The Total Biomarker Blog

Biomarkers: A Band-Aid for Bioscience?

Introduction

There is no disputing that the pharmaceutical industry has a problem. It is widely acknowledged that R&D productivity is declining, with new drug registrations falling to their lowest levels for almost half a century. Genuine medical advances are rare – those products that are registered increasingly offer only a small incremental benefit over existing medicines.

Changing business models, such as slimming down internal R&D in favour of acquisition for example, may be part of the solution. But financial engineering can only go so far. Reversing the trend and re-igniting the biotechnology boom requires a seismic shift in the way we discover and develop drugs.

One such change is already underway: the increasing use of biomarkers provides both obvious and less obvious benefits across the whole of the drug discovery and development cycle. Biomarkers are defined by the NIH as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention". They are not new; many have been with us for a century or more. Some biomarkers are so well engrained in our consciousness that we often cease to recognise them as such. Some, such as plasma cholesterol levels and blood pressure have even become regarded as disease entities in their own right, independent of any clinical symptoms associated with them.

Here we discuss some of the many and varied ways in which the use of biomarkers can help in the drug development process, and discuss the access to biomarker expertise in small to mid-size biotechnology and pharmaceutical companies.

Clinical studies

One of the most important uses of biomarkers is as surrogates for clinically relevant end-points, particularly in Phase II studies. In a few cases, biomarkers have become sufficiently well accepted to gain regulatory acceptance in pivotal trials (although the wisdom of doing so was thrown into question when some agents approved as cholesterol-lowering drugs were found to be much less effective in preventing heart attacks than other, ostensibly similar, agents). For the most part, though, pivotal trials have to demonstrate actual clinical benefit – and that usually requires long, large and therefore expensive studies. The purpose of Phase II studies, therefore, is primarily to predict the outcome of these pivotal studies, so that only those that will generate a positive outcome ever get run.

Such biomarkers can be physiological (such as measuring FEV1 to predict efficacy in respiratory disease) or molecular (typically levels of certain proteins in blood samples). Molecular measures are often cheaper and more robust, but there are few diseases where a sufficiently predictive marker has been found. Newer, "omics" approaches, which measure hundreds or thousands of biomarkers, offer real prospects for improving the efficiency of late stage clinical development – but discovering such predictive biomarker signatures is costly and time-consuming because you need large clinical studies to validate the candidate signature. This restricts identification and validation of predictive biomarker profiles, at least in the indications that need them the most (those where pivotal trials are the largest and longest), to big pharmaceutical companies, who (not unreasonably) do all that they can to restrict dissemination of that knowledge.

Drug discovery

Biomarkers are not just useful for achieving clinical proof-of-concept – they can increase efficiency at every stage of the drug discovery process, from earliest discovery through to the market and beyond.

The insight that can be gained with biomarkers during discovery is illustrated by our project seeking biomarkers for osteoporosis. Metabolite profiles of serum samples from women with osteoporosis or with normal bone mineral density were captured by NMR spectroscopy, and comparing the spectra between the two groups using Partial Least Squares modelling identified the amino acid proline as a potential biomarker. Women with low bone mineral density had, on average 25% lower levels of proline in their serum than women with normal bone mineral density. This observation was later confirmed using a specific colorimetric assay specific for proline.

However, proline is more than just a biomarker for bone mineral density. Women with lower levels of proline in their serum are at greater future risk of non-traumatic bone fractures (the major clinical consequence of osteoporosis), even after correction for bone mineral density. Moreover, the association could even be causal: proline is a major constituent of collagen, the major bone protein and proline deficiency could plausibly become rate limiting for new bone synthesis by osteoblasts. Consistent with this theory, proline and glycine (the other major amino acid in collagen) are the only amino acids actively salvaged by the kidney.

This biomarker identification programme has therefore lead to a whole new field of research, together with candidate products in the area of clinical diagnostics, food supplements (serum proline deficiency can be corrected, at least in the majority, by dietary supplementation with proline) and even pharmaceuticals. Proline is not an essential amino acid (meaning mammals can make it metabolically themselves) and some drugs, most notably paracetamol, can stimulate proline production. It is not inconceivable that a paracetamol may have similar benefits in osteoporosis to the protective effect of an aspirin after a heart attack.

