Integrating diagnostics and therapeutics: revolutionizing drug discovery and patient care

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Over the next five years it is widely anticipated that the molecular diagnostics industry will continue to grow at double-digit pace to meet increasing demand for personalized medicine. A wide variety of drugs in late preclinical and early clinical development is now being targeted to disease-specific gene and protein defects that will require co-approval of diagnostic and therapeutic products by regulatory agencies. For clinical laboratories and pathologists, this integration of diagnostics and therapeutics represents a major new opportunity to emerge as leaders of the new medicine, guiding the selection, dosage, route of administration and multi-drug combinations, and producing increased efficacy and reduced toxicity of pharmaceutical products.

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▼ The introduction of targeted therapeutics into clinical practice has created major opportunities for further development of the molecular diagnostics industry. The approvals of Herceptin™ [Genentech; http://www.gene.com/gene] for the treatment of *HER-2/neu* overexpressing breast cancer and Gleevec™ [Novartis; http://www.novartis.com] for the treatment of chronic myelogenous leukemia (CML) featuring a *bcr–abl* translocation and gastrointestinal stromal tumors with selective *c-kit* oncogene-activating mutations, have brought to the diagnostic laboratory an expanding role for the testing of patients to determine their eligibility to receive these new therapies [1,2]. The molecular diagnostics industry is in a state of rapid evolution featuring continuous technology developments and new clinical opportunities for drug selection, predicting efficacy and toxicity and monitoring disease outcome [3–5]. The *in vitro* diagnostics industry is now believed to consist of a US$33 billion market of which molecular diagnostics is currently <3%. The worldwide pharmaceuticals market is believed to encompass >US$1.1 trillion. Gene-based and molecular diagnostics testing is currently listed at only US$1 billion in worldwide sales, but is growing at a 30–50% rate. It is currently believed that as many as 1500 genes and 5000 proteins are candidates for molecular tests. The view is widely held that, in the next 5–10 years, the clinical application of molecular diagnostics will further revolutionize the drug discovery and development process, customize the selection, dosing, route of administration of existing and new therapeutic agents and truly personalize medical care [6].

Forces driving unprecedented change in healthcare

The sequencing of the human genome, expansion of proteomics research and the emergence of other exciting technologies including functional imaging, biosensors and enhanced computational biology are causing unprecedented changes in modern healthcare. The emergence of rapid communication and electronic information sharing has created a more-informed and demanding consumer. The past 120-year era of phenotypically-derived pharmaceuticals (treating symptoms rather than the cure of disease) is no longer acceptable to the public. Moreover, adverse drug reactions caused by the failure to predict individual drug toxicity or toxic drug–drug interactions now account for 100,000 patient deaths, two million hospitalizations, and US$100 billion in healthcare costs in the USA every year [7]. It is currently believed that 20–40% of people receiving pharmaceutical agents are on the wrong drug [8].

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Personalized medicine

Personalized medicine includes the concepts that for a given disease, individuals have differential rates of progression of the disease and responsiveness to drugs [9]. In the past, medicine has relied on non-specific clinical signs for diagnosis and empirical treatment strategies. However, the emerging genomic and proteomic technologies and information are now resulting in the molecular sub-classification of disease as the basis for diagnosis, prognosis, and therapeutic selection. For example, expanded knowledge of the molecular basis of cancer has shown that significant differences in gene expression patterns can guide therapy for a variety of solid tumors and hematological malignancies [10]. In cardiovascular disease, genetic heterogeneity has been identified in long QT syndrome and choice of therapy (Na^+ channel blocker versus K^+ channel blocker versus β-adrenoceptor blocker) is now determined by the genetic etiology of the syndrome [11]. Inherited forms of long QT syndrome can be caused by high affinity drug blockade associated with mutations in the HERG potassium channel regulatory gene [11].

