Roche integrates HIV therapeutics and diagnostics

Roche Holding (Basel, Switzerland) has made a preemptive strike into disease management by recently implementing Integrated Healthcare Solutions, a novel global business strategy whereby the company will market selected drugs with diagnostic tests—some gene-based—for infectious diseases. By integrating its therapeutic and diagnostic divisions, Roche, which has pulled several of its own therapies from late-stage clinical trials, is the only company to implement this novel approach to health care. The company hopes that the use of genotyping methods to determine those at risk, following disease progression, and identifying responder individuals will remove the black box component of drug therapy, leading to a lucrative world of individualized preventive medicine.

Roche is testing the disease management waters by marketing worldwide PCR (polymerase chain reaction)-based diagnostic tests for HIV with protease inhibitors like Fortovase and Viracept. "The aim of all this is to make medicine more scientific," says newly appointed president of worldwide research, Jonathan Knowles. If governments and insurers refuse to pay for drugs unless tests are used to see if a patient is likely to respond, prescribing could finally be driven by science."

Physicians initially determine viral load in HIV subtype B infected individuals and AIDS patients using Roche's Amplicor HIV-1 Monitor T test, which was approved in 1996. The company expanded its target market to included additional subtypes this year with the European release of Roche's newest version of the microtiter based PCR test, Amplicor HIV-1 Monitor version 1.5. Awaiting FDA approval in the US, the new assay uses a single set of primers to amplify a slightly different portion of the HIV gag coding sequence, allowing the amplification detection of all the nine major HIV subtypes (A–I).

"In the case of patients with no detectable RNA viral titer, future and current drug therapies will be monitored using a quantitative PCR test, currently in development, that targets proviral DNA." Roche awaits FDA approval of its "ultrasensitive" diagnostic test, which detects as few as 50 viral genomes per milliliter of plasma. "Our overall goal is health management as well as disease management," says John Sninsky, Senior Director of Discovery Research at Roche Molecular Systems (Alameda, CA).

Economically, this approach is a health insurance company's dream—a single PCR test, costing a few hundred dollars, may save over $12,000 per year in ineffective AIDS treatments. Officials at Roche indicate that insurance companies have bought into this strategy in that they are reimbursing patients for the tests. But, quantifying HIV disease management in the US has been difficult, says Sninsky, "the diagnostic kit and drug are bought by two different consumers. . . The end user, the patient, or the phsyician is the same; however, the pharmacy will purchase and dispense the drug while the diagnostic lab will buy the kit."

IMAGE UNAVAILABLE FOR COPYRIGHT REASONS

The way forward: The Roche HIV diagnostic test (above) paves the way for other diagnostic-led therapeutics.

Patients not responding to drug therapy due to lack of adherence to drug therapy and drug-resistant strains present more complex problems, however. Resistance to one drug in a cocktail of drugs appears to affect additional mutations selected by a second drug. If this pattern of resistance is important in determining a drug regime, future diagnostic tests will require greater sophistication. Roche is currently tackling the problem by genotyping virus isolated from patients by sequencing the entire viral protease gene and over 300 amino-acid codons of the polymerase gene for each patient.

It is clear that this approach requires the concomitant development of methods in fast high throughput diagnostic tests that provide accurate information in order to direct patient care (*Nature Biotechnology* **16**:725). Roche has agreed to work with the photolithography based GeneChip technology developed by Affymetrix (Santa Clara, CA) as part of a three-year research agreement between the two companies that began in January 1998.

Several companies, including Affymetrix (GeneChip HIV PRT), Visible Genetics (TruGene HIV genotyping Gene kit), and the Belgium-based Innogenetics (DNA Line Probe Assay), are already tracking HIV resistance using diagnostics that detect single nucleotides changes in the viral genome. It remains to be seen whether the presence of specific mutations or groups of mutations can accurately predict the efficacy of specific drugs within individuals.

According to Sninsky, continued collaborative research with such companies as Visible Genetics into understanding the phenotype and drug response of specific mutations is critical but he emphasizes, "It is imperative that we move to genotyping: It is faster and less expensive than phenotyping."

Most pharmaceutical companies do not appear to be rushing to develop similar drug–diagnostic combinations, apart from Genentech (South San Francisco, CA), whose major stockholder is Roche. (Genentech plans to market its breast cancer drug, Herceptin in the US with DAKO's [Copenhagen, Denmark] HER2/neu based diagnostic test this fall. [*Nature Biotechnology* **16**:615]).

Indeed, some analysts claim that the revolution in genetic research may simply be long on promise but short on profitable drugs and that Roche's money would have been better spent on a pure pharmaceutical takeover to reinforce its thin research pipeline. "There probably will be some low-hanging fruit [in the gene diagnostic market]," says James McKean, a London-based pharmaceutical analyst with Morgan Stanley Dean Witter. "But I suspect there will be limits on where the industry really wants to go with all this."

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