editorial

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Genetics – getting personal

The pharma and biotech industries are facing a shift away from the blockbuster drug business model. Big pharma has been unable to create enough new drugs to offset the declining sales of blockbuster drugs coming off patent. The increasing costs of drug development and time to market, competition from generics manufacturers in the emerging economies and a changing patenting and regulatory landscape are all factors that are forcing companies to develop new business strategies. This has led to a significant amount of M&A activity within the sector and increasing levels of outsourcing as companies try to fill their pipelines and achieve economies of scale. However, one of the most significant developments has been the emergence of stratified approaches to drug development and drug prescription based on an individual's genetically determined response to a given therapy – it is a well known fact that most medicines are only effective in <30% of patients.

In the late 1990s, genomics was seen as the answer for boosting the pharma and biotech industries' ailing novel drug target pipeline. It cannot be disputed that genomics certainly offered up many new and interesting targets; however, this has not translated into an increased number of FDA approved NMEs (average 33 per year 1993–1997; 26 per year 1997–2003) and the return on investment has yet to be fully realised. A popular view is that the industry is awash with targets; the challenge now is how to select which targets to take forward with a high degree of confidence of success. What's more, in contrast to the 'one size fits all' approach, many of these new therapies will be targeted in their action, treating only a subset of the patients with a given disease.

We are at a very exciting time in genetics and medicine. The past year has seen astonishing advances in technology that now allow a million separate DNA loci to be analysed in a single experiment – something that seemed unachievable only a few years ago. This technology has resulted in the identification of new genes that predispose individuals to common diseases such as diabetes, heart disease and arthritis. New DNA sequencing technologies mean that the ability to sequence a person's entire genome is a reality, indeed, only recently, a US-based company, Knome Inc., announced that it is offering whole genome sequencing for $350,000. The challenge over the next 5–10 years will be to develop third generation sequencing technologies that can drive the price down to as little as $1000 per genome. This will undoubtedly provide major new opportunities to use genetic data for the development of diagnostic and prognostic markers, new therapies and personalised medicine.

Not surprisingly, most of the early developments in personalised medicine have been in the field of oncology and, in particular, breast cancer. In the past 5 years, oncology drugs for patients with specific genetic characteristics have increased from 10% to 40% of all drugs in clinical trials. A well-known example is the use of trastuzumab (Herceptin®; Genentech) for breast cancer tumours that express high levels of the receptor tyrosine kinase HER2 (ERBB2) – approximately 20–30%. This has also provided a new economic model for the industry – by charging a premium

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price for higher efficacy in a target group, stratified medicines can generate high financial returns (Herceptin® sales for 2005 were $476M).

New products for breast cancer based on genomic and genetic data are emerging. OncotypeDX® (Genomic Health), a clinical laboratory improvements amendment (CLIA) approved product, comprises a panel of 21 genes and is aimed at women treated with tamoxifen. OncotypeDX® is used to predict recurrence and response to therapy and is validated for breast cancer patients whose disease is newly diagnosed, stage I or II, node negative and estrogen-receptor (ER) positive.

In 2007, the FDA approved MammaPrint® (Agendia) for predicting breast cancer recurrence. MammaPrint® comprises a panel of 70 genes involved in cell cycle, invasion, metastasis and angiogenesis and is used in patients with stage I disease who are ER positive or negative and stage II disease patients who are ER positive or negative and lymph node negative. Interestingly, these two products only have one single gene in common and were cleared under different regulatory pathways.

Genetic variation within the estrogen receptor genes may also have important consequences given that tamoxifen is a selective ER modulator. Tamoxifen acts via binding and modulation of two classes of estrogen receptors – ERα and ERβ encoded by the genes ESR1 and ESR2. The expression of the estrogen receptors is determined by genetic polymorphism and estrogen receptor mutations have been identified in tamoxifen-resistant tumours.

Many studies have used gene expression techniques to identify specific gene signatures that can predict drug response, outcome and guide disease management. It is likely that many more companion diagnostic tests will be approved by the FDA in the coming years.

