Business strategy for implementation of biomarkers in drug development

With pharmacoproteomic biomarkers being the subject of focus among regulatory agencies as well as research institutions, many pharmaceutical companies are increasing their interest and investment in biomarker strategies. This article discusses the potential for new efficiencies and cost savings that can be achieved from the utilisation of biomarkers at different stages along the drug development pathway.

By Miles Flamenbaum

The application of advanced target discovery technologies such as genomics and proteomics has solved a conundrum of the pharmaceutical industry, namely, the identification and validation of an increasing number of therapeutic targets. This, in turn, has led to an increased number of candidate compounds and other therapeutic candidates. There continues to be a need to utilise improved discovery technologies to speed the elucidation and validation of therapeutic candidates. Although the rate of identification of novel therapeutic targets has improved, we must move down the development pathway to find additional efficiencies and improve the timelines for the introduction of new therapeutics.

The next problem to be tackled in drug development, viewed as a 'bottleneck' by the industry, is improvement in pre-clinical and clinical development. How will the industry manage and prioritise the burgeoning number of development candidates? How can the industry improve success rates in selecting the appropriate candidates for pre-clinical and clinical development? Are there technologies available to develop approaches that will enable faster regulatory approvals? The industry has also been grappling with the idea of personalised medicines and the utilisation of variations within a clinical population to more specifically address the needs of focused subgroups. Can an approach be developed to properly identify these subgroups in parallel with the development of a therapeutic?

The answer to these questions is to invest in the development and implementation of biomarkers. Biomarkers can illuminate pre-clinical and clinical development to create efficiencies and facilitate novel strategic approaches to overall drug development.

Firstly we must consider what a biomarker is as the term is subject to a wide variety of interpretations. Certainly, followers of a pharmacogenomics approach would contend that a biomarker consists of certain gene traits or SNPs (single-nucleotide polymorphisms) that predict biological predispositions, which distinguish between groups and even individuals. However, to consider the application of biomarkers within the context of pre-clinical and clinical assessment it is more practical to

define a biomarker in terms of what is actually occurring within the body rather than a predictive genetic measure. Therefore, the definition of a biomarker is an indicator of a discernable biological event or concerted events that can be directly associated with a particular event or status.

The US Food and Drug Administration (FDA) has already begun to identify what should be the characteristics of an ideal biomarker. These characteristics are summarised in **Table 1**[1].

Although the preliminary guidelines under consideration by the FDA are clear and reasonable, the question is what technological approaches might be utilised to develop relevant biomarkers? There are certainly several potential approaches. However, given the characteristics of an 'ideal' biomarker, it is necessary to focus on measurement biophysical reactions and interactions. Arguably the best measurement to rely upon would be to identify and quantify proteins (and, importantly, their isoforms) and interrelate those proteins with clinical information. Proteins, unlike DNA or RNA, are secreted into bodily fluids such as serum or urine in response to a physiological reaction, negating the need for a tissue sample. More particularly proteins, and their relative expression and changes within the body, as well as their direct connection to genetic, external and internal influences, represent an identifiable articulation of biological status. Proteins are what disease processes effect and are the inevitable target for drugs. Therefore, the technology most applicable in this context is proteomics.

Proteomics is defined as the separation and identification of proteins. Advances in proteomics technologies and approaches have enabled researchers to not only identify proteins but also to assess the amount of expression proteins present in a given sample, associate protein expression to biological phenomena, and ultimately identify the genetic derivation of a protein. The ability to combine disease status and information, clinical information and quantitative protein expression, including expression at various time points, provides the opportunity to measure a particular response within the body. To understand how proteomics achieves this, a brief review of a proteomics discovery process is necessary.

There are several proteomics processes currently implemented by a variety of biotechnology and pharmaceutical companies. The ideal process is one that does not require prior knowledge of the identity of a protein to identify it and associate it with biological information. In addition, a proteomics process for biomarkers must also identify protein isoforms, as ancillary forms of a protein are also associated with a biological state.

Table 1

Specific	Robust
Sensitive	Bridges pre-clinical and clinical trials
Predictive	Non-invasive/accessible

1. Specific (association to a particular disease or disease state and able to differentiate among similar physiological conditions)
2. Sensitive (measurable and standard baseline to act as a reference point)
3. Predictive (clear association between the measurable state and potential conditions)
4. Robust (rapid, simple, accurate and inexpensive detection of the relevant markers)
5. Bridges pre-clinical and clinical trials (enables development of the relevant measurements and then application of those measurements in a clinical development context)
6. Non-invasive/accessible (allows for use of standard biological sources such as serum and urine as the basis of measurement)

Antibody-based chips are limited by the need to know the protein structure prior to conducting the assay. Protein affinity chips, such as those used by Ciphergen Biosystems (Freemont, CA, USA) can be effective but do require specific antibody development to detect protein isoforms. ICAT™ (Isotope Coded Affinity Tag), developed by the Institute for Systems Biology at the University of Washington and licensed to Applied Biosystems (Foster City, CA, USA), can discover novel proteins but cannot necessarily detect specific protein isoforms. Therefore, based on the requirements for finding biomarkers, particularly identification of protein isoforms, the 2D Gel (two-dimensional gel electrophoresis) process is the most viable. This process is employed in various forms by Oxford GlycoSciences (Oxford, UK) as well as GeneProt (Geneva, CH) and Large Scale Biology (Germantown, MD, USA).

