Biomarkers, 2009; 14(3): 203–205

informa
healthcare

MEETING REPORT

SMi biomarkers summit, 2–3 February 2009, London, UK

Alan Paine, Editor in Chief *Biomarkers*

Professor of Toxicology, University of London, Charterhouse Square, London, EC1M 6BQ, UK

Introduction

We are at an exciting time in biomarker discovery because the technological advances of the past decade mean that biomarkers specific to many human diseases and their therapeutic intervention, including diagnosis, disease progression, drug efficacy and drug toxicity can now be identified efficiently.

The meeting began with Wil van den Hoven (Astellas Pharma Europe) introducing the business case for biomarker discovery which was a recurrent theme throughout the meeting. In brief, the main reason why Pharma is interested in biomarker research is that they see this as a panacea to cut development costs and attrition rates of new chemical entities. Accordingly, a number of contract research organisations are now involved in biomarker discovery. Some of these Almac Diagnostics (RNA analyses from formalin-fixed paraffin-embedded tissues), Bioscan Europe (preclinical imaging of isotope-labelled drugs in both experimental animals and humans), Epistem (plucked hair biomarkers as surrogate of epithelial tissue in oncology studies) and RBM (Rules Based Medicine offering a range of multiplexed immunoassay platforms) sponsored the meeting and provided speakers: Austin Tanney, York Haemisch, Lydia Meyer Turkson and Sabine Kuesters, respectively. Another sponsor was Asterand (preclinical studies with human tissue) who had an exhibition stand. Wil van den Hoven concluded that the strategic use of biomarkers can diminish late-phase attrition rates and may reduce development costs by between 25% and 50% in conservative and optimistic scenarios, respectively.

Systems biology and biomarkers *in silico*

Ananth Kadambi from Entelos Inc. elegantly described how computer-based mathematical models of human pathophysiology could assist not only biomarker identification but also assess their impact on therapeutic outcomes. Of course, such simulation techniques employing 'crash dummies' have been used by the aircraft and automotive industries for years so why not 'virtual patients' in Pharma? Indeed, the US Food and Drug Administration's (FDA) Critical Path Initiative recognises the value of computer modelling in drug development. Thus, nine large-scale, mechanistic, mathematical models of disease have been developed by Entelos. These cover metabolic disorders, e.g. type 2 diabetes/obesity, drug-induced liver injury, oncology, erythropoiesis, type 1 diabetes, induction of skin sensitisation, rheumatoid arthritis, respiratory and cardiovascular diseases. The objective here is to improve probability of clinical success by predicting clinical outcomes in trial design scenarios prior to running expensive clinical trials, not only by taking account of the underlying disease driving the mechanisms but also patient variability for existing therapies. The latter was illustrated by the response of patients with rheumatoid arthritis who are methotrexate (MTX)-naive and MTX- or anti-tumour necrosis factor (TNF)-inadequate responders to a new candidate drug. The simulations predict four groups of patients:

1. Those in whom monotherapy with MTX is better than a new drug candidate;
2. Those in whom monotherapy with a new drug candidate is better than MTX;
3. Those in whom monotherapy with a new drug candidate is as efficacious as infliximab, a cytokine inhibitor, in MTX-naive patients;
4. Those in whom a new drug candidate and MTX was expected to outperform anti-TNF and MTX combination therapy in MTX-inadequate responders;

(Received 17 March 2009; accepted 24 March 2009)

ISSN 1354-750X print/ISSN 1366-5804 online © 2009 Informa UK Ltd
DOI: 10.1080/13547500902922048

and two classes of patients unlikely to respond to therapy.

Obviously, unless patients enrolled in clinical trials are stratified the efficacy of the new drug candidate will be obscured in the general population of rheumatoid arthritis patients. Furthermore, the simulations predict the 10 best biomarkers, out of a pool of 50, to measure in order to demonstrate efficacy of the new chemical entity. This trial is underway so proof of concept of *in silico* approach remains to be established.

The 'other side of the coin' presented by Kadambi is that long-term cardiovascular risk often means that drugs are removed from the market (e.g. Vioxx for rheumatoid arthritis, Rofecoxib for colorectal cancer) and he concluded his presentation by considering situations where the use of surrogate biomarkers may be misleading in identifying cardiovascular risk and how the Entelos cardiovascular platform had been employed to identify a novel biomarker. Unfortunately, intellectual property issues prevented him from saying what this was but the 'take home' message was clear that emphasis is now very much being placed on personalised medicine by identifying high-risk patients.

