of cells and/or one or more subsequent pluralities of cells based on the second sequencing and/or third sequencing and/or one or more subsequent sequencings, and a second level of expression of the gene in the second plurality of barcoded cells, and/or fourth plurality of cells and/or one or more subsequent pluralities of cells based on the first sequencing, second sequencing, and/or third sequencing and/or one or more subsequent sequencings.

19. The method of claim 18, further comprising comparing the first level of expression of the gene to the second level of expression of the gene.

20. A method of identifying a cellular program that facilitates adaptation to a pressure, comprising:

a. transducing cells with a plurality of barcodes such that each cell contains a single, unique barcode;

b. expanding the cells in culture to create a starting cell pool of clones of cells containing each barcode;

c. obtaining first genetic, transcriptomic, and/or proteomic information from a first subset of the starting cell pool;

d. culturing a second subset of the starting cell pool in the presence of a selective pressure to expand the starting cell pool and form an intermediate cell pool;

e. obtaining second genetic, transcriptomic, and/or proteomic information from a first subset of the intermediate cell pool;

f. continuing to culture a second subset of the intermediate cell pool in the presence of the selective pressure to expand the intermediate cell pool and form a final cell pool;

g. obtaining third genetic, transcriptomic, and/or proteomic information from at least a subset of the final cell pool;

h. quantifying a level of each barcode in the final cell pool, intermediate cell pool, and/or starting cell pool;

i. assigning cells with barcodes enriched in the final cell pool as resistant clones and/or assigning cells with barcodes depleted in the final cell pool as sensitive clones; and

j. determining a genetic mutation, transcription program, and/or protein expression associated with at least one resistant clone and/or at least one sensitive clone;

wherein approximately equal numbers of clones of cells containing each barcode are used to create the starting cell pool or the numbers of clones of cells are normalized relative to the numbers of cells comprising each barcode as obtained in step (c),

wherein steps (d) and (e) are repeated for one or more iterations thereby obtaining one or more additional intermediate cell pools and one or more additional intermediate genetic, transcriptomic, and/or proteomic information; and

wherein step (h) further comprises quantifying a level of each barcode in the one or more additional intermediate cell pools.

21. The method of claim 20, wherein the single, unique barcode is a unique combination of barcodes.

22. The method of claim 20 or 21, wherein the selective pressure comprises treatment with a therapeutic agent, contact with a contaminant, genomic engineering, engraftment into a host, a culture condition, a growth condition, contact with a stimulus, or contact with other cells.

23. The method of any one of claims 20 to 22, wherein obtaining the genetic, transcriptomic, and/or proteomic information comprises RNA-seq, single cell RNA-seq, DNA sequencing, epigenetic sequencing, or protein sequencing.