The 2D Gel process has existed as a research process for more than a decade. However, it has not been until recent advances in the industrialisation of the process that 2D Gel analysis has begun to reach its potential as a proteomics process. The basic process is to prepare a biological sample, such as serum, and separate the proteins on a polyacrylamide gel in two dimensions (weight and charge). The separated proteins can then be stained and the gel images captured electronically. The images can also be compiled to enable inter-group comparison. Utilising sophisticated bioinformatics technologies and biostatistical techniques, clinical information can be associated with the gel images to assist in seeking particular 'spots' that can be directly associated with clinical state (sex, age, disease progression, genotype, etc). Specific proteins can then be excised, processed and analysed using

mass-spectroscopy. A well-designed experiment joined with comprehensive clinical information can enable the identification of a set of biomarker proteins and the specific protein sequences defined. This combination of the exploration of proteins and associated clinical data for derivation of biomarkers of some type of biological status is known as Pharmacoproteomics.

As mentioned previously, there is increasing exploration of strategies to utilise pharmacoproteomic biomarkers. The idea of using biomarkers in drug development is not new. However, it is gaining momentum and acceptance. Biomarkers are the subject of focus at regulatory agencies as well as research institutions such as the National Institutes of Health[2]. The FDA is sponsoring several initiatives examining the development of biomarkers for use in a variety of applications. One in particular is the Nonclinical Studies Subcommittee Advisory Committee on Pharmaceutical Science[3], which has established Expert Working Groups for investigating biomarkers of cardiac toxicity and vasculitis. Several public and private working groups worldwide are working on implementing biomarkers. Pharmaceutical companies, in response to the interest in biomarkers by regulatory authorities, are also increasing their interest and investment in biomarker strategies.

The strategic implications of biomarkers are wide ranging. Biomarkers can be utilised at several stages along the drug development pathway, creating new efficiencies and cost savings. A list of potential applications is set forth in **Table 2** and a diagram summarising the strategy for integrating the use of biomarkers in drug development is represented in **Figure 1**.

Some of the efficiencies that can be gained through the use of pharmacoproteomics are quite striking. Initial application of toxicology databases, such as those derived from use of biomarkers, in pre-clinical development can trigger an initial estimated saving of $20 million and 0.3 years in development time per drug, leading to an additional $15 million of value[5]. Once utilisation of biomarkers spreads into clinical trials for expedited evaluation of drug effects and faster elimination of weaker compounds, the value gained expands to $70 million in value[6]. The strategic value is that understanding drug effects and modes of biological response clearly is a major advantage in lead selection and development decision-making. In addition, the ability to assess failure of a lead candidate earlier than presently done, as well as eliminate some parallel development would lead to significant cost savings.

Pharmacoproteomic biomarkers will also enable strategic segmentation of a particular market. For instance, it is important to understand whether there is a particular subgroup, based upon serum analysis for specific biomarkers, which will respond more effectively to a particular treatment. This information can be used to establish inclusion and exclusion criteria for clinical trials. Furthermore, clinical assays can be subsequently developed to specifically identify responding versus non-responding patients, definitively guiding appropriate patients towards the correct therapy. In fact, this strategy has already been put into practice by Genentech (S. San Francisco, CA, USA) with the introduction of Herceptin™. Herceptin is an antibody-based treatment for breast cancer that is effective only for the subset of patients who have overexpression the HER2/neu protein. Genentech developed Herceptest™, a clinical diagnostic, as the only approved method for identifying appropriate patients for the treatment. It is estimated that Genentech would have required nine times the number of patients in the Phase III segment of the Herceptin clinical trial if a clinical diagnostic had not been implemented early in clinical development[7]. The key differentiator to pharmacoproteomic biomarkers is that Herceptest is a genetic test that requires a tissue biopsy. A more advantageous and potentially cost-effective approach would be through use of more clinically accessible protein biomarkers such as ones occurring in the blood or urine.

The lesson learned with Herceptin is that co-development of a therapeutic and a biomarker can be manageable as well as introduce efficiencies and value. The data collected during a proteomic analysis to identify and validate a therapeutic target can be utilised to correspondingly seek biomarkers, further increasing efficiency. Biomarkers as indicators of drug response, efficacy and/or increased safety will enable a pharmaceutical company to more

Table 2 – Potential applications of pharmacoproteomic biomarkers[4]

PRE-CLINICAL APPLICATIONS	CLINICAL APPLICATIONS
Target selection	Diagnostics
Drug discovery	Markers of drug response
Target validation	Inclusion & exclusion criteria
Lead candidate selection	Patient subtyping (according to predicted response/adverse reactions)
Drug modes of action	Post-launch tailoring of therapy to prototype
Toxicology	Post-launch differentiation of competitors
– no observed effect level	
– screening	
– mechanism of action	