Biomarkers and personalised medicine

The theme of biomarkers for patient stratification was continued in a philosophical and thought-provoking presentation by Hans Winkler (Ortho Biotech Oncology Division of Johnson & Johnson) because he felt that we can only expect a highly increased benefit in a selected population. For example, he stated that Herceptin® is only effective in 3–5% of patients with breast cancer but if patients are selected for expression of the Her2 biomarker then 60% of these patients respond and their tumour shrinks. Accordingly, the probability of success for Pharma is low if the entire disease population is studied. In addition, the proliferative pathways driving tumour growth are multifactorial – some tumours may be driven by just the activation of the Ras oncogene or epidermal growth factor receptor while other tumours may be driven by up to a dozen different oncogenes. Therefore, again by analogy to the automotive industry who expect 99% of their products to come off the production line working, to expect a single pharmaceutical entity to shrink a tumour may be much too optimistic! However, Winkler felt that while the individual biochemical events driving tumour growth themselves are very complex there are basically two branches of these signalling pathways, namely proliferative drivers and antiapoptotic (survival) components. Therefore, Winkler concluded that while most current cancer therapies are 'one size fits all approaches' we should be looking for biomarker signatures in biochemical pathways in order to weight a tumour's response to a new chemical entity. Such signatures may be provided by extraction of high-quality mRNA from the vast, global, archives of formalin-fixed paraffin-embedded tumour tissue (as in the presentation of Austin Tanney, Almac) followed by quantitative RT-PCR assays, etc. Nevertheless, novel statistical techniques will need to be developed for identifying meaningful signatures from the plethora of array data generated from patient material.

Computational biology in biomarker discovery

The successful discovery of new diagnostic and prognostic biomarker signatures as the cornerstone of personalised medicine will require sophisticated pattern-recognition computational tools such as support vector machines (SVM) and a separate, half-day, workshop was devoted to this topic. However, Herbert Fritsche (MD Anderson Cancer Centre) briefly outlined, in the main meeting, how SVMs facilitated the discovery of a serum biomarker test panel to distinguish benign prostatic hypertrophy (BPH) from prostatic cancer. He described how the biomarker discovery process started by using gene expression data from laser microdissected prostate tissue, then:

1. Pattern-recognition technology was employed to select, from many genes detected by microarray, only those over expressed genes that were highly associated with BPH cells versus normal and dysplastic cells;
2. The genes were grouped according to molecular pathways that are known to be involved in BPH disease;
3. A further subset of 25–50 gene products that are likely to be secreted or released into body fluids was selected;
4. A panel of secreted proteins that are reflective of each of the various gene pathways, which could be altered by the multimodal action of drugs used to treat BPH, was selected reducing the biomarker panel to a subset of 10 proteins in order to assess patient response to therapy and to facilitate development of companion diagnostics.

In the past, therapeutic agents have largely been discovered by serendipity; however, in the new millennium we are dealing with very complex diseases (e.g. cancer in general, Alzheimer's disease/dementia) and computational biology techniques especially in image analysis will become increasingly important in target/biomarker identification. In this respect, Mark Manfredi (Takeda/Millenium Pharmaceuticals) described how

3-D image analysis played an important role in selecting an Aurora A kinase inhibitor for Phase 1 clinical trials. Aurora A kinase inhibitors were claimed to show unprecedented efficacy in a xenograft model of primary neuroblastoma. This is because this kinase is only expressed during mitosis, localising to the centrosome of the mitotic spindle and its inhibition results in mitotic arrest, apoptosis and consequently tumour shrinkage. Difficulties in biomarker discovery in the nervous system diseases were outlined further by Ellen Bech Christensen (Lundbeck). She highlighted that our fragmentary knowledge of the underlying biology in the important area of dementia is severely lacking due to the absence of established biomarkers of cognition. Remember here that a biomarker is defined by the FDA as a physical sign or laboratory parameter linked to a disease that has a diagnostic and/or prognostic utility. Here serendipity could soon meet rational drug design through the ability to quantitatively image radiolabelled compounds such as those currently used successfully to treat depression/schizophrenia and identify targets/biomarkers. This is possible because York Haemisch illustrated how Bioscan's PET imaging of 'biomarkers' in animals as small as mice can be achieved with the same visual acuity as humans enabling us for the first time to conduct a wide range of preclinical studies in neurology, cardiology and oncology, and translate research results from laboratory bench to the patient's bedside. In conclusion, biomarkers are clearly a way forward for Pharma and I hope our journal can provide expert commentaries of what these new techniques have to offer the *Biomarkers* community.