Available online at www.sciencedirect.com
SCIENCE DIRECT®
Toxicology Letters 156 (2005) 227–240
Toxicology Letters
www.elsevier.com/locate/toxlet

Molecular approaches to the identification of biomarkers of exposure and effect—report of an expert meeting organized by COST Action B15☆

Ursula Gundert-Remy*, Svein G. Dahl, Alan Boobis, Pierre Kremers, Annette Kopp-Schneider, Axel Oberemm, Andrew Renwick, Olavi Pelkonen

Federal Institute for Risk Assessment, P.O. Box 330013, 14191 Berlin, Germany

Received 30 September 2004; received in revised form 25 November 2004; accepted 26 November 2004
Available online 8 January 2005

Abstract

In the past, the term biomarker has been used with several meanings when used in human and environmental toxicology as compared to pharmaceutical development. However, with the advent of molecular approaches and their application in the field of drug development and toxicology, the concept of biomarkers has to be newly defined. In the meeting, the experts found consent in defining the term and described the application of biomarkers in toxicology, drug development and clinical diagnostics. Molecular approaches to biomarker identification and selection lead to a large amount of data. Hence, the statistical analysis is challenging and special statistical problems have to be solved in biomarker characterization, of particular interest are attempts aiming at class discovery and prediction. Reliability and biological relevance are to be demonstrated for biomarkers of exposure and effect which is also true for biomarkers of susceptibility. It is envisaged that the application of biomarkers will expand from current use in pre-clinical toxicology to the risk characterization and risk assessment of chemicals and from early clinical phases of drug development to later phases and even into daily clinical use in diagnostics and disease classification.

Keywords: Biomarker of exposure; Biomarker of effect; Toxicogenomics; Biomarker validation; Molecular toxicology; Clinical endpoints

☆ The authors have prepared this paper on behalf of the members of Working Groups 1 and 2 of the COST Action B15 and of the invited experts based on an expert meeting held in Berlin, 28 November 2003. Other members of the COST Action B15 Working Groups were: Gunnar Alvan (Sweden), Luc Balant (Switzerland), Julio Benitez (Spain), Kim Brosen (Demark), Meindert Danhof (Netherlands), Maria Durisova (Slovak Republic), Jaime Kapitulnik (Israel), Jochen Kuhlmann (Germany), Panos Macheras (Greece), Jirina Martinkova (Czech Republic), Constantin Mircioiu (Romania), Jose Morais (Portugal), Gian Maria Pacifici (Italy), Gilles Paintaud (France), Achille van Peer (Belgium), Victor Voicu (Romania), Ümit Yasar (Turkey). Invited experts were: Peter Kramer (Germany), Georges Orphanides (UK), Paul Rolan (UK), Ina Schuppe-Koistinen (Sweden), Ben van Ommen (Netherlands).

* Corresponding author. Tel.: +49 30 8412 3300; fax: +49 30 8412 3003.
E-mail address: u.gundert-remy@bfr.bund.de (U. Gundert-Remy).

0378-4274/$ – see front matter © 2004 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.toxlet.2004.11.016

Contents

1. Introduction: goal of the meeting

The term biomarker has been used in several fields, with somewhat different meanings or restrictions. In pharmaceutical development, biomarkers of effect have been applied to identify effects in early clinical phases. They have also been called surrogate markers, however further discussions lead to the consensus that this term should be restricted to those biomarkers of effect that can substitute for a clinical endpoint. Hence, the term biomarker of effect has a wider meaning. Biomarkers of effect have only relatively recently been introduced into toxicology to characterize early events. In toxicology, it is not only the preclinical testing for potential adverse effects routinely carried out in drug development, but also of industrial chemicals and pesticides that is making increasing use of techniques and tools to identify biomarkers.

The use of the term biomarker (of exposure) is well known in environmental health sciences. Such biomarkers are being increasingly used for a wide variety of chemical exposures.

Several attempts to classify biomarkers have been made and are ongoing. At present, there is no uniform view on the degree of validation required to support these uses. A key concept is that the purpose of the biomarker, i.e. its utility, will be a major determinant of its selection and validation criteria.

Consensus on biomarker classification and utility, perhaps with agreed databases, will assist in their development and application. Collaboration within industry and between industry and academia will be a key req-