Microarrays, Barriers, Analogues and DOPA

Methods in Molecular Medicine 114: Microarrays in Clinical Diagnostics

Edited by *Thomas O. Joos* and *Paolo Fortina.*

Humana Press, Totowa 2005. 288 pp., hardcover $ 135.00.—ISBN 1-58829-394-7

In the past decade, microarray technologies have evolved from a promising research tool to well-established technologies used in laboratories all over the world. Needless to say, the high information content and miniaturization of the microarray format has tremendous potential in diagnostics. Furthermore, the ability to rapidly characterize genetic alterations and proteomic variation opens the door to a more targeted and personalized medicine. *Microarrays in Clinical Diagnostics*, edited by Thomas O. Joos and Paolo Fortina, is a collection of fifteen chapters by authors from both industry and academia, surveying current applications of microarray-based technologies in diagnostics, including universal DNA microarrays, parasite detection/characterization, genotyping SNP, protein and antibody microarrays, as well as the technical aspects of the technology, such as sample preparation, microarray agitation during hybridization, and quality control. While microarray technologies are simple in concept, their practical implementation can be complex. There is a great need for a laboratory manual that gathers the know-how that has been acquired by the practitioners in the field. *Microarrays in Clinical Diagnostics* meets that need and provides protocols in the successful style of the *Methods in Molecular Biology* series, with clarity and sufficient technical detail so that both novice and current microarray users are sure to benefit from this book. It provides detailed protocols for every aspect of the technology, from derivatization of the glass surface and preparation of protein microarrays to validation and quality control of microarray-based analytical methods. Important sample-preparation techniques are also presented, such as noncontact laser microdissection and pressure catapulting to isolate samples of interest homogeneously in an automatable fashion. Importantly, each protocol comes with a list of necessary equipment and reagents as well as tips on troubleshooting problems.

Of course, the widespread use of microarray technologies in diagnostics is still more a vision than a reality, and the use of such technologies must be validated in large-scale clinical studies; however, the first signs of success are clearly here. The first pharmacogenomic microarray has been approved to measure genetic variations for two genes that play a role in the metabolism of about 25% of all prescription drugs; this allows physicians to adjust treatment doses for patients on therapeutics metabolized by these genes. It is also clear that microarray-based technologies will continue to evolve rapidly, and perhaps the biggest limitation of this book is the lack of an adjoining web-site where protocols and relevant information can be kept up to date.

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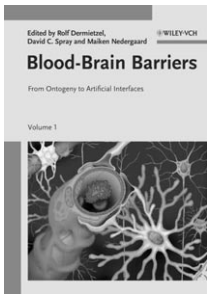
Blood–Brain Barriers: From Ontogeny to Artificial Interfaces

Edited by *Rolf Dermietzel*, *David C. Spray*, and *Maiken Nedergaard.*

Wiley-VCH, Weinheim 2006. xxxii + 741 pp., hardcover € 299.00.—ISBN 3-527-31088-6

One hundred and twenty years ago, the physician Paul Ehrlich observed that intravenous administration of a dye solution to laboratory animals stained all organs except for the brain. Other researchers confirmed his findings, and in 1921 the physiologist Lina Stern used the term "barrière hématoencéphalique" for the first time. In 1929, H. Foertig wrote the first scientific paper entitled "Die Bluthirnschranke" or "the blood–brain barrier", which was rather provocative at that time. An organ had been discovered that is still the subject of intensive studies, but is still far away from being completely understood.



The blood–brain barrier consists of a tight network of blood capillaries that separate the central nervous system from circulating blood and ensure that no xenobiotics or toxic metabolites disturb the sensitive homeostasis of the brain. In the past decade, the blood brain barrier has been the subject of increasing interest, because it also represents an almost insuperable obstacle to many drugs and drug candidates under development for the treatment of CNS-related diseases such as Parkinson's disease, Alzheimer's disease, infections and brain tumors and metastases.

Now, the team surrounding Rolf Dermietzel, David Spray, and Maiken Nedergaard have undertaken the task of gathering the present knowledge about the blood–brain barrier into a book of two volumes with 740 pages. In seven main sections with 28 chapters, the authors describe the structure and function of cerebral microvessels, as well as possibilities to study and to manipulate them.

The introductory section explains the development and differentiation of the blood–brain barrier and describes the factors of angiogenesis and barrier genesis as well as the impact of microvasculature on neurogenesis. In the second section, the authors deal with the various cell types that contribute to barrier function such as endothelial cells, pericytes, macrophages of the brain, microglia, and astrocytes. Section 3 describes factors of

hormonal and enzymatic control, like fibroblast growth factor or cytokines, with their interaction with the blood–brain barrier, glucocorticoids, oestrogens and metalloproteinases. The authors of Section 4 mainly address those readers who are interested in in vitro studies of the blood–brain barrier. Modes of endothelial cell isolation, coculture with astrocytes, and the influence of serum in culture media are discussed, and examples are shown of how the function of the blood–brain barrier can be studied in silico in order to predict the permeability of drugs and drug candidates.