Goals of personalized medicine

The ultimate goal of personalized medicine is to take advantage of a molecular understanding of disease both to optimize drug development and direct preventive resources and therapeutic agents at the right population of people while they are still well. The goals of personalized medicine in drug development include: (1) the selection of optimal drug targets; (2) the selection of optimal drug dosage; (3) the selection and monitoring of patients for shorter, less-expensive advanced clinical trials; (4) the ability to predict which individuals will respond to drugs at high rates and who will be less likely to suffer toxic side effects; (5) reducing the overall cost of drug development and increase drug value; and (6) to ultimately improve and provide more effective healthcare for all individuals whether they be well or suffering from the early or late stages of illness. Genetic variants can be used to predict the predisposition of an individual for future disease development. By applying the principles of personalized medicine it is possible to significantly enhance the productivity of drug discovery and development. Through the identification of the 'right' gene, the 'right' pathway and the 'right' target in the pathway, the 'right' drug can be developed to treat the 'right' patient.

Pharmacogenetics and SNPs

An individual's response to a drug is the complex interaction of both genetic and non-genetic factors. Genetic variants in the drug target itself, disease pathway genes, or drug metabolizing enzymes can all be used as predictors of drug efficacy or toxicity. More than one million SNPs are now available for genotyping and phenotyping studies [12]. Novel genotyping strategies are emerging on a regular basis using a variety of techniques designed to increase the rate of data generation and analysis. A high-resolution SNP map recently developed by the SNP Consortium (http://snp.cshl.org/) could expedite the identification of genes for complex diseases such as asthma, diabetes mellitus, atherosclerosis and psychiatric disorders. In oncology, the SNP technology has focused on detecting the predisposition for cancer, predicting toxic responses to drugs and selecting the best individual and combinations of anti-cancer drugs.

Cancer predisposition testing

SNP genotyping and gene sequencing (see later) have uncovered a variety of familial cancer predisposition syndromes based on single and multiple gene variants [13]. Genotyping has been introduced widely for the detection of familial cancers of the breast, ovary, colon, melanoma and multiple endocrine neoplasia [13].

Prediction of drug toxicity

One of the earliest applications of SNP genotyping in cancer management was the discovery of variations in drug metabolism associated with genomic variations in drug metabolizing enzymes such as the cytochrome P450 system [14]. SNP detection has been used to predict adverse events in anti-retroviral therapy in patients with HIV infections [15]. The potential clinical value of the pharmacogenetics approach for predicting drug toxicity will be uncovered as more candidate polymorphisms are discovered.

Predicition of drug efficacy

The application of genotyping strategies to predict anticancer drug efficacy has recently emerged in a variety of clinical settings [16,17]. Genotype resistance testing of HIV isolates has demonstrable clinical use and provides a way to assist therapeutic decision-making in patients whose HIV RNA levels are rising [18]. Moreover, HIV viral-load testing has served as the major guide to the selection and maintenance of anti-retroviral therapy [19]. In colorectal cancer, pretreatment genotyping on peripheral blood samples is currently being used to select therapy based on the prediction of resistance associated with certain genetic polymorphisms [20].

Pharmacogenomics

Pharmacogenomics can best be defined as the application of whole-genome technologies (e.g. gene and protein

expression data) for the prediction of the sensitivity or resistance of an individual's disease to a single drug or group of drugs.

Transcriptional profiling and genomic microarrays

The development of printed and spotted genomic microarrays has enabled the rapid accumulation of new information concerning gene mutation and expression in human malignancies [21–22]. Microarrays can be used to determine gene mutations and SNPs as well as provide rapid screening information regarding mRNA expression. Transcriptional profiling has the ability to generate hundreds of thousands of data points requiring sophisticated and complex information systems necessary for accurate and useful data analysis. This technique has generated a wealth of new information in the fields of leukemia and lymphoma, and solid tumor classification and prediction of metastasis, drug and biomarker target discovery and pharmacogenomic drug efficacy testing.

