provide an alternative approach to blocking tumor angiogenesis [16]. Finally, angiogenesis-associated markers might also find a role in active tumor immunotherapies. For example, immunization with xenogeneic endothelial cells or proteins, or DNA encoding angiogenic markers, such as VEGFR2, can lead to an effective cytotoxic T cell and antibody response against tumor-associated vessels, thereby blocking tumor growth and metastasis [17–19].

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Exploiting membrane trafficking pathways: cytoskeletal motors and cargo as targets for drug discovery

Molecular defects in intracellular membrane trafficking pathways have been implicated in many human diseases, including cystic fibrosis, Tay–Sachs disease, diabetes, Alzheimer's disease and motor neuron disease, among others [1]. Cytoskeletal motor proteins (kinesins, dyneins and myosins) transport cargo-laden vesicles along intracellular 'highways' formed by the cytoskeleton.

The past five years have seen a welcome explosion in the identification of cargo proteins that interact with motor proteins and are linked with disease [2,3]. An emerging theme is the possibility that cargo molecules themselves could also function as motor receptors or as linkers between motor proteins and vesicles. Some such receptors are transmembrane proteins, whereas others are previously identified scaffolding proteins. In a recent article in *Drug Discovery Today*, Phelps *et al.* discuss the feasibility of therapeutic intervention in membrane trafficking pathways, by targeting the interaction between motor proteins and cargo [4]. They provide an overview of membrane trafficking pathways that are relevant to human disease, together with detailed analyses of recent studies into motor–cargo attachments.

The advantages of targeting the interaction between motors and cargo are: (i) the specificity of motor–cargo interactions can be harnessed to regulate distinct subsets of cargo proteins in membrane trafficking; (ii) drug delivery can be tailored to specific intracellular locations and; (iii) signal transduction pathways that malfunction in disease are intimately tied to membrane trafficking pathways, and could be blocked to prevent aberrant cellular signals from inducing negative effects.

The idea of using the interaction between cytoskeletal motors and cargo as therapeutic drug targets is exciting, but some key challenges remain. To screen for drugs that target cytoskeletal motors and cargo, high-throughput biochemical and cellular assays need to be developed [5]. Biochemical assays for the inhibition of binding between cytoskeletal motors and known cargo proteins can be designed using techniques such as filter-binding assays, ELISAs and fluoresence polarization assays. Although there are already many cellular assays for membrane trafficking

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pathways, they will need to be translated into more-efficient HTS assays.

'Hits' discovered in such *in vitro* assays will then face the challenge of demonstrating efficacy in disease models *in vivo*. The dose-limiting toxicities that such drugs might incur remain unclear, given that cytoskeleton-dependent membrane trafficking pathways are essential in all cells. Nonetheless, success in finding such a molecule would result in the discovery of a novel class of drugs, exploiting cytoskeleton-dependent membrane trafficking pathways to cure disease.

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From PGx to molecular diagnostics and personalized medicine

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The organization of two related IBC conferences entitled *Molecular Diagnostics* and *Personalized Medicine*, held with concurrent sessions on 28–30 May 2003 in Boston, USA, symbolizes how compelling applications of pharmacogenomics/pharmacogenetics (PGx) in drug development and the practice of medicine are leading the renaissance of molecular diagnostics and the emergence of new regulatory policies.

The conferences brought together key speakers from the major pharmaceutical and biotech companies with PGx strategies incorporated in their drug development programs using enabling technologies for high throughput profiling of genotypes or expression of genes and proteins. The inclusion of topics on regulatory perspectives and reimbursement issues revealed major criteria that would be key to successful commercialization of PGx products in the future. Highlights from select presentations are captured here.

From PGx to better drugs and healthcare

In the new era of personalized medicine, the common goal iterated throughout the conferences – 'right drugs for the right patients' – is the primary driver for PGx applications. Yet molecular diagnostics constituted only 3% of the total *in vitro* diagnostics tests in 2002 and only 1500 genes and 5000 proteins were candidate markers. Failure to predict drug toxicity resulted in 100,000 deaths and 20–40% patients received the wrong drug [1]. With the encouragement from regulatory agencies, the pharmaceutical industry is now embracing PGx as the key to personalized medicine [2]. The goals are to identify the best drug targets for the individual disease cases, reduce toxicity and improve efficacy, determine the optimal drug dosage, timing and route of administration, and eliminate in early phase the development of drugs that will fail in the clinic. The expected results include smaller and less expensive clinical Phase III trials, safer drugs and more effective healthcare. The resurrection of failed drugs for use in a highly stratified patient population will also become possible.

Development of PGx products

There are two major areas where speakers applied PGx to drug discovery and development. One relates to the genetics of the host and the other to the pathology of the disease. Host genetics has significant impact on pharmacokinetics and pharmacodynamics. The static nature of genotypes makes genetics testing relatively easy for clinical use. However, the combined effects of host genetics and various environmental factors add

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