More recently, a new class of signatures involving a set of molecules called microRNAs have been described that characterise tumour diagnosis, staging, progression, prognosis and response to therapy. MicroRNAs are short non-coding RNAs, typically 20–22 nucleotides in length that can act either as oncogenes or tumour suppressors. To date, every type of tumour analysed by miRNA profiling has shown a significantly different pattern from paired normal tissue. As we learn more about the role of miRNAs in cancer tumour development and progression it will provide another means to stratify patients and guide personalised treatment.

A highly successful class of new drugs are the tyrosine kinase inhibitors that target the epidermal growth factor receptor (EGFR). In 2003/2004, gefitinib (Iressa; AstraZeneca) and erlotinib (Tarceva®; OSI Pharmaceuticals/Roche/Genentech) were fast-track approved by the FDA for use in patients with advanced non-small cell lung cancer (NSCLC) who had failed on conventional therapies. The EGFR is expressed in 50% of NSCLC patients and is associated with a poor prognosis. It became apparent that these drugs were extremely effective in a specific subset (~10%) of patients, notably non-smokers, women and East Asians. Subsequent molecular analysis showed that this efficacy was associated with somatic activating mutations in the tyrosine kinase domain of the EGFR gene. However, the therapeutic inactivation of essential kinases creates selective pressures for the development of mechanisms of resistance. Acquired resistance to gefitinib and erlotinib was observed in some patients that could be explained by the occurrence of a separate spectrum of mutations in the catalytic domain of the EGFR gene. Dramatic response to treatment with TKIs may occasionally be durable (>3 years), but more commonly will only last for 6–12 months before resistant disease sets in. Therefore, overall, only a modest improvement in total survival rates in unselected patients has been observed in US and European retrospective trials, leading to the high-profile withdrawal of Iressa. This highlights the importance of study design and the selection of patients based on specific genotypes, that is patient stratification.

Another highly effective tyrosine kinase inhibitor is imatinib (Gleevec®; Novartis) that is used to treat chronic myeloid leukaemia and targets the bcr-abl fusion gene product. More than 95% of patients respond positively to imatinib with a 5-year survival rate of 89%. However, drug-resistance will develop over time in a significant proportion of patients. This has been attributed to the occurrence of somatic mutations in the kinase domain of the bcr-abl fusion gene. The clonal expansion of cells carrying these mutations can be monitored using quantitative PCR techniques of the mutant transcript and guide the use of second line therapies when necessary.

Acquired resistance to tyrosine kinase inhibitors is observed in several types of cancer. A new mechanism of resistance was recently identified that involves amplification of the MET oncogene, another gene that encodes a transmembrane tyrosine kinase receptor.

New and targetable mutations can be detected in tumours that are re-biopsied at the time of drug resistance. Paired biopsy specimens (pre- and post- treatment) from tumours that develop drug-resistance are critically important to enable the characterisation of the underlying genetic alterations. Establishing collaborative networks and systems that provide surveillance, as well as the collection and characterisation of tumour resistance, will become increasingly important. The need for good quality biological specimens that have a rich complement of associated clinical data cannot be overstated. The rapid diagnosis of the molecular cause of tumour resistance in patients will provide valuable insights. Historically, the pharma industry has spent little time developing drugs linked to diagnostics (theranostics) but this situation will undoubtedly change as the value of such theranostic approaches are realised.

The examples described all demonstrate the important use of genetic information to diagnose, define and monitor drug treatments. Genetics will play an increasingly important role in the development of new drugs and companion diagnostics as personalised medicine becomes integrated into the mainstream. This individual-based approach to medicine will lead to a progressively fragmented market with a large number of highly differentiated products requiring a sophisticated array of molecular genetic techniques for their delivery. Coupled with this is the need to provide healthcare professionals with the necessary knowledge and training to use these techniques and information effectively in the management of their patients.

Further Reading

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