We claim:

1. A method of identifying a ligand for a biological molecule, comprising:

(a) contacting the biological molecule, a probe molecule and a substrate for the biological molecule;

wherein the probe molecule comprises a binding element, a reporter group, and a reactive moiety;

the probe molecule binds to the biological molecule via the binding element; and

the reactive moiety forms a covalent bond with the biological molecule, thereby forming a conjugate;

(b) contacting the conjugate and a detectable molecule comprising a functional moiety that reacts with the reporter group, thereby forming a detectable conjugate;

(c) contacting the detectable conjugate and a solid support; wherein the solid support comprises a recognition moiety; and the recognition moiety binds to the detectable conjugate, thereby forming a bound detectable conjugate; and

(d) detecting the bound detectable conjugate, thereby identifying the probe molecule as a ligand for the biological molecule,

wherein the amount of the bound detectable conjugate formed in the presence of the substrate for the biological molecule is less than the amount of the bound detectable conjugate formed in the absence of the substrate (i.e., the probe molecule is a substrate-competitive probe); or the amount of the bound detectable conjugate formed in the presence of the substrate for the biological molecule is greater than the amount of the bound detectable conjugate formed in the absence of the substrate (i.e., the probe molecule is a substrate-cooperative probe).

2. The method of claim 1, wherein the binding element is a small molecule fragment or a peptide.

3. The method of claim 1, wherein the binding element is a nucleic acid.

4. The method of claim 3, wherein the nucleic acid is RNA or DNA.

5. The method of any one of claims 1-4, wherein the binding element is a component of a library comprising a plurality of binding elements.

6. The method of claim 5, wherein the binding elements are small-molecule fragments; and each small-molecule fragment has at least one of the following characteristics: molecular weight ≤ 300 Da, cLogP ≤ 3, hydrogen bond donors ≤ 3, and hydrogen bond acceptors ≤ 3.

7. The method of any one of claims 1-6, wherein the biological molecule is a protein.

8. The method of claim 7, wherein the reactive moiety forms a covalent bond with an amino acid of the protein.

9. The method of any one of claims 1-8, wherein the biological molecule is a lipid, a carbohydrate, or a nucleic acid.

10. The method of claim 9, wherein the biological molecule is a nucleic acid; and the nucleic acid is RNA or DNA.

11. The method of any one of claims 1-10, wherein the biological molecule comprises an epitope tag, optionally wherein the epitope tag is FLAG, 6xHis, HA, c-myc, glutathione-S-transferase, Strep-tag, maltose-binding protein, chitin-binding protein, S-tag, V5 tag, or AviTag.

12. The method of any one of claims 1-11, wherein the reporter group comprises an azadibenzocyclooctyne, a thiol, an alkene, an alkyne, an azide, a tetrazine, a *trans*-cyclooctene, a (diphenylphosphino)aryl, (diphenylphosphino)alkyl, or an activated ester (e.g., a hydroxybenzotriazole (HOBt) ester); and/or

the reactive moiety is a photocrosslinker group, a sulfonyl fluoride, a fluorosulfate, a Michael acceptor moiety, a leaving group moiety, or a moiety that forms a covalent bond with a nucleophilic moiety in the side chain of a naturally occurring alpha amino acid (e.g.,

with the thiol group of a cysteine, the amino group of a lysine, the hydroxyl group of a serine or threonine, or the phenol group of a tyrosine); and/or

the detectable molecule comprises digoxigenin, nickel NTA (nitrilotriacetic acid), a chromophore, or a luminophore.

13. The method of claim 12, wherein the chromophore comprises non-fluorochrome chromophore, quencher, an absorption chromophore, fluorophore, organic dye, inorganic dye, metal chelate, or a fluorescent enzyme substrate.

14. The method of claim 12, wherein the detectable molecule comprises a luminophore.

15. The method of any one of claims 1-14, wherein the detectable molecule is biotin.

16. The method of claim 15, wherein the biotin is bound to a streptavidin conjugate, optionally wherein the streptavidin conjugate comprises a HRP, a SulfoTag, a fluorophore, or a metal chelate.

17. The method of any one of claims 1-16, wherein the functional moiety comprises an azadibenzocyclooctyne, a thiol, an alkene, an alkyne, an azide, a tetrazine, a *trans*-cyclooctene, a (diphenylphosphino)aryl, (diphenylphosphino)alkyl, or an activated ester (e.g., a hydroxybenzotriazole (HOBt) ester).

18. The method of any one of claims 1-17, wherein the solid support is a membrane, glass, plastic, synthetically prepared polymer, an eppendorf tube, a well of a multi-well plate, or a surface plasmon resonance chip.

19. The method of any one of claims 1-18, wherein the recognition moiety is an antibody, a DNA binding protein, a RNA binding protein, a carbohydrate binding protein, or a lipid binding protein.

20. The method of claim 19, wherein the recognition moiety is an antibody; and the antibody is an antibody against the biological molecule; or the antibody is an antibody against the epitope tag.

21. The method of any one of claims 1-20, wherein step (d) comprises detecting the bound detectable conjugates via ELISA; or step (d) comprises detecting the bound detectable conjugates via Western blot; or step (d) comprises detecting the bound detectable conjugates via immunofluorescence assay; or step (d) comprises detecting the bound detectable conjugates via fluorometric assay; or step (d) comprises detecting the bound detectable conjugates via fluorometric microvolume assay technology (FMAT); or step (d) comprises detecting the bound detectable conjugates via cell subcellular staining.

22. The method of any one of claims 1-21, wherein the method is performed on a crude cellular extract comprising the biological molecule; or the method is performed on a liposomal preparation of proteins comprising the biological molecule; the method is performed on an isolated organelle comprising the biological molecule; or the method is performed on a purified protein preparation comprising the biological molecule.

23. The method of any one of claims 1-22, wherein the method is performed *in situ*; or the method is a cell based assay.

24. The method of claim 23, wherein the biological molecule is expressed in a cell.

25. The method of claim 24, wherein the cell is engineered to express the biological molecule.

26. The method of any one of claims 1-25, wherein the biological molecule is a cell expressing a tagged creatine transporter.

27. The method of any one of claims 23-26, wherein the cell is lysed prior to step (b).

28. The method of any one of claims 1-27, wherein step (d) further comprises quantifying the amount of the bound detectable conjugate.