Editorial: Biomarkers – The kiss of death

A cavewoman discovered the first biomarker when she kissed her sick child's forehead and detected a fever. We have moved past kissing foreheads to more complex biological indicators: measurement of blood-borne cells and proteins, detection of genetic markers and specialised tests such as electrocardiograms. The beginning of this century brought hoopla, money and promise of a different world – biomarkers, like a panacea, would make every thing better, from diagnosis to treatment. Personalised medicine would bring advances in genomics and the molecular understanding of disease to the masses via more precise biomarkers. Everyone wanted a piece of the action. Unfortunately, that promise melted into a world where biomarker discoveries were few, programmes lacked appropriate funding and economic arguments proved wanting.

To start, we need more research on biomarkers. Doctors need to know why we are unwell and if the selected treatment is effective. Estimates report that half the prescriptions are given to patients who receive suboptimal benefit because of individual patient biology. A 10 per cent figure alone would equate to US$50bn of waste. Pharma desperately needs biomarkers to better target its drugs to proper patients; yet for pharma biomarkers are a double-edged sword. Biomarkers can keep a billion dollar drug development process from getting derailed by stratifying patients into responders and non-responders before entering clinical trials. This will lead to both more approvals and earlier, cheaper failure for non-promising drugs. The problem is other information may also surface. When would Merck have wanted to know Vioxx had problems? Before or after it sold billions?

How have we failed to capitalise on the promise of biomarkers? Pharma did it to itself. It outsourced the job to small companies, gave each a little bit of cash to develop their own unique platform to discover novel biomarkers, whether it be mass spectroscopy, flow cytometry or 2D gel based, and then grew upset when results lagged. Pharma paid on a per test basis to search for new biomarkers in small cohorts of patients – hoping to strike a biomarker with minimal investment. It relied on entrepreneurs to fund development of the technology to pan for these novel biomarkers. Unfortunately this strangled the very innovation it wanted to foster. Instead of returning some of the value of an early failure or a rescued drug, it offered the diagnostic rights to the biomarker pioneers. Unfortunately, the economics behind developing a diagnostic test are not particularly attractive to risk capital. Getting 10 per cent royalty on a test manufactured and distributed by someone else yields sales in tens of millions, sometimes not even that much. The venture community turned and ran. The diagnostic companies, the most logical backer of biomarkers, spend a pittance on research (~7 per cent of sales) and never showed interest in the first place.[1]

Unfortunately, biomarkers are not lurking in our blood just waiting for someone to see a spike in a histogram, nor do genomic markers explain very much by themselves. Even if the US$1,000 genome becomes a reality,[2] it is unclear what that information will do for us. Complex technologies that look at vast numbers of parameters, simultaneously, and in some cases in sequence need to be developed. Biomarkers of the future will probably be a pattern of multiple genetic and proteomic factors. Fifteen hundred dollars a sample will not get the job done. A failed drug will need to be rescued, a group of clinical trial patients will need to be weeded out and large cheques will need to be written – cheques that reflect the value of the information, which as we have

learned often commands little value. Small molecule powder is more important than the steps leading to its creation.

HOW DO BIOMARKERS MAKE IT OUT OF THE BARN?

There is a gap between the technologies employed to discover new biomarkers (protein chips, mass spectroscopy, even gene chips), and the technologies commonly used in clinical testing labs (enzyme-linked immunosorbent assay (ELISA), flow cytometry). Biomarkers discovered with complex technologies will only be made accessible to the masses through established technologies. It is unlikely that clinical laboratories will begin using mass spectroscopy, protein and gene chips in the near future. Introduction of new platform technology is a long, capital-intensive slog that is not financially justified by the economics of a diagnostic product.

WHAT IS THE SOLUTION?

It will take a while and the outcome will be dependent on a number of factors. Rather than pay for the discovery of new biomarkers on a case-by-case basis (as now with Pharma), we need a large-scale effort which fosters the development of new biomarker seeking technologies. Those discoveries also need to be translated into tests which can be performed in existing clinical laboratories. Recent advances have shown that testing multiple genomic and proteomic factors can detect early development of ovarian cancer[3] (the work of Lance Liotta and Emmanuel Petrocoin of the NCI and FDA, respectively). However, this test has been become bogged down in the regulatory process and lack of acceptance in the medical community. Regulatory bodies and the medical community need to speed up the acceptance of this emerging class of biomarkers. In the late 1990s, numerous pharmaceutical companies came together to fund the development of a SNP database – the SNP consortium. Is this a model for the development of biomarker technologies – or will we continue to kiss and wait for life or death?

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References and notes

1. From a review of income statements of diagnostic companies (Baxter, Dade-Behring, IVAX), these companies spend roughly 7 per cent of revenue on R&D, whereas most pharmaceutical companies spend 18 per cent of revenue on R&D.
2. A number of venture-backed companies are attempting to develop technologies to bring the cost for sequencing the entire genome of an individual into the range of US$1,000.
3. Petricoin, E. F., Ardekani, A. M., Hitt, B. A. *et al.* (2002), 'Use of proteomic patterns in serum to identify ovarian cancer', *Lancet*, Vol. 359, pp. 572–577.