

~~What is claimed is~~ Claims:

1. A method for identifying lymphocytes belonging to a functional subset that have infiltrated a solid tissue, ~~the method comprising the steps of:~~
 - ~~sorting into one or more subsets~~ a sample of lymphocytes from an accessible tissue of an individual into at least one functional subset;
 - generating a clonotype profiles for each of the one or more functional subsets of lymphocytes from the accessible tissue by amplifying recombined nucleic acid molecules obtained from said at least one subset to obtain a plurality of amplicons and performing high throughput sequencing of the resulting plurality of amplicons to provide a list of clonotype sequences that identify individual lymphocytes of each functional subset;
 - generating at least one clonotype profile from at least one sample of the solid tissue by amplifying recombined nucleic acid molecules obtained from said at least one sample of solid tissue to obtain a plurality of amplicons and performing high throughput sequencing of the resulting plurality of amplicons to provide a list of clonotype sequences in each sample; and
 - ~~detecting~~ identifying lymphocytes of belonging to a each functional subset that have infiltrated from the accessible tissue into the in the solid tissue from their respective clonotypes by identifying a clonotype sequence sequences from the solid tissue that is present in the list of clonotype sequences of a functional subset from the accessible tissue,
 - wherein one or more of the clonotype profiles for one or more of the functional subsets comprise at least 1000 clonotypes of at least 30 nucleotides.
2. The method of claim 1 wherein at least one of said ~~one or more~~ at least one functional subsets of lymphocytes comprises ~~B cells, T cells~~, cytotoxic T cells, helper T cells, regulatory T cells, Th1 T cells, Th2 T cells, Th9 T cells, Th17 T cells, and/or Tfh T cells, ~~at least one subset of antigen-specific B cells and/or at least one subset of antigen-specific T cells.~~
3. The method of claim 2 wherein said step of ~~detecting~~ identifying further includes determining numbers, levels, and/or ratios of lymphocytes of each of said at least one or more functional subsets.
4. The method of claim 3 wherein said solid tissue is a solid tumor.

5. The method of claim 4 wherein said at least one or more functional subsets of lymphocytes comprise regulatory T cells and cytotoxic T cells.
6. The method of claim 5 wherein said step of ~~detecting~~ identifying includes determining a ratio of levels of ~~regulation~~ regulatory T cells to cytotoxic T cells in said solid tumor.
7. The method of claim 3 wherein said at least one or more functional subsets of lymphocytes comprise at least one subset of antigen-specific T cells.
8. The method of claim 1 wherein said accessible tissue is peripheral blood, bone marrow, lymph fluid, synovial fluid, or spinal cord fluid of said individual.
9. The method of claim 8 wherein said accessible tissue is peripheral blood of said individual.
10. The method of claim 1 wherein said step of ~~detecting~~ identifying further includes enumerating said lymphocytes in each of said functional subsets by counting their respective clonotypes.
11. The method of claim 1 wherein said sample of said solid tissue comprises multiple tissue samples taken from different locations in said solid tissue.
12. The method of claim 1 wherein said at least one or more functional subsets of lymphocytes comprise helper T cells and cytotoxic T cells.
13. The method of claim 12 wherein said helper T cells are FoxP3⁺ regulatory T cells.
14. The method of claim 13 wherein said cytotoxic T cells are identified by a CD8⁺ marker and wherein said regulatory T cells are identified by markers CD4⁺, CD25^{+(high)}, and CD127^(low).
15. The method of claim 14 wherein said solid tissue is a solid tumor.
16. The method of claim 1 wherein said at least one or more functional subsets of lymphocytes are sorted into separate containers on the basis of at least one or more cell surface markers or intracellular markers.

17. The method of claim 16 wherein said step of sorting said at least one or more functional subsets of lymphocytes is implemented with a fluorescence-activated cell sorter (FACS).

18. The method of claim 1 wherein each of said clonotypes of said clonotype profiles comprises a recombined portion of a T-cell receptor gene ~~or a recombined portion of an immunoglobulin gene.~~

19. The method of claim 18 wherein each of said clonotypes of said clonotype profiles comprises at least a portion of a V(D)J region of a nucleic acid encoding a T-cell receptor β chain ~~or at least a portion of a V(D)J region of a nucleic acid encoding an IgH chain.~~

~~20. The method of claim 19 wherein each of said clonotype profiles comprises at least 1000 clonotypes of at least 30 nucleotides.~~

~~21~~20. The method of claim ~~20~~19 wherein ~~each~~ all of said clonotype profiles comprises at least ~~10^4~~ 10^6 clonotypes.

~~22~~21. The method of claim 1 wherein said solid tissue is a solid tissue affected by an autoimmune disease.

~~23~~22. The method of claim ~~22~~21 wherein at least one of said at least one or more functional subsets of lymphocytes is selected from ~~B cells, T cells, cytotoxic T cells, helper T cells, regulatory T cells, Th1 T cells, Th2 T cells, Th9 T cells, Th17 T cells, and/or Tfh T cells, antigen-specific B cells and antigen-specific T cells,~~ and wherein said step of detecting further includes determining numbers, levels, and/or ratios of lymphocytes of each of said one or more functional subsets.

~~24~~23. The method of claim ~~23~~22 wherein said at least one or more functional subsets of lymphocytes comprise regulatory T cells, Th1 T cells, Th2 T cells, Th9 T cells, Th17 T cells, Tfh T cells, and/or at least one functional subset of antigen-specific T cells.

~~25~~24. The method of claim ~~24~~23 wherein said solid tissue is selected from the group consisting of colon tissue, small intestine tissue, skin, connective tissue, subcutaneous tissue, lung tissue, and kidney tissue.

~~26~~25. The method of claim 1 wherein said solid tissue is a normal tissue, and wherein at least one of said at least one or more functional subsets of lymphocytes is selected from ~~B~~ cells, T cells, cytotoxic T cells, helper T cells, regulatory T cells, Th1 T cells, Th2 T cells, Th9 T cells, Th17 T cells, Tfh T cells, ~~antigen-specific B cells~~ and antigen-specific T cells, and wherein said step of detecting further includes determining numbers, levels, and/or ratios of lymphocytes of each of said at least one or more functional subsets.

~~27. A method for determining a prognosis from a state of lymphocyte infiltration into a solid tumor of a patient, the method comprising the steps of:~~
~~sorting into one or more subsets a sample of lymphocytes from peripheral blood of the patient;~~
~~generating clonotype profiles for each of the one or more subsets of lymphocytes from the peripheral blood;~~
~~generating at least one clonotype profile from at least one sample of the solid tumor; and~~
~~determining numbers, levels, and/or ratios of lymphocytes of each of the one or more subsets.~~

~~28. The method of claim 27 wherein said one or more subsets include regulatory T cells and cytotoxic T cells.~~

~~29. The method of claim 28 wherein said step of determining includes indicating a greater than average rate of patient survival whenever a ratio of levels of said cytotoxic T cells to regulatory T cells is higher than that in a non-tumor tissue of said patient.~~

26. The method of claim 1 further comprising sorting a sample of lymphocytes from an accessible tissue of an individual into at least 2 functional subsets.

27. The method of claim 1 further comprising sorting a sample of lymphocytes from an accessible tissue of an individual into at least 3 functional subsets.

28. The method of claim 1 further comprising sorting a sample of lymphocytes from an accessible tissue of an individual into at least 4 functional subsets.

29. The method of claim 1 further comprising sorting a sample of lymphocytes from an accessible tissue of an individual into at least 5 functional subsets.