References

1 http://www.fda.gov/ohrms/dockets/ac/01/briefing/3798b1_04_HOLT/sld005.htm.
2 For example, amongst several initiatives, the National Institute of Arthritis and Musculoskeletal and Skin Diseases of the NIH has been exploring biomarkers for osteoarthritis (http://www.niams.nih.gov/ne/oi/oabiomarwhipap.htm).
3 http://www.fda.gov/ohrms/dockets/ac/01/briefing/3798b1_02_background.HTM
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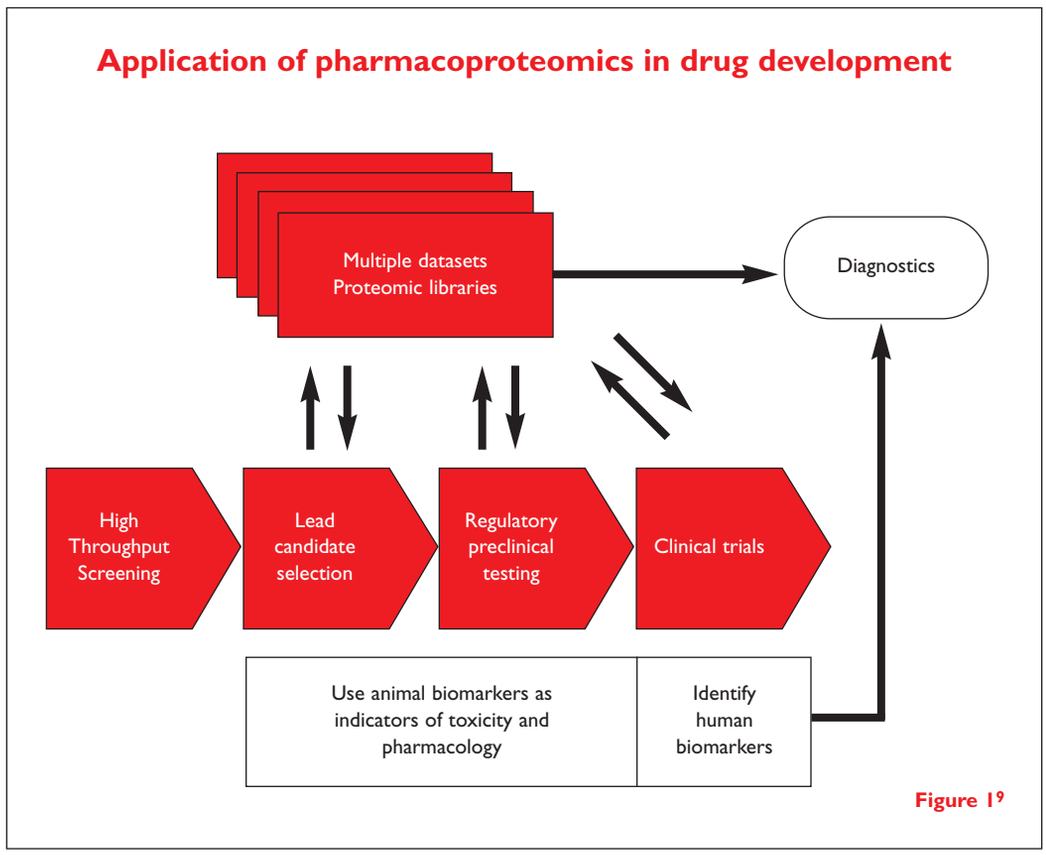

Figure 1[9]

deeply penetrate a particular market as well as speed approval into the focused treatment area. It is estimated that this strategy could add $290 million in value to a drug with cost savings of $420 million and development time savings of 0.7-1.6 years[8]. The savings and speed reduce the concern that such an approach may reduce the size of a potential market. A biomarker strategy will also place the therapeutic in an advantageous position relative to competitors. Furthermore, it can be argued that companies will be able to achieve a price premium for increased specificity as well as receiving a preference from clinicians treating that particular therapeutic area.

Biomarkers will also improve current understanding and approaches to toxicity. Toxicoproteomics, the application of pharmacoproteomics to toxicological analyses, will develop sets of biomarkers that can assess toxic reactions to drugs in pre-clinical and clinical development. Biomarkers will also be useful in post-marketing clinical monitoring for measuring response effectiveness as well as modification of dosage. The next logical step is the establishment of toxicology databases, both human and animal, that can promote efficiency in lead selection. These databases, once populated with sufficient and specific data, can be utilised in a predictive manner to identify toxic drug candidates in the early stages of preclinical development and save enormous time and value within the drug development process.

In conclusion, pharmacoproteomic analysis of biomarkers can provide an important strategic tool to be considered within the context of drug development. Significant cost savings can be found through the efficiencies afforded by developing and using biomarkers. Biomarkers will also enable pharmaceutical companies to promote additional value from a specific therapeutic by closely associating a drug with its appropriate clinical population. DDW

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