

Foreword

In recent years, few methods have changed so dramatically as those used *in vitro* for drug development. The main areas of progress involve target finding and validation with molecular biology, and *in-vitro* testing of drug safety to the production of biological molecules. The application of these methods has made all steps of drug development not only faster, but also less costly.

As research in all areas is continuing apace with major efforts, we can expect major breakthroughs with the maturation of human micro-organoid *in-vitro* cultures in the near future. Clearly, however, because of the increased sophistication and specialization of these investigations, an even greater need for team work is indicated.

Hence, it is mandatory for those of us involved in drug development to keep pace with the continuous progress in methodology, by receiving the experts' overview, as presented in this book.

Frankfurt a. M., July 2006

Prof. Dr. Rolf Krebs
former Chairman of the
Board of Managing Directors
of Boehringer Ingelheim GmbH



Preface

At the beginning of the 21st century, the development of medicine is suffering from two major obstacles.

First, new drug candidates directed at *pivotal human receptors* can have unprecedented positive or negative biological effects involving systemic interactive networks specific to humans. None of the animal species or human cell lines can properly imitate the biological effects on these networks. Consequently, few relevant data on the efficacy and safety of new drugs can be obtained for evaluation prior to human testing. A prime example is the super-agonist antibody TGN1412, which was developed to direct the immune system to fight cancer cells or to reduce arthritis pain, and has triggered multiple organ failure in healthy volunteers undergoing experimental testing. In binding the CD28-receptor, the antibody overrides the basic control mechanism of the whole immune system. Yet whilst adhering to standard clinical research guidelines, the drug showed absolutely no adverse effects in studies with animals.

Second, significant drawbacks – such as severe adverse side effects – often occur after drugs have entered the market. Today, there are increasing indications that *specific genetic predisposition* is one of the key reasons for these high-profile recalls. This human genetic diversity is rarely addressed in preclinical and clinical safety studies at the present time. A sound hypothesis on the correlation of morbidity of patients treated with roferoxib (Vioxx) with the genotype for 5-LOX and 5-LOX activating protein polymorphisms, is one of many examples describing this obstacle.

The breakthrough might be to develop high-throughput, human micro-organoid *in-vitro* test systems. In mammals, organs and systems are built up by multiple identical functionally self-reliant structural units, with easily remembered examples *in vivo* being the liver acinus, β -cell islets in the pancreas, alveoli in the lung, or germinal centers in lymph nodes. When science and industry succeed in designing human micro-organoids *in vitro* that fully emulate these *in-vivo* counterparts, the dream of drug testing predictive to individual human exposure might become reality. For at least 30 years the vision of proper modeling of these human micro-organoids *in vitro* to gain knowledge about their performance and function in man – and consequently to use them for highly predictive drug screening and testing purposes – has been set back by prohibitive scientific and technological bottlenecks. However, achievements made over the past seven

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years have substantially changed this starting position, and the multidisciplinary contributions in this book introduce different aspects leading towards anticipated short-term progress in that area.

- Part I brings together an overview of new and forthcoming tissue models, the challenges to be met by the development of bioreactors, and the biosensoric microstructures for control and measurement. An illustration of complexity is provided by the biomonitoring of airborne contaminants *in vitro*.
- Part II combines overviews of state-of-the-art *in-vitro* techniques in conventional monolayer and suspension culture systems, with the potential of two relatively new technological platforms – the creation of human designer cell lines and stem cell technologies. The latter provides basic guidelines of how to overcome the chronic bottleneck of sustainable, human genotyped cell and tissue supply.
- Part III emphasizes the tension between ethical, regulatory and commercial aspects of drug testing and screening on human micro-organoids *in vitro* as a viable alternative to animal testing.
- Part IV concludes with the tremendous potential of the anticipated emerging *in-vitro* drug evaluation platform technology, including a road map enforcing them.

The book is introduced by a personal statement of Rolf Krebs, former chairman of the Board of Managing Directors of Boehringer Ingelheim.

Progress anticipated in the emerging platform technology can have significant impact beyond the borders of drug screening and testing. In Europe, at least, legislative pressures such as the cosmetics directive and the retrospective REACH (Registration, Evaluation and Authorisation of Chemicals) program for 30 000 chemicals, has created a dramatic increase in industrial interest in predictive human *in-vitro* tissue culture test systems for the evaluation of cosmetics, chemicals, or nutraceuticals. Hence, this book also provides useful inside information for professionals from those areas.

Finally, the book would not exist with the outstanding creative assistance of Silke Hoffmann and Philip Saunders.

Berlin, October 2006

Uwe Marx and Volker Sandig

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