CLAIMS

1. A method of analysing a sample comprising a circulating microparticle or a sample derived from a circulating microparticle, in which the circulating microparticle is a membranous vesicle, in which the circulating microparticle comprises at least three target molecules, in which at least two of the target molecules are fragments of genomic DNA and at least one of the target molecules is a target polypeptide, and in which the method comprises measuring a signal corresponding to the presence, absence and/or level of each of the target molecules to produce a set of at least two linked signals for the circulating microparticle, in which at least one of the linked signals corresponds to the presence, absence and/or level of the fragments of genomic DNA in the sample and at least one of the linked signals corresponds to the presence, absence and/or level of the target polypeptide in the sample, and in which the step of measuring a signal corresponding to the presence, absence and/or level of the fragments of genomic DNA comprises linking at least two of the at least two fragments of genomic DNA to produce a set of at least two linked fragments of genomic DNA.

2. A method according to Claim 1, in which the fragments of genomic DNA comprise a specific sequence of nucleotides and/or in which the fragments of genomic DNA comprise at least one modified nucleotide or nucleobase, optionally in which the modified nucleotide or nucleobase is 5-methylcytosine or 5-hydroxy-methylcytosine.

3. A method according to Claim 1 or 2, in which the target polypeptide comprises a specific amino acid sequence and/or in which the target polypeptide comprises a post-translational modification, optionally in which the target polypeptide comprises an acetylated amino acid residue and/or a methylated amino acid residue.

4. A method according to Claim 1, 2 or 3, in which the method comprises measuring the signal corresponding to the presence, absence and/or level of each of the target molecules of the circulating microparticle to produce a set of at least three linked signals for the circulating microparticle, in which one of the linked signals corresponds to the presence, absence and/or level of a first fragment of genomic DNA of the circulating microparticle, one of the linked signals corresponds to the presence, absence and/or level of a second fragment of genomic DNA of the circulating microparticle, and one of the linked signals corresponds to the presence, absence and/or level of the target polypeptide of the circulating microparticle.

5. A method according to any preceding claim, in which the step of measuring a signal corresponding to the presence, absence and/or level of the fragments of genomic DNA comprises analysing a sequence of each of at least two of the at least two fragments of genomic DNA, optionally in which the step of measuring a signal corresponding to the presence, absence and/or level of the fragments of genomic DNA comprises sequencing at least a portion of each of at least two of the at least two fragments of genomic DNA.

6. A method according to any preceding claim, in which the step of measuring a signal corresponding to the presence, absence and/or level of the fragments of genomic DNA further comprises sequencing at least a portion of each of at least two of the linked fragments of genomic DNA in the set to produce at least two linked sequence reads.

7. A method according to any preceding claim, in which the step of measuring a signal corresponding to the presence, absence and/or level of the fragments of genomic DNA comprises:

(a) linking at least two of the at least two fragments of genomic DNA by appending each of at least two of the at least two fragments of genomic DNA of the circulating microparticle to a barcode sequence to produce a set of linked fragments of genomic DNA; and, optionally,

(b) sequencing at least a portion of each of at least two of the linked fragments in the set to produce at least two linked sequence reads, in which the at least two linked sequence reads are linked by the barcode sequence.

8. A method according to any of Claims 1 to 6, in which the step of measuring a signal corresponding to the presence, absence and/or level of the fragments of genomic DNA comprises:

(a) linking at least two of the at least two fragments of genomic DNA by appending each of at least two of the at least two fragments of genomic DNA of the circulating microparticle to a different barcode sequence of a set of barcode sequences to produce a set of linked fragments of genomic DNA; and, optionally,

(b) sequencing at least a portion of each of at least two of the linked fragments in the set to produce at least two linked sequence reads, in which the at least two linked sequence reads are linked by the set of barcode sequences.