Animal models of disease

Another important application of biomarkers in the discovery phase is the validation of animal models of diseases. Animal models still play a vital role in preclinical target validation, because it is essential to increase confidence in a predicted mode of efficacy before venturing into human studies. But a string of high-profile failures to translate impressive efficacy in animals (particularly rodents) into benefit in the clinic has seriously undermined confidence in the use of animal models. Too often animal models are used where the symptoms mirror a human disease, but the causal intervention bears little resemblance to the pathogenic mechanisms in man. For example, apoE-deficient mice are often used as an efficacy model in atherosclerosis research – but the massive hyperlipidemia that results from apoE-deficiency in mice is rarely seen in man, and is actually a model of type III hyperlipoproteinemia rather than coronary artery disease.

Again, biomarkers can help. By comparing the signature of analytes that are changed in the animal model with the biomarker signature in the human disease, you can get a sense of the extent to which the animal model recapitulates the molecular pathways involved in the disease. If the molecular signatures are similar, there is a much greater chance that efficacy in the animal model will translate into the clinic. We performed such a validation study, for a transgenic mouse model of Huntington's Disease, published in the journal *Brain* in 2006. We found a substantially overlapping biomarker signature in mouse and man, in both cases with a strong catabolic component, which provided significant validation of the model's utility for research into the pathogenic mechanisms behind the disease, and for drug development.

Toxicology

A similar approach has also been adopted for predicting toxicology, as opposed to efficacy. Toxicology studies in animals are used to predict harms (or rather to try and predict safety) in man. Failures in predictive toxicology don't just cost money – in the worst cases, such as the Te Genero trial of anti-cytokine antibodies, they can even cause significant harm to the study participants.

Through the COMET collaboration, big pharmaceutical companies have invested heavily in identifying biomarker signatures of specific organ toxicities. Such signatures can be used to validate the species used in predictive toxicology, and perhaps more importantly can be used in man to predict impending toxicity at low doses before further dose escalation causes harm. The greatest advances in this area have come from biomarkers of metabolic toxicities that are difficult to detect in conventional phase I studies, such as phospholipid syndrome and dysregulation of glycolipid metabolism. These effects, which are relatively common across a range of structurally distinct drug classes, take weeks or months of treatment to reveal themselves and were a common cause of expensive, late stage failures. Today, they can be reliably predicted using biomarker profiles.

An extension of this idea is to try and gain toxicology information from microdosing (or 'Phase 0') studies. Administration of very low (universally safe) doses of compound are now used quite regularly to get an indication of pharmacokinetics. Using biomarker profiles, it may be possible to identify the earliest changes of certain toxicities, further aiding the ability to select molecules from within a series for full clinical development, or to explore the effects, in man, of modulating an entirely new target.

Personalised medicine

As new drugs in later stage development increasingly offer only a small benefit over existing medicines, biomarkers are increasingly being used to predict efficacy in a given individual, so called "personalised medicine". A decade ago, the idea of a companion diagnostic was an anathema to most pharmaceutical companies: testing people to see if they needed a drug, or would respond to it would reduce market size, decreasing profits (which are maximal if you can sell your drug to everyone, even it only works in half of them). Today, the reverse is true. If a drug has only a small benefit over an incumbent (particularly a lower-priced generic) then it may be necessary to boost apparent efficacy, and this may be most easily done by identifying ahead of time the responders and only recruiting them to your clinical studies. The resulting label will be narrower, but the margin of superiority large enough to achieve some penetration. A smaller market is better than no market at all, and enterprising companies can exploit the companion diagnostic to create another profitable product.

