CLAIMS

1. A method of identifying a binding polypeptide that specifically binds to a cell-surface antigen, the method comprising:

(a) contacting a variegated nucleic acid-display library of binding polypeptides with a cell-surface antigen naturally expressed on an exterior surface of a first cell type, wherein the variegated nucleic acid-display library is a DNA-display library, wherein each member of the DNA-display library comprises a binding polypeptide linked through an intervening DNA linker to a DNA coding sequence encoding the binding polypeptide, and wherein the DNA linker comprises a restriction endonuclease site not present in the coding sequence of members of the DNA-display library;

(b) washing unbound library members from the first cell type;

(c) enzymatically separating bound library members from the first cell type by cleaving the restriction endonuclease site with a suitable restriction endonuclease; and

(d) isolating from the library at least one library member that specifically binds to the cell-surface antigen on the exterior surface of the first cell type, thereby identifying a binding polypeptide that specifically binds to the cell surface antigen.

2. The method of claim 1, wherein prior to step (a), an unselected precursor of the variegated nucleic acid-display library of binding polypeptides is contacted with a second cell type that does not express the cell-surface antigen on its exterior surface, and library members that bind to the second cell type are isolated and removed from the unselected precursor of the variegated nucleic acid-display library to produce the variegated nucleic acid-display library used in step (a).

3. The method of claim 1, further comprising:

(e) contacting the variegated nucleic acid-display library of binding polypeptides with a second cell type that does not express the cell-surface antigen, and isolating from the library at least one library member that specifically binds to the second cell type; and

(f) selecting library members that specifically bind to the first cell type but not to the second cell type, thereby identifying a binding polypeptide that specifically binds to the cell-surface antigen.

4. The method of claim 1, wherein the method further comprises determining the DNA coding sequence of at least a portion of the isolated library members.

5. The method of claim 11, wherein the DNA coding sequence is determined by pyrosequencing.

6. The method of claim 1, where the antigen is a naturally occurring protein, glycan or lipid.

7. The method of claim 1, where the antigen is a glycophosphatidylinositol (GPI) anchored protein.

8. The method of claim 1, wherein the first cell type is a disease-associated variant of a normal cell.

9. The method of claim 1, wherein the first cell type is a tumor cell.

10. The method of claim 1, wherein the binding polypeptide is an antibody or fragment thereof.

11. The method of claim 1, wherein the binding polypeptide is an antibody VH or VL domain.

12. The method of claim 1, wherein the first cell type is a live cell.

13. The method of claim 3, wherein the first and second cell types are live cells.