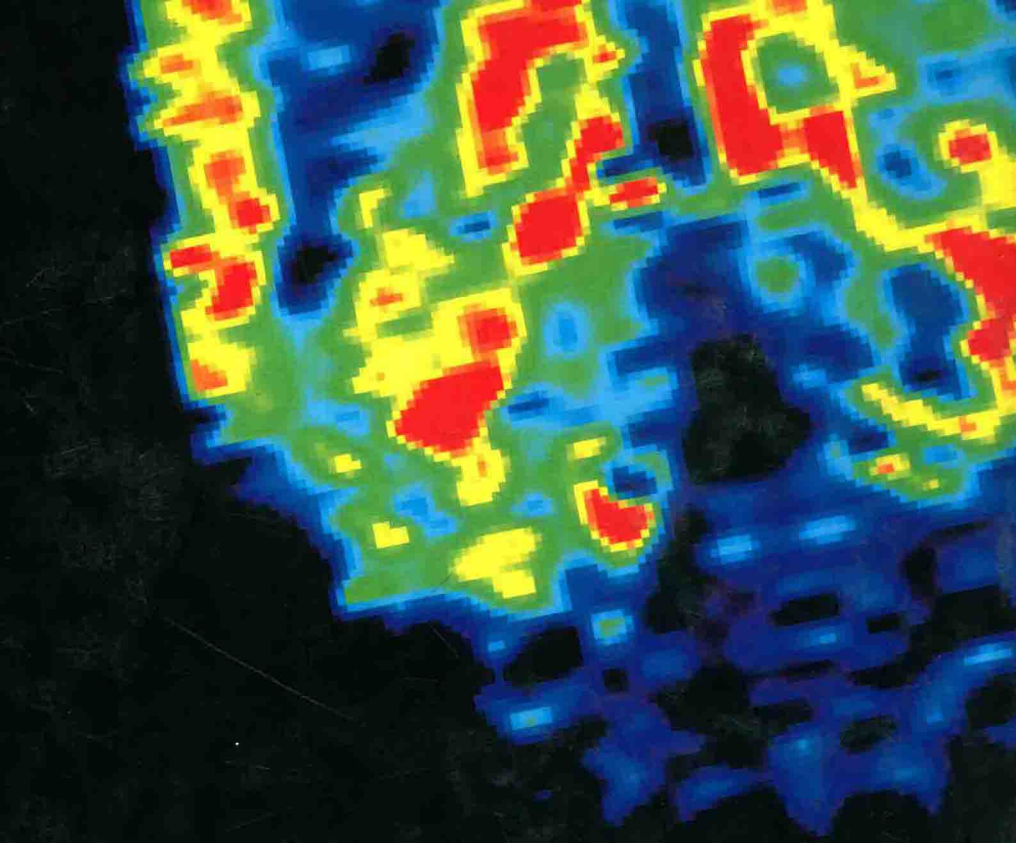

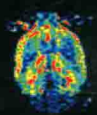

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Basic Principles and Applications in Biomedical Research

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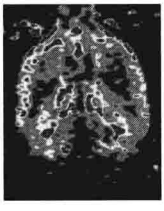

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Molecular Imaging

Basic Principles and Applications in Biomedical Research

To Verena

Foreword

Many scientists state that *molecular imaging is not a new discipline*; nuclear imaging approaches such as positron emission tomography and single-photon emission computer tomography have used molecular imaging concepts since more than a decade to visualize the biodistribution of labeled compounds including analyses of receptor occupancy. In these studies image contrast is not governed by the anatomical features of the sample but rather by the local concentration of the radiolabeled reporter compound, i.e., by a molecular property.

Other scientists claim that *molecular imaging is a new scientific area merging concepts of molecular biology with noninvasive imaging technologies*. This allows the study of biological processes in a noninvasive manner. These concepts go beyond labeling of reporter ligands. They involve the development of a battery of reporter assays that are used to probe specific biological questions: Is the expression of a receptor modified under specific pathological conditions? Does the receptor exert its biological activity; does it activate its associated signaling cascade? Can these molecular markers be used as early indicators of a pathological transformation?