A similar approach can be used to rescue a drug that is struggling in the clinic as a result of a rare but serious side effect. With such a liability, drugs rarely reach the market, with regulators ever more stringent on safety profiles, unless there is no viable alternative. Such is the case with the atypical antipsychotic clozapine – a small proportion of patients suffer a severe neutropenia after treatment, but the drug is the most effective antipsychotic medicine available. As a result, at great expense, neutrophil counts must be regularly monitored during treatment. How much better it

would be if you could reliably predict which subjects would go on to suffer neutropenia ahead of time, and avoid monitoring the majority who are not at risk? Where the drug doesn't have a substantial efficacy advantage, such a liability may well be the death knell for a multi-million pound investment. Finding biomarkers that can avoid treating the small number who respond to excellent drugs with rare side effects therefore has huge commercial value.

Access to biomarker expertise

As mentioned briefly above, the cost of identification, and particularly validation, of a biomarker can be large, due to the expense of the studies required for the process to be successful. For larger companies, the cost becomes part of their operating budget. However, it is a significant issue for smaller biotech companies, who don't have access to big pharma's knowledge base, but at the same time have to provide sufficient evidence of efficacy as early as possible in clinical development to tempt a buyer.

Several solutions present themselves. The most obvious is the proliferation of companies offering biomarker services. Because biomarker discovery, validation and (in many cases) analysis is both capital intensive and a highly specialised skill it makes little sense for smaller companies to try and build such a capability (and 'small' in this context may reach up as far as billion-dollar mid-size pharma's).

Specialist knowledge in assay design and validation, analytical chemistry and clinical study design is required to collect the measurements in the first place, followed by a deep understanding of multivariate modelling to mine the vast datasets which result for the desired "signature". It's easy to spot apparent signatures in very large datasets – there is always "an answer", but it's very much harder to tell if it's the "right answer" without sophisticated model validation. A fair proportion of biomarker discovery studies published in the academic literature are guilty of reporting something that was true just in that one experiment as if it were generally true and could be reproduced. For an academic, this rarely has any repercussions. For drug developers, however, who are putting to use the information gained from such studies to predict outcomes from large, expensive trials, the consequences of finding a false-positive biomarker signature are costly, and for a small company most likely catastrophic.

The growing availability of specialised out-sourcing operations is only one part of the jigsaw that will allow biomarkers to deliver their full potential for increased efficiency in drug development. A change in policy at large publicly-funded organisations (whether government agencies like the MRC in the UK or NIH in the USA, or charities such as the Wellcome Trust or British Heart Foundation) would also be of tremendous help. Funding academic research into biomarkers at clinical sites where the patient populations are found would be a very cost-efficient way of identifying new biomarkers that could be exploited by pharma' companies of all sizes, not just those that can afford to run the clinical validation studies themselves. If charities with a focus on a particular disease really want to see the money that they are entrusted with improve clinical management in their disease, then biomarker research will receive a greater priority than it does at present.

Conclusions

The examples given here, and other applications of biomarkers, illustrate the potential for biomarkers to improve the efficiency of drug discovery, killing molecules early, and driving up the success rate in later clinical development. Today, though, much of this promise remains unfulfilled despite the growing interest in the biomarker field. Mostly, this stems from the inherent difficulty of cross-disciplinary biomarker research, discovery and validation. For something conceptually simple, it is surprisingly difficult to do well. This in turn leads to issue of accessibility, particularly to smaller companies (a problem which new entrants like Total Scientific seek to solve). But it also leads to an ever-growing academic literature laden with false-positive claims for biomarker associations. Drug developers are in danger of being buried under such a large pile of poorly-validated candidate biomarkers, that they become disillusioned with the whole approach. Done well, biomarkers really can make a difference to the drug development pipeline. It would be a shame if this opportunity were lost by a widespread failure to differentiate the robust and predictive from the typical flimsy associations that abound in the literature.

If biomarkers are one of the answers to the problems in the pharmaceutical sector, then their use may lead to clinical validation being achieved more quickly and cheaper, leading to greater clinical innovation and increased efficiency. Moreover, with large companies seeing predictive biomarker signatures as valuable commercial know-how, there is a real opportunity for expertise in both the contract services and academic science to step into the breach, narrowing the information gap between smaller and larger companies, and enhancing the pathway to clinical validation for all.

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