

CLAIMS

It is claimed:

1. A method of identifying a cognate pair of a ligand species and a receptor species, the method comprising:
 - a. providing a set of ligand species, wherein each ligand species is represented at least one time;
 - b. providing a set of receptor species, wherein each receptor species is represented at least one time;
 - c. contacting the set of ligand species with the set of receptor species in a microreactor, wherein upon selective binding of a ligand species with a receptor species an enhanced signal is produced;
 - d. detecting a cognate pair of ligand species and receptor species by the production of the signal; and
 - e. identifying the cognate pair of ligand species and receptor species.
2. The method of claim 1, wherein each ligand species and/or each receptor species comprises a barcode sequence.
3. The method of claim 1 or 2, wherein each ligand species and/or each receptor species is expressed by or displayed on the surface of a cell or bead or is expressed or present in a cell free extract or in solution.
4. The method of claim 3, wherein the antigen-presenting cell is selected from a macrophage, a dendritic cell, a Langerhans cell, a B cell, a monocyte derived dendritic cell, or another cell expressing a MHC class I or II molecule.
5. The method of claim 1 or 2, wherein the microreactor is selected from an aqueous droplet, a microcapsule, a microbead, a compartment of a microfluidic chip, or a well; and/or the signal is selected from a morphological change of any one of a cell, a ligand, or a receptor; a fluorescent signal enhancement; a modification of a fluorescent signal using a caged compound or by a quenching reaction; a light absorption; a visible structure modification/creation; or a combination of signals thereof.
6. The method of claim 2, wherein identifying the cognate pair of ligand species and receptor species comprises amplifying the ligand species and/or the receptor species, wherein at least one of the amplified ligand species and receptor species are sequenced for identification.
7. The method of claim 1 or 2, wherein (a) the set of ligand species is selected from T cell antigens, B cell antigens, viral antigens, bacterial antigens, parasitic antigens, neoantigens, tumor associated antigens (TAAs), tumor specific antigens, immune checkpoint molecules, cytokines, carbohydrates, members of the immunoglobulin superfamily, selectins, chemokines, hormone,

growth factors, G-protein coupled receptor ligands, or enzyme substrates; and/or (b) the set of receptor species is selected from T cell receptors, B cell receptors, immune checkpoint receptors, cytokine receptors, selectins, integrins, members of the immunoglobulin superfamily, cadherins, chemokine receptors, hormone receptors, growth factor receptors, G-protein coupled receptors (GPCRs), or enzymes.

8. The method of any claim 1 or 2, wherein:

a) the ligand species is a T cell antigen and the receptor species is a T cell receptor, and upon selective binding of the T cell antigen with the T cell receptor, the enhanced signal is produced, wherein the enhanced signal produced is the result of T cell activation;

b) the ligand species is a viral antigen and the receptor species is a T cell receptor, and upon selective binding of the viral antigen with the T cell receptor, the enhanced signal is produced, wherein the enhanced signal produced is the result of T cell activation; or

c) the ligand species is a B cell antigen and the receptor species is a B cell receptor, and upon selective binding of the B cell antigen with the B cell receptor, the enhanced signal is produced.

9. The method of claim 8, wherein contacting the set of ligand species with the set of receptor species in a microreactor occurs for:

a) about 0.001 hour to about 8 hours; or

b) at least about 8 hours.

10. The method of claim 9, wherein the ligand species and the receptor species bind with high affinity and the enhanced signal produced is an early marker or late marker for T cell activation.

11. The method of claim 9, wherein the ligand species and the receptor species bind with low affinity and the enhanced signal produced is an early marker or late marker for T cell activation.

12. The method of claim 10 or 11, wherein (a) the early marker for T cell activation is selected from CD69, CD107a, or a transferrin receptor; and/or (b) the late marker for T cell activation is selected from CD137, HLA-DR, VLA1, PTA1, CD71, CD27, PD-1, TIM3, LAG3, or CTLA4.

13. The method of claim 12, wherein the enhanced signal is detected with an anti-CD69 antibody, an anti-CD107a antibody, an anti-transferrin receptor antibody, anti-CD137 antibody, an anti-HLA-DR antibody, an anti-VLA1 antibody, an anti-PTA1 antibody, an anti-CD71 antibody, an anti-CD27 antibody, an anti-PD1 antibody, an anti-TIM3 antibody, an anti-LAG3 antibody, or an anti CTLA4 antibody.

14. The method of claim 13, wherein the signal is detected with an anti-CD138 antibody, an anti-CD19 antibody, an anti-CD45R antibody, an anti-CD45 antibody, an activation of fluorescent reporter expression, or an inhibition of fluorescent reporter expression.