Biomarkers

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Diagnostic methods are of major importance in medicine. To fulfill scientific and economic requirements, procedures must be sensitive, specific, fast, cost-effective, and applicable at the point-of-care. A major aspect of medical diagnostics is clinical chemistry using advanced analytical methods to identify and quantify a variety of compounds in blood, urine, saliva, cerebro-spinal fluid, pleural effusions, etc.

During recent decades substantial effort has been devoted to searching for biological marker substances which are specifically linked to a disease or a diseased state. Special attention has been devoted to biomarkers that might indicate the presence or absence of cancer. Many cancerous diseases still have poor prognosis, because diagnosis is usually too late. When bronchial carcinoma is recognized, for instance, the tumor stage is very often already advanced and effective therapy is no longer possible. Overall, five year survival for all bronchial carcinomas is as low as 5%. If diagnosis can be made in earlier tumor stages survival of up to 60% will be possible. These figures emphasize why so much effort has been spent

in searching for early markers of cancerous diseases. Many candidate substances, for example CEA (carcinoembryonic antigen), TNF (tumor necrosis factor), α -FP (alpha-feto-protein), CA-19.9 (carcinoma antigen 19.9), PSA (prostate-specific antigen), and many more, have been discovered in recent decades. Although good correlations have been found between appearance or concentration changes of these marker substances and the presence of a variety of diseases, diagnostic sensitivity and specificity of these biomarkers have always been a problem. One of the most crucial problems is that correlations between biomarkers and the corresponding diseases are reasonably good only if disease prevalence is high in the population under investigation. When the prevalence is low, as it usually is when a normal population has to be screened for a disease, false negatives and false positives cause unsolvable problems. One percent of false positives in a population of 100,000 means that for prostatic cancer screening 1,000 healthy individuals will be scared and will possibly undergo biopsy or even surgery without any benefit but with all the possible adverse side effects of the invasive diagnostic procedures. On the other hand, 1% of false negatives means that in a population of 100,000 1,000 patients having cancer will be told they are healthy, and timely diagnosis may be missed. The ongoing intense debate on the use of PSA for recognizing prostatic cancer illustrates this problem most emphatically.

Another general problem linked to screening by means of biomarkers can be seen when prostatic cancer is investigated. Even with effective screening, survival with the disease could not be improved because the progress of this cancer is slow and many patients die of other illnesses, so not only must biomarkers be sensitive and specific but prognosis of the underlying disease must also be affected significantly by early diagnosis. A third problem is

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statistical. If more than one marker is used to identify disease-specific patterns in populations with high disease prevalence, the correlations obtained may be accidental or may be obtained because too many markers and too few distinct measurements were used. In the latter case, perfect characterization of a disease-specific set of markers seems possible. But, because of the unfavorable ratio of markers to distinct measurements, it will not be possible to reproduce the results in any other population. These phenomena have been observed in neuroscience, genomics, proteomics, and metabolomics.

With regard to the requirements of non-invasiveness and bedside applicability, breath analysis is a promising alternative to serum chemistry and may even replace RX or MR imaging. Breath analysis is completely non-invasive, quick, cost effective, and can be done repeatedly, even continuously, without any burden on the patient and without any risk to the staff gathering the samples. Exhaled breath contains a large number of different volatile substances. This includes inorganic gases, for example CO₂, CO, and NO, simple, branched, or substituted alkanes, unsaturated compounds, and oxygen, nitrogen, or sulfur-containing compounds. A variety of mediators, proteins, and even RNA or DNA fragments have been found in exhaled breath condensate (EBC). In recent years many of these substances have been linked to physiological and pathological conditions in the human body. Unfortunately, the problems with sensitivity, specificity, and “voodoo” correlations mentioned above exist for breath analysis, also.

Hence, except for very few compounds, variations in the appearance or concentration changes of biomarkers are too large to enable primary diagnosis of a disease. Nevertheless, biomarkers are important for staging purposes and for detection of disease progress. Basic principles for rational and beneficial use of biomarkers consist of thorough knowledge of the underlying disease, sound and robust analytical methods, and meticulous consideration of statistics.

In this special issue, the state of the art of analysis of urinary nucleosides and micro-RNA is reviewed, recent developments in mycotoxin detection in human tissue are described, and aspects of non-invasive drug monitoring and online metabolic profiling by means of breath analysis are

addressed. In two review articles and four original papers crucial aspects of sample preparation, substance separation, chemical analysis, and data processing are discussed.

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