Focus group meetings:

Title: Proteomic Strategies to Enhance Biomarker Discovery in Biofluids

<u>Abstract:</u> Tasso Milliotis lecture 18 November, 2004 Molecular Sciences, AstraZeneca R&D Mölndal, Sweden

During the last years the pharmaceutical industry has shown a growing interest in identifying biomarkers, as they can help to prioritize the drug discovery and development process. New methodologies are being developed and applied to biomarker research. Most of these methods are based on some kind of mass spectrometric protein or peptide identification strategy preceded by an efficient sample preparation and separation step (Proteomics approach).

Biomarker analysis has to deal with a range of biological matrices most of them biofluids such as serum or urine. Commonly encountered biofluids contain high concentrations of proteins, such as albumin, which are present at fairly constant concentrations independent of an ongoing disease process. Such proteins may easily mask the presence of potential biomarker proteins or peptides that are present at much lower concentrations and are responding to the disease process. Presently, this problem is overcome by using highly selective assay formats mostly based on marker-specific antibodies. However, if one wishes to discover new, presently unknown proteins that may later serve as biomarkers, it is necessary to capture as much as possible of the proteome that is present in a given sample.

Early disease markers are often present at low concentrations (e.g. ng/ml levels) necessitating the removal of high-abundance proteins and/or the enrichment of parts of the proteome of interest. Furthermore, it is critical to develop highly resolving often multi-dimensional separation techniques in conjunction with efficient mass spectrometric routines to reach into the area of low-abundance markers.

Sample preparation is one key for successful biomarker discovery. More specifically, the removal of abundant proteins combined with chromatographic pre-fractionation prior mass spectrometric analysis is a prerequisite in order to penetrate the proteome. Examples of our current strategies for enhancing biomarker discovery will be

presented and furthermore, illustrated by an example from an ongoing biomarker discovery project within cardiovascular disease.