Institute of Microelectronics
A*STAR

TECHNICAL RELEASE

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A NEW ERA IN CARDIAC HEALTH DIAGNOSTICS WITH SILICON-BASED INTEGRATED SYSTEM

1. Researchers at A*STAR's Institute of Microelectronics (or IME) have developed a rapid and sensitive integrated system to test for specific cardiac biomarkers in blood. Compared to the conventional testing platform known as ELISA (Enzyme-linked Immunosorbent Assay), the new integrated system significantly cuts sample preparation and analysis time which typically requires 6 hours to just 45 minutes.

2. The new system has demonstrated promising multiplexing capability, meaning that the new system can measure several cardiac biomarkers simultaneously; thereby contributing to the detail and certainty of diagnosis. It is also less invasive since it uses just a finger prick amount of blood. In the event of a suspected heart attack, these new features could save precious minutes in helping doctors arrive at the right diagnosis for timely medical intervention, which would make a world of difference between life and death.

3. The potential healthcare implications of the promising research outcome has attracted the interest of Singapore National Heart Centre who, in working with IME, proposed the clinical problems and the 'chokepoints' for rapid point-of-care (POC) test for diagnosis of heart attacks.

4. On the future outlook for the IME-developed silicon-based integrated system, Dr Philip Wong, Senior Consultant of Singapore National Heart Centre said, "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. The test kits can be rapidly deployed, and tests to confirm clinical diagnosis can be completed within short time frames. 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."

Silicon-based Integrated System: What is it and how does it work?

5. The IME-developed silicon-based integrated system is a label-free[1] technology that uses semiconducting silicon nanowires (SiNWs) as biosensors. The working principle behind the nanowire biosensors is the field-effect transistor (refer to Figure 1 in ANNEX), which is responsible for generating a measurable electrical response when specific antibody-antigen interactions occur on the nanowire surface.

6. Cardiac protein biomarkers are substances that are released into the blood when the heart is injured. Specific antibodies that are immobilized onto the nanowire surface will elicit

[1] In classical biochemical methods, the tagging of a fluorescent dye to the targeted analyte is used as a means for detection and quantification of the targeted analyte. Label-free technology eliminates the tagging step, which saves time and reagent consumption costs.

antibody-antigen interactions when allowed to come into contact with the variety of charged cardiac biomarkers. Such parallel detection of several biomarkers is made possible by the new microsystem that integrates the following elements into one single system:

- In-built filtration system 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

7. The first demonstration of the full system capability revealed impressive sensitivity and speed as the system is able to attain a low detection limit of 1 pg/ml for cardiac biomarkers, troponin-T and creatinine kinases, from 2 μl blood in just under 45 minutes. 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 the fabrication of this integrated device have also yielded two patents to date.

8. "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 Professor Kwong Dim-Lee, Executive Director of IME.

Significance of Cardiac Biomarkers

9. 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.

10. 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[2].

11. Contrary to what a layman might assume, a heart attack is not straight forward to diagnose. Unlike what is often shown on television dramas, a heart attack may not present itself with the classical symptoms such as sudden chest pain and shortness of breath. Approximately one fourth of all heart attacks are atypical i.e. without showing obvious signs of chest pains or shortness of breath. To accurately diagnose an atypical heart attack would therefore require an experienced medical eye, detailed medical history as well as efficient, sensitive and accurate diagnostic tests.[3]

12. 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. Contrary to popular belief,

[2] M.H. Crawford, J.P. Dimarco and W.J. (ed.) in *Cardiology*, Elsevier Inc., 2009
[3] American Heart Association, viewed 9 November, 2009, http://www.americanheart.org/presenter.jhtml?identifier=4595.

the normal results from an ECG do not rule out the occurrence of a heart attack. This is because the ECG 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.[3]

13. ELISA, which is the current method for detecting cardiac biomarkers, uses fluorescent labelling 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 favour prompt diagnosis for critical split-second medical decisions.

Enclosure:

ANNEX - Field-Effect Transistor in Nanowire Biosensors

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About the Institute of Microelectronics (IME)

The Institute of Microelectronics (IME) is a research institute of the Science and Engineering Research Council of the Agency for Science, Technology and Research (A*STAR). Positioned to bridge the R&D between academia and industry, IME's mission is to add value to Singapore's semiconductor industry by developing strategic competencies, innovative technologies and intellectual property; enabling enterprises to be technologically competitive; and cultivating a technology talent pool to inject new knowledge to the industry. Its key research areas are in integrated circuits design, advanced packaging, bioelectronics and medical devices, MEMS, nanoelectronics, and photonics. For more information, visit IME on the Internet: http://www.ime.a-star.edu.sg.

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ANNEX: Field-Effect Transistor In Nanowire Biosensor

Figure 1 : Schematic diagram of a field effect transistor biosensor used in the IME-developed integrated system to specifically detect for cardiac biomarkers