THERANOSTICS

an emerging tool in drug discovery and commercialisation

The increasing cost of healthcare along with new opportunities for improved treatments puts ever increasing pressures on healthcare budgets. In recent years the diagnostic industry in particular has been the target of a number of cost-cutting exercises by governments and payers aimed at restricting the utilisation of diagnostic tests. This in turn has exerted significant pressure on the diagnostic industry to maintain innovation and product enhancement in the face of restricted market growth. More recently, similar pressures have built on the pharmaceutical industry with increasing demands from payers for proof of efficacy and cost-effectiveness as well as regulators demanding proof of safety. Help may be at hand, however, from the emerging field of theranostics in which the developing technologies and capabilities of the diagnostic sector are increasingly applied to improving efficiency and economics of the discovery, development and marketing of medicines. This paper explores the principles of theranostics, current and future applications as well as attempting to define the real potential gains for pharmaceutical and diagnostic companies.

By Dr Ian Gilham

The term theranostics was probably first used by PharmaNetics president and CEO John Funkhouser in describing his company's business model in developing diagnostic tests directly linked to the application of a specific therapies. In the case of PharmaNetics this takes the form of new generations of point of care coagulation tests supporting coagulation therapies:
Diagnostics – the ability to define a disease state.
Theranostics – the ability to affect therapy or treatment of a disease state.

Some examples of theranostics

CASE STUDY 1: Herceptin® and HercepTest® – the birth of Theranostics?

September 25, 1998 was a key day for theranostics. On that day the FDA granted simultaneous approval for both Genentech's Herceptin® for the treatment of Stage IV breast cancer and Dako's HercepTest® for diagnosis of Her2 overexpression. Below are the key components of this groundbreaking strategy:

Disease

Breast cancer is a severe and life threatening disease for which treatments receive premium reimbursement in the larger markets. The disease is staged between I and IV. Of the stage IV disease approximately 30% shows significant overexpression of Her2 which is linked with more aggressive disease and a poorer overall prognosis[1]. The importance and implications of Her2 overexpression are well known with many reference labs offering Her2 testing via a variety

of 'home-brew' methods throughout the 1980s and 1990s.

Treatment
The standard treatment regime for breast cancer has long been established. However, the launch of Genentech's Herceptin® provided a new and highly effective tool in targeting the stage IV breast cancers over-expressing Her2. Herceptin®, or Trastuzumab, is a humanised monoclonal antibody to Her2 which is effective by binding to the Her2 expressed on the cell surface of the tumour cells.

Diagnostic
Although Her2 testing had been established for some time, the testing was performed using different methods and therefore presented the risk that lab to lab variation would be high thereby presenting a risk to the therapeutic strategy. Genentech addressed this risk by collaborating with Dako to produce a diagnostic test that could be used in any laboratory thereby standardising testing and reducing lab to lab variation

Outcome
The outcome was the FDA approval of Herceptin® with a label stating that the treatment is approved for patients overexpressing Her2. Since launch Herceptin® has become an important product for Genentech and its marketing partner Roche with sales reaching $346 million in 2002. In addition the availability of Her2 testing has moved into improved DNA-based tests with Abbott receiving FDA approval for a DNA-based Her2 test in 2002. The Herceptin® label in the US has now been updated to include the new test.

CASE STUDY 2: $LpPLA_2$ – tandem drug discovery and theranostic development
In October 2000 Chris Packard and colleagues at the West of Scotland Coronary Prevention Study Group (WOSCOPS) published data demonstrating the predictive value of Lipoprotein-Associated phospholipase A_2 (Lp-PLA_2) as an independent predictor of coronary artery disease[2]. This data has reinforced ongoing research into $LpPLA_2$ as both a predictive marker for atherosclerosis and as a potential target for new classes of atherosclerosis drugs.

Disease
Atherosclerosis is a widely acknowledged factor in cardiovascular disease which is a leading cause of death in the US, Europe and Japan. It is estimated that more than seven million Americans have cardiovascular disease with more than 500,000 deaths each year from heart attacks.

Treatment
GSK postulated a role for Lp-PLA_2 in atherosclerosis in the early 1990s using gene-sequence databases to clone the gene encoding production of Lp-PLA_2 for further study. Laboratory studies have since demonstrated that Lp-PLA_2 generates inflammatory substances, and that inhibition of Lp-PLA_2 reduces atherosclerosis in animal models. Currently, GSK is progressing drug candidates towards initial safety trials in human subjects.