9. A method according to any preceding claim, in which the fragments of genomic DNA comprise at least one modified nucleotide or nucleobase and in which the step of measuring a signal corresponding to the presence, absence and/or level of the fragments of genomic DNA comprises measuring a signal corresponding to the presence, absence and/or level of the modified nucleotide or nucleobase of the fragments of genomic DNA, optionally in which the modified nucleotide or nucleobase is 5-methylcytosine or 5-hydroxy-methylcytosine.

10. A method according to Claim 9, in which the signal corresponding to the presence, absence and/or level of the modified nucleotide or nucleobase is measured using (i) a barcoded affinity probe, in which the barcoded affinity probe comprises at least one affinity moiety linked to a barcoded oligonucleotide, in which the barcoded oligonucleotide comprises at least one nucleotide, and in which the affinity moiety is capable of binding to the modified nucleotide or nucleobase, optionally in which the signal is measured by determining the presence, absence and/or level of the barcoded oligonucleotide by sequencing; and/or (ii) an optically-labelled affinity probe and/or a fluorescently-labelled affinity probe, optionally in which the signal is measured by flow cytometry and/or fluorescence-activated cell sorting.

11. A method according to any preceding claim, in which the signal corresponding to the presence, absence and/or level of the target polypeptide is measured using (i) a barcoded affinity probe, in which the barcoded affinity probe comprises at least one affinity moiety linked to a barcoded oligonucleotide, in which the barcoded oligonucleotide comprises at least one nucleotide, and in which the affinity moiety is capable of binding to the target polypeptide, optionally in which the signal is measured by determining the presence, absence and/or level of the barcoded oligonucleotide by sequencing; and/or (ii) an optically-labelled affinity probe and/or a fluorescently-labelled affinity probe, optionally in which the signal is measured by flow cytometry and/or fluorescence-activated cell sorting.

12. A method according to any preceding claim, in which the circulating microparticle comprises at least 3, at least 4, at least 5, at least 10, at least 50, at least 100, at least 500, at least 1000, at least 5000, at least 10,000, at least 100,000, or at least 1,000,000 target molecules, and in which the method comprises producing a set of at least 3, at least 4, at least 5, at least 10, at least 50, at least 100, at least 500, at least 1000, at least 5000, at least 10,000, at least 100,000, or at least 1,000,000 linked signals for the circulating microparticle.

13. A method according to any preceding claim, in which the target molecules comprise at least 3, at least 4, at least 9, at least 49, at least 99, at least 499, at least 999, at least 4999, at least 9,999, at least 99,999, or at least 999,999 fragments of genomic DNA, and optionally in which the method comprises producing a set of at least 3, at least 4, at least 5, at least 10, at least 50, at least 100, at least 500, at least 1000, at least 5000, at least 10,000, at least 100,000, or at least 1,000,000 linked signals for the circulating microparticle.

14. A method according to any preceding claim, in which the target molecules comprise at least 2, at least 3, at least 4, at least 9, at least 49, at least 99, at least 499, at least 999, at least 4999, at least 9,999, at least 99,999, or at least 999,999 target polypeptides, and optionally in which the method comprises producing a set of at least 3, at least 4, at least 5, at least 10, at least 50, at least 100, at least 500, at least 1000, at least 5000, at least 10,000, at least 100,000, or at least 1,000,000 linked signals for the circulating microparticle.

15. A method according to any preceding claim, in which the sample comprises first and second circulating microparticles, in which each circulating microparticle comprises at least three target molecules as defined in any preceding claim, and in which the method comprises performing the step of measuring in accordance with any preceding claim to produce a set of linked signals for the first circulating microparticle and performing the step of measuring in accordance with any preceding claim to produce a set of linked signals for the second circulating microparticle; optionally in which the sample comprises n circulating microparticles, in which each circulating microparticle comprises at least three target molecules as defined in any preceding claim, and in which the method comprises performing the step of measuring in accordance with any preceding claim for each circulating microparticle to produce a set of linked signals for each circulating microparticle, optionally in which n is at least 3, at least 5, at least 10, at least 50, at least 100, at least 1000, at least 10,000, at least 100,000, at least 1,000,000, at least 10,000,000, or at least 100,000,000 circulating microparticles.