Section 5, the first section of the second volume, turns towards drug delivery to the brain. It starts with a discussion of p-glycoprotein, the export protein in the luminal membrane of the endothelial cells, which is a key player for the barrier function. P-glycoprotein recognizes an exceptionally broad variety of substrates and transports them back into blood circulation, thus hampering effective treatment of many CNS-related diseases. The development of redox-controlled prodrugs or the use of cytotic pathways are some of the ways to bypass the export pump and to overcome the barrier.

In Section 6, the dynamics of cerebral blood flow and oxygen are described as well as possibilities of displaying metabolic functions with imaging techniques. The final section discusses various pathological conditions of the brain, like inflammation, stroke, parasitic infection, and diabetes. The main text ends with a description of the blood–retina barrier. Embryologically, this barrier can be regarded as part of the central nervous system, and its blood vessels share many characteristics with those of the brain. In contrast to brain capillaries, the vessels of the retina can be studied in situ, and therefore, they may be used as an easily accessible model of the blood–brain barrier. The book closes with a comprehensive subject index.

It took 13 years from the famous book about the molecular biology of the blood–brain barrier by William Pardridge to the publication of the present book by Dermietzel and colleagues, and the result is very convincing. The book can easily be read by experts and laymen, facilitated by the many coloured illustrations. It has only some minor weaknesses. Considering the complexity of the subject, it becomes obvious that not every aspect can be discussed in the same detail, but, beside p-glycoprotein, there are other important transport proteins located in the blood–brain barrier that could have been included in the discussion. In addition, the Choroid Plexus, an important blood–CNS barrier, would also have been worth more than just some passing mentions. In view of the many authors, it is also not surprising that one or two aspects are pointed out twice or that not all illustrations are made in the same style.

Despite these small limitations, the authors have succeeded in making a great leap forward towards a better understanding of the structure and function of cerebral microvessels. Hopefully the book will find a broad readership and become a benchmark for blood–brain barrier textbooks.

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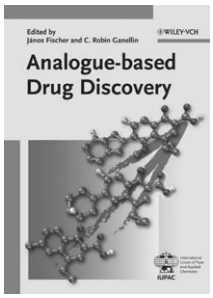
Analogue-based Drug Discovery

Edited by *IUPAC*, *Janos Fischer* and *C. Robin Ganellin*.

Wiley-VCH, Weinheim 2006. XXXI + 575 pp., hardcover € 155.00.—ISBN 3-527-31257-9

The similarity principle is an important strategy in medicinal chemistry. It states that similar compounds have similar biological activity. Thus, a biologically active compound provides a good starting point for finding new compounds with better pharmacological properties. The similarity principle can be successfully used in early drug design as soon as the first ligands are known. On the other hand, drugs on the market provide a wealth of information about pharmacokinetic parameters, adverse effects, etc., that can direct the development of optimised drugs. The latter scenario is addressed in the book "Analogue-based Drug Discovery".



For this purpose, the editors distinguish between *pioneer drugs* and *analogues*. Analogues, in this context, have a relationship to an existing drug. The term analogue is not only used for compounds with structural similarity, but also for compounds with a similar pharmacological activity, so-called pharmacological analogues, such as nifedipine and verapamil, which are structurally unrelated, though both block L-type calcium channels.

The book contains three main parts. Part I covers a brief definition of analogue-based drug design and explains general strategies for using analogues in drug discovery. Examples are chemical modifications frequently used in medicinal chemistry (homologisation, cyclisation, etc.) and the use of privileged fragments. Several examples of the application of the strategy are given.

Part II forms the main part of the book and gives many historic case studies of analogue-based drug discovery. The examples are taken from different therapeutic areas such as anti-infectives, anticancer agents, and anti-hypertensives and cover a broad range of chemical classes.

Part III contains a tabular overview of a collection of drug analogues for different targets and therapeutic indications, nicely illustrating the structural relationships of many compounds.

The different chapters are mostly well written with only few minor errors. The index is sufficiently detailed for drugs to be found quickly in the relevant chapters. Unfortunately, the chemical structures are not consistently drawn.

Important general aspects of analogue-based drug discovery are discussed in the first part of the book (e.g. homologous variations, SOSA approach, chemogenomics). This part is rather short, and a broader introduction to the field would have been valuable. For example, the successful use of modern