Diagnostic
Under the terms of the formation of the company in 1997, diaDexus has exclusive rights from GSK to the diagnostic applications of $LpPLA_2$. DiaDexus has developed a diagnostic test for $LpPLA_2$ in a format suitable for routine laboratory use.

Outcome
The development of a diagnostic test for $LpPLA_2$ and drugs targeting the $LpPLA_2$ molecule are progressing in parallel with each potentially supporting the other. While the final result of GSK's drug discovery programme awaits outcome of further studies, it is clear that the existence of the $LpPLA_2$ test, and its potential acceptance in routine risk assessment, has the potential to identify patients for a future drug and increase awareness of the target in the medical community. In addition sales of the diagnostic could benefit significantly from marketing activities linked to a future medicine.

Other collaborations
A number of key theranostic alliances are listed in **Table 1**.

Impact of theranostics
A key challenge to the pharmaceutical industry today is the ballooning cost and decreasing productivity of research and development driven to a large extent by the ever-increasing need to prove clinical efficacy and cost-effectiveness of new medicines. The need to satisfy these demands in advance of product launch has the effect of increasing product development times thereby also decreasing the window of opportunity afforded by the patent life of the compound. The selective application of theranostics has the potential to positively impact these challenges, reducing risk and costs, speeding market entry

Table 2
Key theranostic deals – 1998-2002

COMPANIES	OBJECTIVES	YEAR
DiaDexus and GlaxoSmithKline	Support of a potential atherosclerosis medicine targeting $LpPLA_2$ with an $LpPLA_2$ diagnostic test	1997
Genentech and Dako	Development of Herceptest® immunocytochemical test to detect over expression of Her2 to support targeting of Herceptin" breast cancer therapeutic	1998
GlaxoSmithKline and Quidel	Development of a point of care, rapid Flu test in support of targeting of Relenza®, GSK's flu medicine	1999
GlaxoSmithKline and Amrad	Co-marketing of rapid point of care test for hepatitis B in support of GSK's lamivudine hepatitis B treatment	1999
GlaxoSmithKline and Quidel	Development of a point of care, rapid herpes tests in support of targeting of Valtrex®, GSK's Herpes anti-viral therapy.	1999
Aventis and Pharmanetics	Rapid point of care heparin testing in support of the Aventis's Enoxaparin®	2000
Millenium and Roche	Diagnostic and therapeutic discovery for rheumatoid arthritis	2000
Millenium and Abbott Laboratories	Pharmacogenetic tests and drug discovery for diabetes and obesity	2001
Myriad and Abbott Laboratories	Diagnostic and therapeutic discovery for depression	2001
Novartis and Variagenics	Novel diagnostics and therapeutics for prostate cancer	2002

and, ultimately, enhancing the commercial success of the medicine. In practice theranostics can be applied in five key areas[3]:

- Treatment selection and medicine response testing to provide information on the selection of appropriate treatment for individuals which are likely to provide an appropriate balance of efficacy and side effects.
- Predisposition profiling, the ability to assess and individuals risk of developing a specific disease so that a medicine can be given to prevent the development or minimise the impact of a disease.
- Health status monitoring, to enable the development of more effective tools to monitor health, especially in high risk groups.
- Diagnostics, the investigation and diagnosis of disease in symptomatic individuals.

