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New understanding of biomarkers could lead to earlier diagnosis of fatal diseases

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A new research paper sheds light on the way antibodies distinguish between different but closely related 'biomarkers' - proteins which reveal information about the condition of the human body. This new understanding could enable pharmaceutical companies to develop new technologies for quickly diagnosing and treating fatal diseases.

All diseases have proteins, or concentrations of proteins, specifically linked to them called biomarkers. Identifying these can prove a powerful diagnostic tool. These biomarkers are detected by immunoassays – a test which mixes a substance (eg blood, urine) with antibodies, which bind to the protein if it is present. The antibodies can then be measured to identify the level of the biomarker, which in turn indicates the presence and extent of an illness.

Antibodies bind with high specificity to one protein molecule or a limited group of molecules (eg hormones), which is why we can use antibodies to test for specific biomarkers. Problems arise when they bind to groups of similar hormones that are associated with normal bodily changes. This leads to false positives and therefore unreliable information.

New research, carried out by the National Physical Laboratory (NPL), the University of Edinburgh and industrial partners from the UK (Mologic ltd), US (IBM's Watson Research Center) and the Netherlands (Pepscan Presto BV), changes this. The research shows how different proteins are made up, and therefore how they can be identified reliably.

The highly sought solution is 'intelligent selection' of antibody-specific interaction sites on hormones that can differ from similar sites of other hormones by just one molecule.

The research focused on hCG (human chorionic gonadotropin), a hormone produced during pregnancy. A subunit of hCG - hCGβ - is secreted by some cancers, meaning detection can give early warning of tumors.

hCG is very similar to other reproductive hormones, known as LH and FSH, which are always present in the body. Detecting hCG can be confused with these other hormones, leading to unreliable results.

The immunoassay antibodies bind to a tiny part of the hormone called an epitope. Hormones are made up of thousands of 'building blocks', with epitopes making up less than 10 of these blocks. The difference between hormones can be as little as one of these epitope blocks.

The research team took a variety of precise measurements of the hCG hormone, drawing on NPL's world-leading measurement technology and expertise, which were supported by atomistic computer simulations.

The team showed how very subtle, atomic level characteristics define the antibody selectivity in closely related epitopes of different proteins. They identified that specific antibodies are highly selective in immunoassays and can distinguish between hCGβ and closely related LH fragments.

Understanding these structural differences explains the observed selectivity in the full hormones. Armed with this knowledge, scientists can develop intelligent epitope selection to achieve the required assay performance. This means reliable tests can be developed to indentify the presence of different hormones – in this case the presence of hCGβ

which indicates cancer, as opposed to LH, which is always present.

The advances described in this research will enable development of further immunoassays to identify other biomarkers from similar groups. Pharmaceutical companies could use this to develop new technologies for diagnostics and clinical disease treatments, for example tests for tumour as part of routine screenings.

Max Ryadnov, Principal Research Scientist at the National Physical Laboratory, says "This work answers one of the big questions in distinguishing biomarkers which are critical for identifying and treating serious diseases. We hope this breakthrough will underpin the development of a range of new diagnostic techniques and treatment."

Prof Paul Davis, Chief Scientific Officer of Mologic ltd – a UK diagnostic company that initiated the study, said: "It was a great collaborative effort, and it stands as a fine example of what can be achieved when motivated scientists work together openly across boundaries."

Provided by National Physical Laboratory