The last years experienced rapid growth in the field of molecular imaging. Many of the assay systems originally developed for studying biochemical systems in homogeneous solutions or isolated cells have been successfully translated to the *in vivo* situation allowing the testing of a biomedical hypothesis in the context of the intact

organism. Molecular or target-specific imaging potentially provides a holistic view on a biological system in contrast to the reductionistic approaches of classical molecular biology and biochemistry. Despite the rapid progress that has been achieved in the last couple of years the field is still in its infancy and major developments are still required. This relates to the imaging technologies, which should provide high sensitivity, high temporal and spatial resolution, and most importantly quantitative data, as well as to the probe design. Highly specific probe constructs should provide the desired information with little interference from nonspecific background signals. Multiplexed probes that allow the monitoring of several biological processes simultaneously would be of outmost relevance.

There are considerable expectations associated with molecular imaging techniques. First, the study of molecular events in the intact organism will *enhance our basic molecular biological knowledge*. For instance, specific receptor systems or signal transduction pathways can be studied in their biological context. Second, tissue functional or structural aberrations are always preceded by molecular events such as abnormal cellular signaling. It is reasonable to assume that *molecular markers might serve as early indicators of a disease process*, long before a pathomorphological or pathophysiological transformation of tissue occurs. It may furthermore improve the specificity of diagnosis and may help to select the patient population that is most likely to respond to a specific therapy. Third, modern pharmaceutical drugs are designed to interact with a well-characterized molecular target. As clinical drug development is becoming increasingly expensive (today the development of a drug to reach the market will cost approximately 800 million USD), early information on clinical efficacy is of crucial importance. Molecular imaging might provide a *direct proof that a therapeutic concept is valid* also in man; e.g., the target enzyme is in fact inhibited by the drug candidate or inhibition of a specific receptor shuts down the associated molecular signaling cascade. For these reasons, molecular imaging will soon become an indispensable tool in biomedical research in particular for drug discovery and development.

This book is aimed to give the reader an introduction into this fascinating and dynamically evolving field. It discusses basic aspects of molecular imaging technology and probe design, which are illustrated

with numerous selected examples from the literature. It does, however, not provide a comprehensive review of the current activities in the field. This was never intended as such a book would probably never be finished: new exciting applications are being reported almost on a daily basis.

The first part of the book discusses technological aspects of molecular imaging. In Chapter 2, the various imaging modalities such as X-ray computer tomography (CT), magnetic resonance imaging (MRI), single photon emission computer tomography (SPECT), positron emission tomography (PET), fluorescence and bioluminescence imaging, as well as ultrasound imaging are discussed in some detail. Chapter 3 describes the various reporter systems that are being used for the various imaging approaches, from short-lived radionuclides to microbubbles suited for ultrasound studies. The design of reporter constructs for molecular imaging applications is the topic of Chapter 4. Important aspects to consider are target-specificity, delivery of the probe to the target site, and signal amplification. Most molecular targets are expressed at low concentration (nano- to femtomolar); hence, strategies to enhance the signals produced by the reporter system are essential.

The second part deals with applications of molecular imaging in biomedical research. Knowledge of the drug biodistribution and pharmacokinetics (PK) is highly relevant for drug development as many drug candidates fail due to inadequate PK properties. Chapter 5 deals with drug imaging using PET techniques. In Chapter 6, methods to visualize the expression of the drug targets are being discussed. Levels of transcription products can be probed using labeled antisense molecules, receptor imaging relies on the availability of small molecular probes or labeled antibodies. Enzymatic drug targets are attractive for imaging as the enzyme activity can be exploited to activate or trap a reporter substrate thus yielding high degrees of signal amplification and minimal interference by background signals. A different approach to visualize gene expreesion is the use of the reporter genes, which allows unique questions to be addressed. Drug–target interaction will initiate a series of downstream processes. Measurement of these *effector readouts* are the topic of Chapter 7, which discusses methods to visualize protein–protein interactions or apoptotic activity as an example. Further downstream a ligand

receptor interaction will initiate a physiological response that can be visualized using conventional imaging approaches such as the measurement of glucose utilization, energy turnover, tissue perfusion, or second messenger turnover. Chapter 8 describes techniques for monitoring of cell trafficking. Myeloid and lymphoid cells are important mediators of inflammation and visualization of the infiltration of these cells into inflamed tissue are sensitive indicators of the disease process. Novel therapeutic approaches in degenerative diseases try to exploit the pluripotency of stem cells for tissue repair. Obviously, such therapy concepts will benefit from the ability to monitor the fate of such cells under *in vivo* conditions.

While many of the techniques and applications described will undergo further development in the coming years, most of the basic concepts outlined in this book will remain valid and will be applicable also to these advanced procedures. In this regard, the book is designed as a textbook summarizing basic principles and potential applications of molecular imaging in biomedical research.

Zurich, June 2005 Markus Rudin

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Zurich, June 2005

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