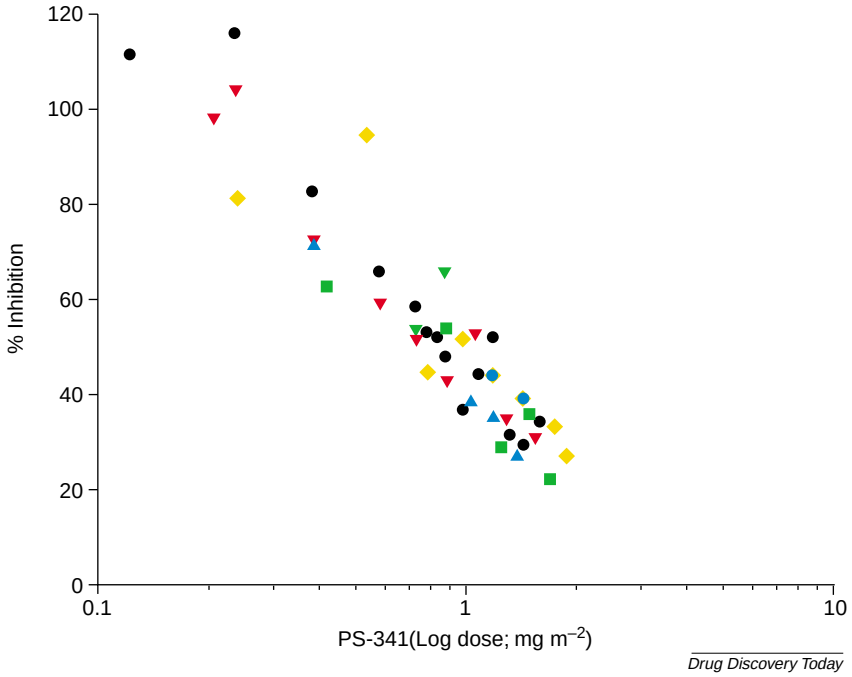

Figure 1. Effect of PS-341 treatment on 20S proteasome activity in humans. These data represent 20S inhibition data taken 1 h after dosing in blood samples collected from >130 cancer patients treated with PS-341 in multiple Phase I clinical trials. The data points were compiled regardless of age, sex, race, dosing regimen or cancer type and clearly show a dose–response relationship between 20S inhibition and the dose of PS-341. In the Phase I clinical trials, well-tolerated and active doses of PS-341 in the range of 1.1–1.3 mg m^{-2} produced an average of 70% 20S proteasome inhibition. At this dose, with interval administrations timed to allow full proteasome recovery, minimal toxicity has been seen with biologic activity observed against a variety of hematopoietic and solid tumors.

Transcriptional profiling and pharmacogenomics

The hierarchical clustering technique of data analysis from transcriptional profiling of clinical samples known to have responded or been resistant to a single agent or combination of anti-cancer drugs has recently been employed as a guide to anti-cancer drug therapy [23–24]. Using cDNA microarrays, several groups have now reported on their success at discovering gene expression that can be linked to resistance and responsiveness to standard of care chemotherapy [20–24]. In the next few years, the ability of this approach to personalize the treatment of newly diagnosed cancer patients with individualized selection and dosage of chemotherapeutic agents will be tested on a large scale.

Pharmacodynamics

In addition to the pharmacogenetic and pharmacogenomic tests, a series of bioassays, gene expression profiles and tissue-based biomarkers have recently emerged to guide the dose, timing and route of administration for novel therapeutics. These tests are used to speed the preclinical and early phase clinical development of drugs by enhancing the achievement of the ideal therapeutic dose while avoiding dose-related toxicity. Recent examples of these novel assays include the blood-based bioassay of the proteasome, which is designed to guide the use of the proteasome inhibitor PS-341 in multiple myeloma and solid tumors (Fig. 1) [25] and the immunohistochemical determination of the epidermal growth factor receptor (EGFR) target and cell proliferation markers on skin biopsies of patients receiving the anti-EGFR small-molecule tyrosine kinase inhibitor Iressa™ [26].

