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Novel biomarkers of renal diseases using extracellular vesicles

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A critical need for disease diagnostic, prognostic, monitoring and therapeutic decisions is currently studied; regularly, biomarkers (proteins, DNA, etc) for diseases are measured from specific tissues. Methods to obtain these tissues of interest for analysis are often invasive, costly and pose complication risks for the patient. Furthermore, use of bodily fluids to isolate or detect biomarkers often significantly dilutes a biomarker resulting in readouts that lack requisite sensitivity. The identification of specific biomarkers (proteins) can provide bio-signatures that are used for the diagnosis, prognosis or theranosis of a disease. Exosomes are a good source for assessing one or more biomarkers. Furthermore, identifying particular characteristics of an exosome (e.g., size, surface antigens and cell-of-origin) can itself provide a diagnostic, prognostic or theranostic readout. The secretion of exosomes by cancerous cells, other diseased cells or at certain times of a physiological process (e.g., pregnancy) can be leveraged to aid in diagnosis as well as individualized treatment decisions. Exosomes have been found in a number of body fluids (blood plasma, breast milk, urine, etc). Exosomes also take part in the communication between cells as transport vehicles (proteins, DNAs, viruses and prions). The present inventions provide an improvement to prior art assays. Products and process are provided for improved assay sensitivity and specificity allowing for disease detection, prognostic prediction, disease monitoring, disease staging and therapeutic decision-making as well as physiological state identification. Also provided herein are methods of determining biomarkers and bio-signatures for exosomes without prior concentration or purification of the exosomes from a sample.

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3D structural fluctuation of IgG1 antibody revealed by individual particle electron tomography

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Commonly used methods for determining protein structure, including X-ray crystallography and single-particle reconstruction, often provide a single and unique three-dimensional (3D) structure. However, in these methods, the protein dynamics and flexibility/fluctuation remain mostly unknown. Here, we utilized advances in electron tomography (ET) to study the antibody flexibility and fluctuation through structural determination of individual antibody particles rather than averaging multiple antibody particles together. Through individual-particle electron tomography (IPET) 3D reconstruction from negatively-stained ET images, we obtained 120 ab-initio 3D density maps at an intermediate resolution (~1-3 nm) from 120 individual IgG1 antibody particles. Using these maps as a constraint, we derived 120 conformations of the antibody via structural flexible docking of the crystal structure to these maps by targeted molecular dynamics simulations. Statistical analysis of the various conformations disclosed the antibody 3D conformational flexibility through the distribution of its domain distances and orientations. This blueprint approach, if extended to other flexible proteins, may serve as a useful methodology towards understanding protein dynamics and functions.

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