Claims:

1. A hybridization buffer comprising a crowding agent and at least one of human Cot-1 DNA, a destabilizing agent, salt, and a blocker, wherein the blocker comprises at least one of:
(a) a plurality of T_m-enhancing modifications;
(b) a plurality of modifications that increase the T_m of the blocker comprising at least one of a crosslinked oligonucleotide; a modified 5-methyl deoxycytidine (5-methyl-dc); 2,6-diaminopurine; a locked nucleic acid (LNA); a bridged nucleic acid (BNA); a tricyclic nucleic acid; a peptide nucleic acid (PNA); a C5-modified pyrimidine base; a propynyl pyrimidine; a morpholino; a phosphoramidite; and a 5'-Pyrene cap;
(c) an oligonucleotide; wherein the blocker is capable of binding to an adaptor, wherein the adaptor comprises a universal primer sequence and at least one of an index region or a unique molecular identifier (UMI); and wherein the region of the blocker capable of binding to the index region and/or UMI of the adaptor comprises: at least three thymine bases, at least four thymine bases, at least five thymine bases, at least six thymine bases, at least seven thymine bases, at least eight thymine bases, at least nine thymine bases, or at least ten thymine bases; or universal bases and at least one non-universal base; or
(d) two non-connected oligonucleotides; wherein the blocker is capable of binding to at least a portion of an adaptor, wherein the adaptor comprises a universal primer sequence and at least one of an index region or a unique molecular identifier (UMI); and wherein the non-connected oligonucleotides comprise bases that do not correspond to the index region and/or the UMI of the adaptor.

2. The hybridization buffer of claim 1, wherein the crowding agent comprises at least one of dextran, dextran sulfate, polyethylene glycol (PEG), Ficoll, glycerol, and betaine.

3. The hybridization buffer of claim 1 or claim 2, comprising a crowding agent and a blocker.

4. The hybridization buffer of claim 1 or claim 2, comprising a crowding agent, human Cot-1 DNA, a blocker, a destabilizing agent, a buffer, salt, and a detergent.

5. The hybridization buffer of any one of claims 1 to 4, wherein the hybridization buffer comprises a buffer and the buffer is a phosphate buffer.

6. The hybridization buffer of any one of claims 1 to 5, wherein the hybridization buffer comprises salt and the salt is NaCl or sodium citrate.

7. The hybridization buffer of any one of claims 1 to 6, wherein the hybridization buffer comprises a destabilizing agent and the destabilizing agent is formamide or urea or a mixture thereof.

8. The hybridization buffer of any one of claims 1 to 7, wherein the hybridization buffer comprises a detergent and the detergent is TWEEN 20, TWEEN 80, or sodium dodecyl sulfate (SDS).

9. The hybridization buffer of claim 1, wherein the hybridization buffer comprises:

0.5% to 10% dextran sulfate,
0.05 mg/mL to 0.5 mg/mL human Cot-1 DNA,
1% to 15% (v/v) formamide,
40 mM to 80 mM KH_2PO_4 - K_2HPO_4,
0.1 M to 4 M NaCl, and
0.001% to 10% (v/v) TWEEN 20.

10. A method of preparing an enriched library comprising forming a hybridization mixture comprising library members, a hybridization buffer of any one of claims 1 to 9, and a probe to form a hybridization mixture, under conditions sufficient for the probe to hybridize to a region of interest within a library member, wherein the probe comprises a ligand.

11. The method of claim 10, comprising:

capturing the probe after it has hybridized using a capture means, and

eluting the captured library members from the capture means into an eluant comprising enriched library members, wherein the DNA concentration of the eluant is in the range of 1.3 pM to 250 pM.

12. The method of claim 10 or claim 11, wherein the hybridization mixture comprises samples from at least two library preparations, wherein at least 10 ng, at least 25 ng, at least

50 ng, at least 100 ng, at least 200 ng, or at least 500 ng of DNA from each library preparation are combined.

13. The method of any one of claims 10 to 12, wherein the DNA concentration of the hybridization mixture is in a range of 0.1 ng/μL to 120 ng/μL.

14. The method of any one of claims 10 to 13, comprising sequencing the enriched library members and wherein the method does not comprise amplifying the library members prior to capturing the library members.

15. The method of claim 14, wherein the sequencing occurs on a flow call and the method comprises loading the enriched library members onto the flow cell at a concentration of at least 1.1 pM, at least 1.2 pM, at least 1.3 pM, at least 10 pM, or at least 100 pM and at a concentration of up to 100 pM, up to 200 pM, up to 250 pM, or up to 300 pM.

16. The method of claim 15, comprising loading the enriched library members onto a flow cell using a direct flow cell loading jig.

17. A kit comprising the hybridization buffer of any one of claims 1 to 9 and instructions for use.

18. The kit of claim 17, further comprising a probe or panel of probes.

19. A blocker comprising an oligonucleotide; wherein the blocker is capable of binding to an adaptor, wherein the adaptor comprises a universal primer sequence and at least one of an index region or a unique molecular identifier (UMI); and wherein the region of the blocker capable of binding to the index region and/or UMI of the adaptor comprises: at least three thymine bases, at least four thymine bases, at least five thymine bases, at least six thymine bases, at least seven thymine bases, at least eight thymine bases, at least nine thymine bases, or at least ten thymine bases.

20. A blocker comprising two non-connected oligonucleotides; wherein the blocker is capable of binding to at least a portion of an adaptor, wherein the adaptor comprises a

universal primer sequence and at least one of an index region or a unique molecular identifier (UMI); and wherein the non-connected oligonucleotides comprise bases that do not correspond to the index region and/or the UMI of the adaptor.

21. The blocker of claim 19 or claim 20, wherein the universal primer sequence comprises at least one of P5 (SEQ ID NO: 19), P7 (SEQ ID NO: 20), P5' (reverse complement of SEQ ID NO: 19), P7' (SEQ ID NO: 21), V2.A14.METS (SEQ ID NO: 24), V2.B15.METS (SEQ ID NO: 25), the complement of V2.A14.METS, and the complement of V2.B15.METS.

22. The blocker of any one of claims 19 to 21, wherein the blocker comprises a modification that increases the T_m of the blocker relative to the same blocker that does not include the modification.

23. The blocker of any one claims 19 to 22, wherein the blocker comprises at least one of a DNA or RNA oligonucleotide modified to capture low GC regions; a crosslinked oligonucleotide; a modified 5-methyl deoxycytidine (5-methyl-dc); 2,6-diaminopurine; a locked nucleic acid (LNA); a bridged nucleic acid (BNA); a tricyclic nucleic acid; a peptide nucleic acid (PNA); a C5-modified pyrimidine base; a propynyl pyrimidine; a morpholino; a phosphoramidite; and a 5'-Pyrene cap.