Toxicogenomics

Toxicogenomics is the study of gene expression patterns using high throughput microarrays, automated RT-PCR, NMR and proteomic strategies designed to detect up- and down-regulation of genes associated with drug toxicity risk [27–30]. Toxicogenomic markers for adverse side effects can influence selection and optimization of lead compounds before human studies. The limitations and uncertainties of gene expression profiling associated with data mining

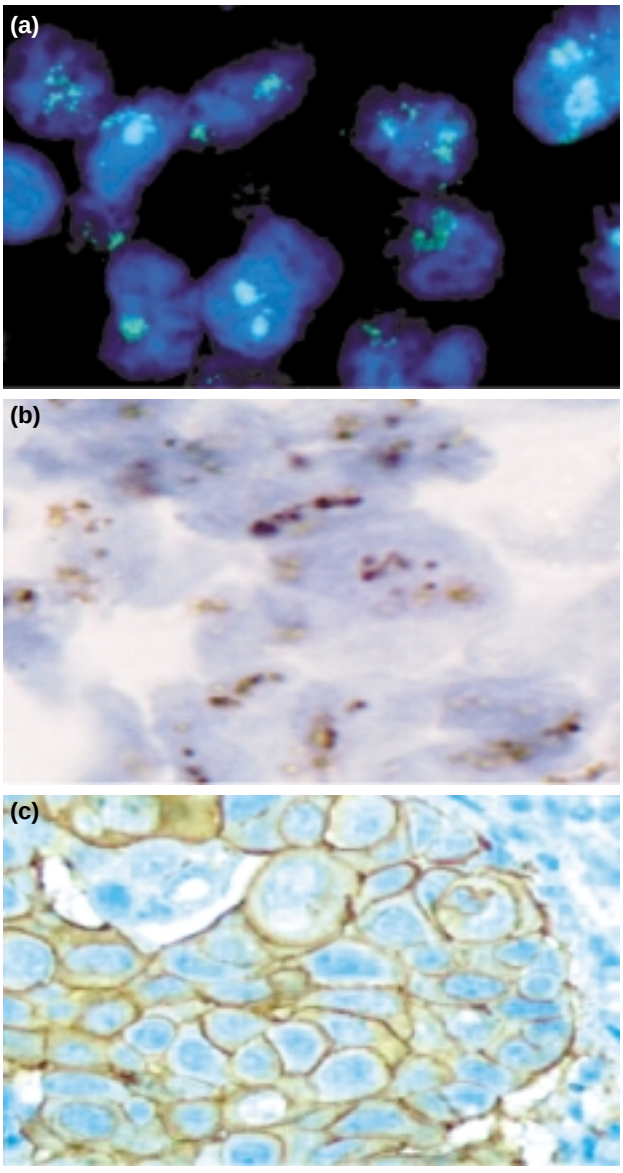

Figure 2. *HER-2/neu* testing in breast cancer. **(a)** Immunohistochemistry using Herceptest™ system (Dako Corporation; http://www.dako.com) with continuous membranous 3+ positive immunostaining (i.e. the staining is restricted to the cytoplasmic membrane) for *HER-2/neu* protein. **(b)** *HER-2/neu* gene amplification detected by fluorescent *in situ* hybridization (FISH; Ventana Inform™ System, http://www.ventanamed.com). **(c)** HER-2/*neu* gene amplification detected by chromogenic *in situ* hybridization (CISH; Zymed; http://www.zymed.com).

constraints on mechanistic and predictive toxicology have recently been emphasized and the clinical value of toxicogenomics is currently mostly unrealized.

Targeted therapies

The integration of diagnostics and therapeutics is realized in the discovery and development of targeted therapies. In 1999, the FDA approvals of Herceptin™ and Herceptest™ [Dako Corporation, http://www.dako.com] for patients with *HER-2/neu* overexpressing breast cancers marked the first simultaneous regulatory review of a targeted therapeutic with its companion diagnostic test [31,32]. A variety of modifications of the *HER-2/neu* testing platform have recently been introduced to achieve the best prediction of Herceptin™ response (Fig. 2). This integration of drug selection based on a diagnostic test result remains among the foremost of targeted therapy strategies currently available for cancer patients. Another recent example of targeted therapy in oncology is the detection of either the *bcr–abl* translocation in patients with CML or activating mutations in the *c-kit* tyrosine-kinase receptor in patients with gastrointestinal stromal tumors to select for the use of the small-molecule drug, Gleevec™ [33,34]. A significant number of small-molecule drugs currently in clinical trials are targeted to a variety of growth factor receptors, angiogenesis promoters, cell-cycle regulators and invasion or metastasis biomarkers [35,36]. Similarly, a variety of anti-tumor antibodies have been specifically targeted to cell-surface antigens and designed to deliver cytotoxic radioisotopes [37] and cellular toxins [38]. In the next five years, the impact of the targeted approach where diagnostic tests guide the clinical selection of anti-cancer drugs will become known.

