

Steven Gygi, PhD, Department of Cell Biology, HMS spoke on: “Quantitative Proteomics: Past, Present, and Future”. Proteomics was described as the systematic analysis of proteins for their identity, activity, function and molecular interactions. In the 1990s mass spectrometry (MS) techniques led to a revolution in protein analysis by providing physical methods of mass analyzing large biomolecules. Mass spectrometry involves three steps: ionization of the molecules of interest, separation by m/Z (mass/charge) and detection. MALDI (Matrix-Assisted Laser Desorption and Ionization) and electrospray are common methods of ionization while separation can be accomplished by time-of-flight or quadrupole systems. Detection of the analyzed fragments leads to mass analysis of proteins, peptides and DNA. Initially (~ 1985) 2-D gel electrophoresis, in which proteins are separated by both their molecular weight and by their (pH-dependent) net charge, was used to obtain specific protein samples for analysis. These samples were then trypsinized to yield peptides which would be analyzed by MS. However, the gel approach only allows collection of the most abundant proteins. The 2-D gel approach is now often replaced by liquid chromatography (LC)/tandem MS, in which protein mixes are digested to yield peptides, which are then separated by LC and mass analyzed. The first MS is used to preselect ions, which are then fragmented, for example by collisions with an inert gas, and then analyzed by a second MS. The resulting molecular weight fractionation patterns are then compared with existing databases to yield the peptide sequences which can be used to identify the original proteins. Quantitative proteomics seeks to determine how much of a specific protein is present. For examples, isotopically-coded affinity tags can be used to label the proteins.

Bruce Korf, MD, PhD, Director, Harvard-Partners Center for Genetics and Genomics spoke on “Application of Genomics and Proteomics to Clinical Practice”. Genomics and proteomics offer major opportunities to improve the approaches to clinical diagnosis, prevention of disease, and patient management. A number of clinical examples were presented. Chromosome analysis is used in detection of Down syndrome, in which chromosome 21 is has extra material. Numerous forms of prenatal diagnosis are in use. Some, like amniocentesis, have been in use since the 1960s. A more recent technique is preimplantation diagnosis for in-vitro fertilization. One cell is removed from an 8-cell embryo and analyzed to determine if the embryo should be reimplanted. Screening of newborns is another area in which numerous tests can be applied. The older technique of blood-spot analysis for detecting infants at risk for a number of diseases is being replaced by the use of tandem MS on blood samples from newborns. DiGeorge syndrome, characterized by cardiac and facial anomalies, can be detected by a missing portion of a chromosome. Similarly, mutations of the connexin 26 gene are strongly linked to childhood deafness. A web site, www.genetest.org, gives sites of laboratories testing for a particular disorder. However there is still a need to link research genetics labs to clinics. Partners Healthcare is developing genetic information systems that will allow genetic testing for both population screening and for individual patient treatment options. Two convergent forces, information technology and genetics, are likely to lead to more individualized medicine. For example, a number of drug side-effects can be linked to genotype; pharmacogenetics uses such genetic information to select drugs for efficacy and safety with specific patients. Gene chips will be an important tool in implementing such pharmacogenetic testing.

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