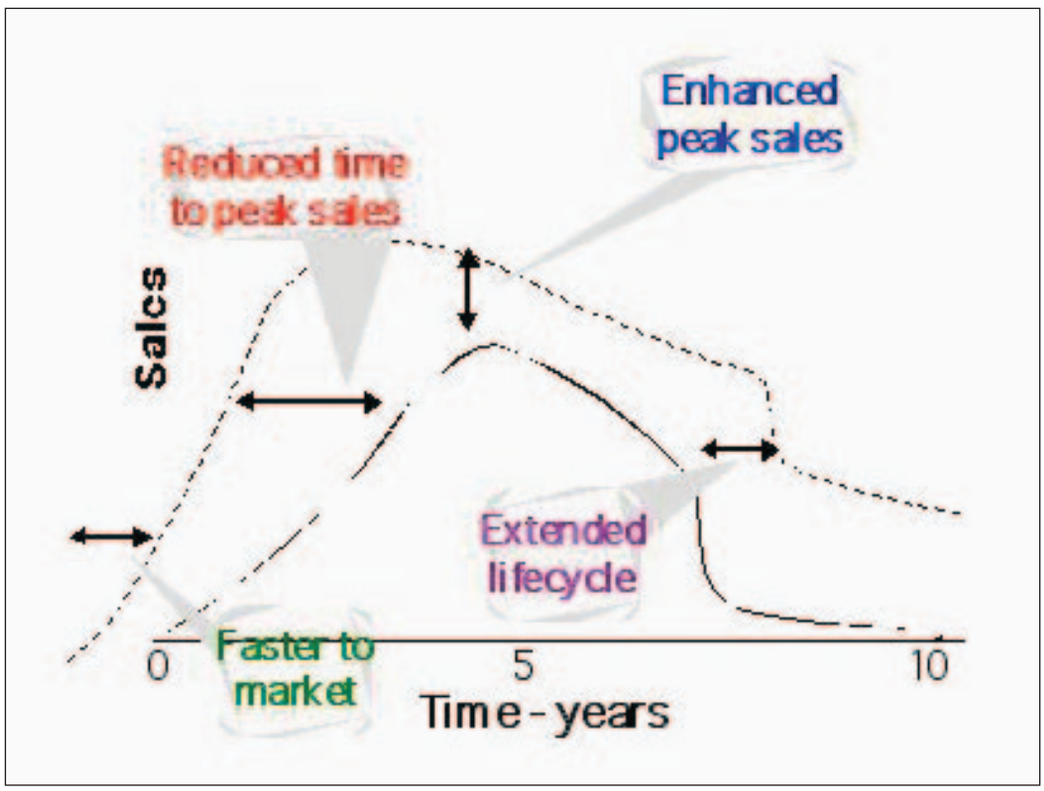

Figure 1
Potential impact of theranostics on the commercial value of a medicine

- Monitoring for treatment response, the development of tests to monitor compliance levels and promote optimal outcomes.

Commercialisation

There are several potential ways that theranostic tests can impact the commercialisation of new medicine (**Figure 1**). These include:

- Earlier to market due to enhanced drug development including faster and more targeted clinical studies.
- Reduced time to peak sales due to an enhanced ability to identify appropriate patients and measure efficacy with objective diagnostic criteria.
- Enhanced peak sales due to a larger patient group being targeted for the medicine.
- Extended product life where prescribing of a medicine is tightly linked to a diagnostic test which has patent protection beyond the expiry of the medicine patent.

Clinical studies

It has been postulated that the application of theranostic tests can have a profound effect on the practise of pharmaceutical clinical studies. In particular it has been suggested that pharmacogenomic tests in particular have the potential to significantly reduce the size and cost of pre-market clinical studies while offering the possibility of post-market surveillance as a viable alternative[4]. While this is still at a relatively early stage, it is clear that the impact of theranostic type testing as an integral part of drug clinical studies is worthy of deeper investigation.

Drivers and influencers

Regulators

It has been estimated that there are more than 100,000 deaths annually in the US due to adverse side-effects of prescription medicines with associated costs reaching more than £75 billion each year[5,6]. Understandably, therefore, the regulatory authorities have a keen interest in employing diagnostic technology in the assessment of medicines both before approval and on a surveillance basis once a medicine is in the market place. Of particular concern is the development and validation of new generations of toxicology markers that have the potential to predict the toxicity of medicines. This has the potential to become an area of significant focus for diagnostic and pharmaceutical companies alike in the near future and will undoubtedly play a significant role in the future of theranostics.

Payers

With the increasing cost of healthcare, payers are focusing on technologies which have the ability to

predict which patients will respond to a specific medicine before agreeing to fund the treatment. As a result there is an increasing interest on the part of payers in tests that will select appropriate patients for a specific therapy and are more likely to approve funding for a medicine where such a test exists and is readily accessible and affordable.

Patients

Advances in information technology, particularly the explosive growth of Internet access, offers patients unprecedented opportunities to access information on diseases including the costs and benefits of treatments. At Axis-Shield we have seen a consistent growth in demands for information and educational materials on homocysteine and its role in cardiovascular disease and dementia. This demand for information comes from a variety of sources including people either with cardiovascular disease or in high risk groups as well as, increasingly, physicians who are seeking to be able to answer the questions posed to them by their increasingly knowledgeable patients. This is certainly one key driver of the increasing demand for homocysteine testing and the associated treatments.

