nanoparticles is related to toxicity. *Pharm. Res.* 16, 1836–1842

William M. Pardridge
Department of Medicine
UCLA School of Medicine
Warren Hall 13-164
900 Veteran Avenue
Los Angeles, CA 90024, USA
e-mail: wpardridge@mednet.ucla.edu

Genetic approach to chemical genetics ▼

Many drugs on the market today were initially identified because they demonstrated activity in patients, animal models or cellular assays that were believed to be physiologically relevant. The advent of molecular biology allowed more detailed dissection of biological processes into their component biochemical processes. Thus, clear links between the physiological effects of compounds and their molecular mechanisms are relatively recent in the history of the pharmaceutical industry. Some of the clearest associations between genes and disease processes come from analyses of naturally arising mutations in the human population. Only in very few cases, however, is there a tight link between a single gene and a particular human disease that identifies a clear target for pharmaceutical intervention.

There are a number of molecular biology approaches that can help to delineate the functions of individual genes at the gene, transcript or protein level. These include genetic tools such as transgenic animals where only one (or a group) of genes are altered. Current techniques enable the expression of the gene to be restricted to specific tissues, and there is some degree of regulation possible by exogenous intervention, but in the vast majority of transgenic animals available today, this type of regulation was not engineered in. Biochemical approaches such as RNA interference (RNAi) can be use to reduce specific protein levels by interfering with the transcript, but it is technically difficult to apply these approaches to a broad range of cells or in whole animals. Alternatively, dominant–negative mutants, either virally encoded or stably transfected, can be used to probe gene function by reducing protein activity.

In their recent paper, Skokat and Velleca [1] describe a hybrid of these approaches where they introduce a mutant copy of a gene of interest that possesses wild-type activity but is engineered to bind to specific unique ligands. Replacement of the wild-type copy of this gene by homologous recombination with this engineered version results in mice where the activities of the encoded mutant proteins can be examined specifically by dosing with exogenous low molecular weight ligands. Because the engineered proteins are wild type in every other respect, these recombinant mice provide excellent models of what might be expected if unique selective inhibitors were developed as therapeutic agents. Not only can the overall physiological response to inhibition be measured, but more detailed analyses can also be performed; for example, assessing changes in transcriptional and/or proteomic profiles or direct quantitation of downstream products.

As with any method designed to be a surrogate for the effects of a novel drug, there are drawbacks. Creating the mutants, although no longer scientifically challenging, is technically demanding. In addition, the high degree of selectivity that can be achieved with compounds interacting with mutants is in many cases extremely difficult if not impossible to achieve using drug-like molecules designed to interact with the endogenous target. Despite these limitations, Shokat and Velleca have demonstrated the potential power that can result when genetics and chemistry are ingeniously combined.

Reference

1 Shokat, K. and Velleca, M. (2002) Chemical genetics: novel approaches to the discovery of signal transduction inhibitors. *Drug Discovery Today* 7, 872–879

Paul R. Caron
Vertex Pharmaceuticals
130 Waverly St
Cambridge, MA 02139, USA

Mining the human ‘kinome’

David A. Dunn, Research Manager, Pharmacopeia, PO Box 5350, Princeton, NJ 08543, USA; tel: +1 609 452 3731; fax: +1 609 655 4187, e-mail: ddunn@pharmacop.com

Whenever there is a major advance in science, new tools and paradigms change and accelerate the pace of discovery. The sequencing of the human genome has had a major effect on the way we pursue the discovery and development of new drugs.

The now commonly used ‘omics’ terminology has come to refer to the paradigm shift that genomics has had on the way we see biology. At the *2nd International IBC Conference on Protein Kinases* held in Boston (MA, USA; 9–10 September 2002), use of the terms ‘kinomics’ and ‘phosphonomics’ reflect the impact that

  PII: S1359-6446(02)02506-0