HAP Typing in Drug Discovery

a report by

Genaissance Pharmaceuticals Inc.

Introduction

Scientists in the pharmaceutical industry are clamouring to make use of the large amount of genomic sequence information currently available. Researchers are now able to avail themselves of this data to identify useful genetic variations (single nucleotide polymorphisms (SNPs)) in the population, and use them as tools in a variety of different types of research and development programmes.

In the area of clinical testing of experimental drugs, the US Food and Drug Administration (FDA) now recommends the pharmacogenetic approach pioneered by Genaissance – using polymorphisms as prescriptive tools to segment market populations for efficacy and safety. In animal and human forensics, it is possible to use SNPs to inexpensively and unequivocally match two specimens. In classical genetics, SNPs are useful as recombinational markers in mapping and linkage experiments. Additionally, some SNPs are predictive of familial inheritance of traits, such as disease susceptibility or resistance.

To date, the public genome projects have identified more than 16 million polymorphisms in 25 species. There are nearly 4.5 million validated polymorphisms in *Homo sapiens* alone, with allele frequency information deposited for almost one million of these.

Company Overview

Genaissance Pharmaceuticals is a global leader in the genetic analysis services industry. The company offers high-throughput research genotyping services, as well as good laboratory practice (GLP) and clinical laboratory improvement amendments (CLIA) regulated genotyping. The company has laboratory facilities at four locations – Houston, TX; Morrisville, NC; Takeley, England; and New Haven, CT. At the New Haven headquarters, the HAP™ Typing Facility has established a high-throughput genotyping process based on the Sequenom MassARRAY™ platform.

This facility services a wide range of clients from academic researchers, to government agencies, to biopharmaceutical companies. Since the inception of the facility in 2000, more than 25 million genotypes have been generated. Currently, the facility has a yearly capacity of greater than 52 million genotypes.

High-throughput Genotyping Services

There are significant advantages to outsourcing high-throughput genotyping services. Genaissance has built a solid infrastructure around the Sequenom genotyping platform, including custom laboratory information management systems (LIMS) software to handle the complete chain of custody of both samples and polymorphisms from receipt to delivery. The company also has industry-leading experience in population genetics and high-throughput data analysis, which ensures the highest quality of data delivered.

Importantly, this genotyping platform offers rapid turnaround of client projects with highly competitive pricing and an accuracy rate of >99.7%. Project size can range from dozens to millions of samples, with an SNP number ranging from one to thousands. Any combination of samples and SNPs can be accommodated, and is priced appropriately. Turnaround times range from 48 hours to several weeks or months, depending on project size and urgency.

The Genaissance Genotyping Process

A project begins with the submission of biological samples and a list of polymorphisms of interest. At the end of the project, fully analysed data is exported from the LIMS and transmitted to the client by e-mail or on a CD. The following key steps occur during the process, and are controlled within a software-intensive, workflow-driven, LIMS environment.

Sample Management

a. Samples are received in a variety of formats.
b. All samples are accessioned in the LIMS.
c. DNA is extracted (if necessary).
d. Individual samples are arrayed in a standardised format in bar-coded plates.

Assay Development

a. Polymorphisms are received.
b. Assays are designed and reagents are ordered.
c. Assays are applied to a control cohort:
   i. For human SNPs that are found within the proprietary Genaissance database, genotype information obtained in sequencing is compared with genotype data generated on the Sequenom platform.
   ii. Approximately 150,000 polymorphisms from 7,900 genes were scored during the resequencing of DNA from 93 individuals of diverse ethnic background contained within Genaissance's proprietary 'index repository'. Many of these are not within the public domain.
   iii. The identification of SNPs adjacent to SNPs of interest substantially improves the quality of designed assays.

Genotyping Production

- Assays that pass the performance criteria in 'assay development' are released to production, along with DNA from 'sample management'.
- The genotyping production process is highly automated, and software driven.
- Bar-coded samples, reagents, and instruments provide complete chain of custody.
- Genotype calls are automatically generated, and deposited into the LIMS for analysis.

Genotype Delivery

a. Genotyping data is analysed by laboratory managers.
b. Data is exported from the LIMS in the form of a tab-delimited text file, or an Excel document.
c. Data is delivered to the client by CD or e-mail.
d. Client is billed for delivered genotypes only, with an average 95% of the possible data points.

Contract Research – There is a growing demand for industrial and academic organisations to perform high-throughput genotyping for on-going research projects. Genaissance serves as a 'core facility' for these organisations, both for SNP discovery and SNP genotyping.

Pharmacogenomics – Genaissance has pioneered the field of pharmacogenomics since its inception in 1996. Currently, the company is applying this approach to an in-licensed drug compound, Vilazodone, in order to segment the patient population based on haplotype markers.

Genotyping and the Drug Discovery Pipeline

Genaissance provides value at numerous positions in the drug development pipeline. From gene discovery and genetic mapping on animal models, to using SNPs as diagnostic markers, to segmenting patient populations in clinical trials, genotype data has allowed researchers to make critical scientific decisions that affect research outcomes.

Genaissance's high-throughput genotyping laboratory can be strategically leveraged as a 'back room' for processing third-party samples, or as a 'core facility' for any organisation's routine genotyping needs. The company can also provide valuable insight into the genetics of populations, and provide proprietary SNPs, which are of exceptional value to discovery programmes. ■