Pharmaceutical marketing strategies

Pharmaceutical companies have long perceived the diagnostics industry as a low margin business not affording the 'blockbuster' opportunities of medicines. In addition, the application of diagnostic tests to support the marketing of medicines has been a rarely used tool in the pharmaceutical marketing portfolio due, in part, to fears of driving market segmentation reducing the potential market for specific medicines. The application of genetic and, more recently, proteomic-based technologies to the study of disease has, however, begun to shed an increased level of light on the underlying mechanism of key diseases such as respiratory disease, cancer and cardiovascular diseases with each disease's segment calling for a specific therapeutic approach. Increasingly the traditional 'one size fits all' approach is proving to be less successful with, in particular, payers demanding better identification of the group of patients that will best respond to a specific medicine as an integral part of the evaluation of the cost effectiveness of a particular treatment. In the UK, the National Institute of Clinical Excellence (NICE) in its evaluation of Relenza® (the GSK influenza medicine) deemed that one factor in the cost effective prescription of the drug was enhancing the ability of physicians to accurately diagnose influenza versus other respiratory infections that would not respond to Relenza®. This approach strengthened GSK's focus on the collaboration with Quidel to develop a rapid point of care Flu test for use in the doctor's office.

Options for pharmaceutical companies

So what options face the pharmaceutical company in developing a theranostic strategy in order to reduce the risk and increase the chances of success for a medicine? The first real question is whether to go with an internal programme or entrust the test development to a diagnostic partner. While each decision must be made on a case by case basis, it is clear that many pharmaceutical companies are seeking to form alliances with diagnostic companies that offer a greater depth of knowledge and experience in diagnostic development and commercialisation. Diagnostic companies are likely to be able to provide a tangible route through the intellectual property environment surrounding diagnostic tests and technologies. In addition, should the theranostic strategy require broad global availability of the test, the only realistic way to achieve that is via a diagnostic partner that has a global network of appropriate laboratory instruments and the logistics to distribute and support the test kits and reagents.

Options for diagnostic companies

And what about the diagnostic company – what options does it have in capitalising on the evolution of theranostics? At Axis-Shield, when analysing new potential diagnostic markers for a specific disease we use the 'so-what' test. It is simply not enough to have a better test that will more sensitively or specifically diagnose or stage a disease. We need to know what that test will offer to clinical practice and management of that specific disease and increasingly the key driver in our decision-making is the availability of therapies that will benefit from our new test thereby giving the test a high clinical value. If the 'so-what' test cannot be passed we are much less likely to pursue a specific test as the marketing demands of successfully establishing a market for the new test would be too great and the timelines too long.

Within Axis-Shield we are working on a number of tests with theranostic applications. We have recently begun marketing a test for anti-cyclic citrulinated peptide (anti-CCP) which is a new, sensitive and specific marker of rheumatoid arthritis[7]. In addition we have been successfully co-marketing

our proprietary tests for homocysteine with a number of vitamin suppliers where the vitamins are prescribed as a direct therapy for homocysteine which has strong associations with cardiovascular disease and has more recently been proposed as a risk factor for Alzheimer's disease[8,9]. A key part of the future strategy of Axis-Shield is, along with our pharmaceutical partners, to focus on theranostic tests that have clear potential for linkage to specific therapies.

Conclusions and the future

In summary, it is increasingly clear that the development of new technologies, both genetic and non-genetic, offer new opportunities for a better understanding of the underlying mechanisms of disease. These advances will facilitate the development of new classes of targeted medicines as well as sensitive and specific diagnostic tests. It is highly likely that the maximum value for these advances will be gained where the diagnostic and therapeutic applications of this knowledge are bought together in the developing filed of theranostics. We already have some striking examples of the power of theranostics and it is clear that collaborations between pharmaceutical and diagnostic companies hold much promise to satisfy unmet needs in important diseases. DDW

Dr Ian Gilham *was, until last year, Vice-President, Pharmacogenomics and Applied Diagnostics for GlaxoSmithKline, a company he originally joined in January 1999 (when it was Glaxo Wellcome) in the newly created role of Worldwide Director, Predictive Medicine. Prior to that Dr Gilham held research and development positions with Celltech Ltd and Amersham International in the UK before joining Abbot Laboratories in 1990. He is currently Group Managing Director of the Laboratories Division of Axis Shield.*

References

1 Ravdin, P. Semin Oncol 27 pp33-42 (2000).
2 Packard, CS et al. N Engl J Med, 343 pp 1148-1155 (2000).
3 Gilham, ID and Rowland, T. Int J Medical Mktg 2 pp 18-22 (2001).
4 Roses, AD. Nature 405 pp 857-865 (2000).
5 Lazarou, J et al. JAMA 279 pp1200-1205 (1998).
6 Johnson, JA et al. Arch Intern Med 155 pp1949-56 (1995).
7 Schellekens et al. Arthritis Rheum 43 pp 155-163 (2000).
8 Refsum, H et al. Ann Rev Med 49 pp 31-62 (1998).
9 Seshadri, S et al. N Engl J Med 346 pp 476-483 (2002).