Integrated diagnostics and therapeutics in non-malignant diseases

A wide variety of existing and novel diagnostic tests has recently been integrated into the management strategy of many major non-malignant diseases. Several groups have studied rheumatoid arthritis patients to learn whether germline-based SNP detection or biomarker assays performed on serum or synovial fluid could predict the development of erosive disease and guide the selection of therapy [39]. Inflammatory bowel disease patients have been tested for biomarkers of disease severity as a method for selecting local versus systemic drug therapy [40]. In addition to classic measurements of known risk factors, new strategies for predicting the risk of early onset coronary atherosclerosis have recently emerged using both well-established traditional biomarkers such as serum C-reactive protein levels in new ways [41] and the introduction of novel biomedical imaging and molecular diagnostic tests [42,43]. Similarly, new integrations of genotyping and molecular diagnostics are widening the knowledge and impacting on the management of diabetes mellitus patients [44]. Finally, the widest integration of molecular diagnostics in current clinical practice is in the selection and monitoring of therapy of infectious diseases.

Viral-load testing for patients infected with HIV and hepatitis C viruses are the most frequently performed nucleic-acid-based tests in molecular diagnostics laboratories [45]. In addition, the use of anti-retroviral drug resistance testing has become the standard of care for managing patients with HIV infection [46,47].

Predisposition, screening and early diagnosis of disease

Molecular diagnostic tests are now widely performed to detect cancer predisposition [13,48] and to screen for malignant and non-malignant diseases [49–52] to facilitate early initial and recurrent disease diagnoses when therapy can be most effective [53,54]. High throughput proteomic profiling has emerged as a potential breakthrough in early disease detection and therapy monitoring [55–58]. A recent serum-based study using the surface-enhanced laser desorption ionization (SELDI) technique combined with a self-learning computer pattern recognition software successfully detected early stage ovarian cancer with high sensitivity and specificity [59]. Biomedical and functional imaging such as computed tomography (CT). magnetic resonance imaging (MRI) and positron emission tomography (PET) scanning have also contributed major advances in early disease detection as well as in the monitoring of therapy response [60].

Conclusion

The traditional trial-and-error practice of medicine is progressively eroding in favor of more precise marker-assisted diagnosis and safer and more effective molecularly guided treatment of disease. For the pharmaceutical industry there is an equally desirable outcome of this approach: increased efficiency, productivity, and number of product lines. For the diagnostics industry this represents an unprecedented opportunity for integration, increased value and commercial opportunities for molecularly derived tests. The realization of the integration of diagnostics with therapeutics and the transition to personalized medicine are not without challenges, yet many of these challenges are being addressed. As patients continue to take on more and more of the burden of their own health and well-being, educational forums must be developed for patients and providers alike to understand the complex nature of the genomic and proteomic information that is now driving biomarker-based drug development and the future introduction of integrated diagnostics and therapeutics.

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Free journals for developing countries

The WHO and six medical journal publishers have launched the Access to Research initiative, which enables ~70 developing countries to gain free access to biomedical literature through the Internet.

The science publishers, Blackwell, Elsevier Science, the Harcourt Worldwide STM group, Wolters Kluwer International Health and Science, Springer–Verlag and John Wiley, were approached by the WHO and the British Medical Journal in 2001. Initially, >1000 journals will be available for free or at significantly reduced prices to universities, medical schools, research and public institutions in developing countries. The second stage involves extending this initiative to institutions in other countries.

Gro Harlem Brundtland, director-general for the WHO, said that this initiative was 'perhaps the biggest step ever taken towards reducing the health information gap between rich and poor countries'.

See http://www.healthinternetwork.net for more information.