Rapid cardiac biomarker testing system developed by Singapore scientists

EurekAlert

Scientists at Singapore's Institute of Microelectronics (IME) have developed a rapid and sensitive integrated system to test simultaneously for specific cardiac biomarkers in finger prick amount of blood.

The silicon-based integrated system's features could help physicians quickly arrive at the right diagnosis for timely medical intervention in patients suspected of having heart attacks -- particularly individuals who do not show obvious signs of chest pains or shortness of breath, according to researchers at IME, one of the research institutes sponsored by Singapore's A*STAR (Agency for Science, Technology and Research).

The IME-developed cardiac biomarker testing system significantly cuts the time needed for sample preparation and analysis to just 45 minutes from the six hours typically required for the conventional testing platform known as ELISA (Enzyme-linked Immunosorbent Assay).

Because of its multiplexing capability – measuring several cardiac biomarkers simultaneously -- the new system contributes to the detail and certainty of diagnosis.

"The key to saving lives in heart attack scenarios is time and the quicker and more accurate the diagnosis can be made, the faster proper care and treatment can be instituted," said Philip Wong, M.D., Senior Consultant at the Singapore National Heart Centre, which worked with IME in developing the new system.

"The test kits can be rapidly deployed, and tests to confirm clinical diagnosis can be completed within short time frames," said Dr. Wong. "As the kits are deployed on-site as opposed to a central laboratory, confirmation of condition is rapid without the need to transport patients' specimens."

The IME-developed system is a label-free technology that uses semiconducting silicon nanowires (SiNWs) as biosensors. The working principle behind the nanowire biosensors is the field-effect transistor, which is responsible for generating a measurable electrical response when specific antibody-antigen interactions occur on the nanowire surface.

Specific antibodies that are immobilized onto the nanowire surface will elicit antibody-antigen interactions when allowed to come into contact with the variety of charged cardiac biomarkers. Released into the blood when the heart is injured, cardiac protein biomarkers such as troponin-T and creatinine kinases, are the basis of medical tests of patients in which a heart attack is suspected.

The IME-developed system is a label-free technology – thus eliminating the tagging step, thereby saving time and reagent consumption costs. In classical biochemical methods, the tagging of a fluorescent dye to the targeted analyte is used to detect and quantify the targeted analyte.

The IME-developed system's parallel detection of several biomarkers is made possible by the integration of the following elements into one single microsystem:

- In-built filtration to extract almost instantaneously the test serum from the whole blood sample
- An array of SiNW chips coated with different antibodies for simultaneous detection of several biomarkers
- A recording microchip for concurrent and immediate signal-readout from multiple SiNW sensors

The first demonstration of the full system capability revealed impressive sensitivity and speed because it can attain in just under 45 minutes a low detection limit of 1 pg/ml for cardiac biomarkers, troponin-T and creatinine kinases, from 2 µl blood.

Commercially available test kits require more than 1 ng/ml of cardiac biomarkers in order for them to be detected, which is 1000 times less sensitive than the IME-developed system.

The technology and processes used for fabricating this integrated device have yielded two patents to date.

"IME's proprietary nanotechnology behind the new silicon-based integrated system can be extended to other protein-based diagnostics from blood and saliva samples to provide fast, sensitive, accurate and portable solutions for protein-based disease screening," said Kwong Dim-Lee, Ph.D., IME's Executive Director.

Cardiac biomarkers, such as troponin-T and creatinine kinases are proteins used for heart attack diagnosis. Troponin and creatinine are constituents of the cardiac muscle cells that are released into the blood when the cells and tissues are injured after a heart attack. Hence elevated levels of troponin-T or creatinine kinases in the blood alert the doctors that a heart attack has taken place.

Troponin-T is established as a sensitive marker of myocardial injury in the general population. The troponin-T level in the blood increases within 4 to 6 hours after the onset of a heart attack and peaks at about 24 hours. This increase lasts for 10 to 14 days.

Today, the first test performed on a patient who is suspected of having a heart attack would be an electrocardiogram, commonly known as the ECG. However, normal results from an ECG do not rule out the occurrence of a heart attack, because the test is not sensitive enough to detect minute anomalies in the reading, particularly when the anomaly needs to be captured within a narrow time window of

2 – 30 minutes following the onset of a heart attack. When an abnormal ECG reading cannot be established, the patient has to undergo further blood tests to detect the relevant cardiac biomarkers.

ELISA, which is the current method for detecting cardiac biomarkers, uses fluorescent labeling technology. This biochemical technique is laborious and time-consuming; the entire set-up requires specialized personnel and instruments to implement, thereby contributing to the per analysis cost. Hence, ELISA does not favor prompt diagnosis for critical split-second medical decisions.

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