Edited by Jörg Knäblein

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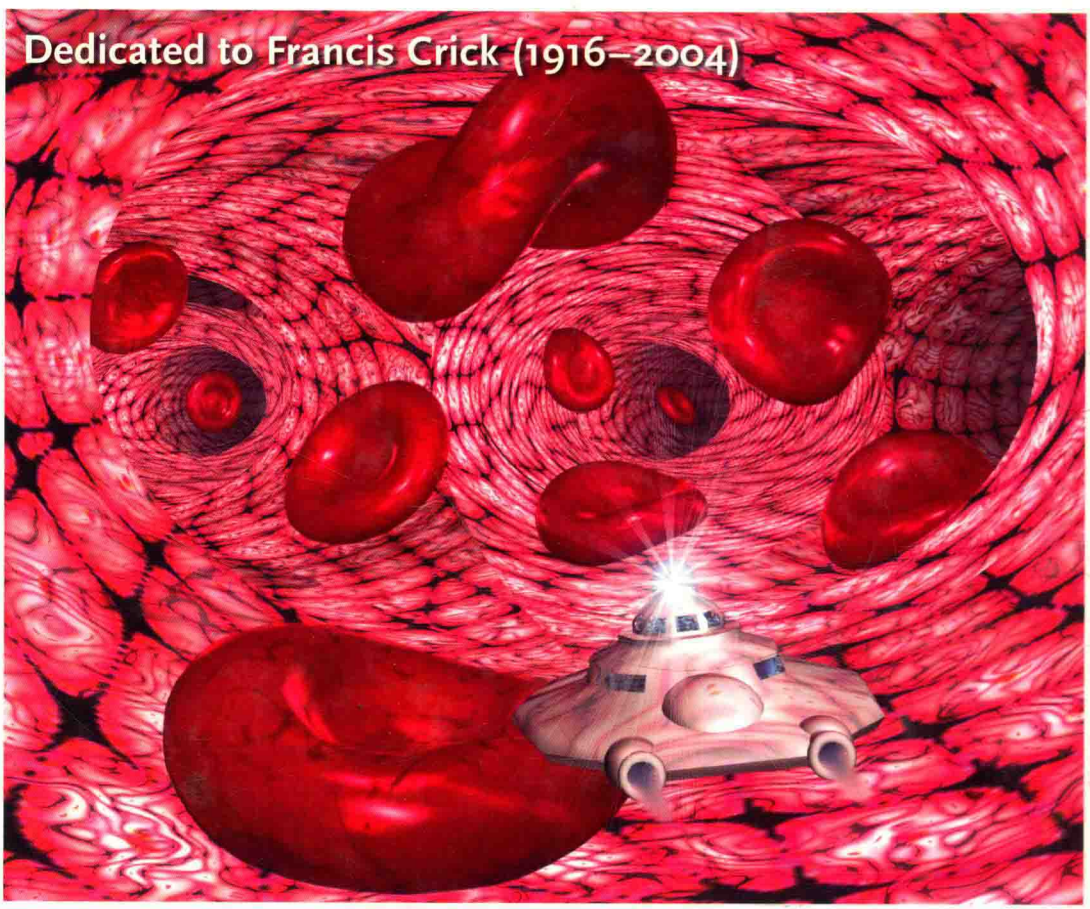
Modern Biopharmaceuticals

Design, Development and Optimization

Volume 1



Modern Biopharmaceuticals

Volume 1

Design, Development and Optimization

Edited by
Jörg Knäblein

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Editor

Dr. Jörg Knäblein
Head Microbiological Chemistry
Schering AG
Müllerstraße 178
13342 Berlin
Germany

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Modern Biopharmaceuticals

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Prologue

Mens Sana in Corpore Sana – Rationale for "Modern Biopharmaceuticals"

"I have a dream ...". Once, on an early Sunday morning in 2003, "the 50th anniversary year of DNA discovery", I woke up and had the idea to bring together all the world-renowned leaders from biotech academia and industry, in order to publish a comprehensive book on modern biopharmaceuticals. As learned from nature, some things happen best – if at all – spontaneously. So, I contacted some of my friends, presented the idea and discussed with them the current hot topics in the LifeSciences arena. Very quickly a list with topics and authors emerged, which I presented to Wiley-VCH – and they spontaneously agreed to publish this book.

From my past career I knew a number of highly educated scientists and managers in the LifeSciences: first, when I studied biotechnology and did my diploma thesis at the GBF (Gesellschaft für Biotechnologische Forschung), then when I worked in the biotech industry with Professor Norbert Riedel, before I went on to also study biochemistry and do my PhD at the Max Planck Institute (MPI) with Professor Robert Huber. This was also a spontaneous move: I remember quite well, when I stopped by at the MPI on my way back from a snowboard trip in the Munich mountains. Quite naively, I asked if I could talk to the Nobel prize laureate Professor Huber – asking for the opportunity to work in one of the most famous laboratories in the world without even having an appointment. It was an incredible honor that he accepted. Now – as my teacher and co-founder of our biotech start-up – he encouraged me to write this book and was also willing to contribute to this endeavor.

I am also pleased that a colleague from this start-up company is contributing with a chapter on genetically engineered factor IXa with 7000 times increased activity. This proves that we had the right concept for the company; needless to say that I am glad that – as well as the scientific success – this company is continuously growing, whereas most of the companies founded at the same time no longer exist.

After this entrepreneurial exercise I switched gear and started working in a high-tech consultancy with a focus on biotechnology, before I started with Schering AG. Heading the Department of Microbial Chemistry again involved a number of state-of-the-art biotechnologies (from expression system design and fermentation process development to downstream processing, Good Manufacturing Practice and analytics). Obviously, over the years I was exposed to a huge variety of different companies, people and "biopharmaceutical en-

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vironments", and it was a great honor for me when I was elected to the Executive Board of the European Association of Pharmaceutical Biotechnology (EAPB, and very recently as its designated president) and to the Editorial Board of the *European Journal of Pharmaceutics and Biopharmaceuticals* (EJPB). Altogether, in my past career, I had the pleasure to meet a vast number of brilliant scientists from world-class universities and academic institutes as well as business leaders from major pharmaceutical companies.

I am very grateful for these various opportunities, which inspired the book project *Modern Biopharmaceuticals* and provided me with the required large number of excellent contacts at the same time, and, I am happy to say, that most of my "contacts" have spontaneously agreed to provide a chapter for this book – colleagues from academia and industry, from regulatory authorities, and from consulting business.

I hope that the reader will agree that this book is the first of its kind, introducing a comprehensive set of technologies recently developed, showing their impact on drug development, discussing paradigm shifts in the healthcare system and also reflecting these changes in industrial research. Compiling this wealth of information in a sophisticated manner was only possible if all chapters were written by the experts themselves, and most of them are working in academic institutes and (often in their own) biotech companies at the same time. The authors come from some of the world's most famous academic institutes, and biotech companies, such as CalTech, Cambridge, Charité, ETH Zürich, Fraunhofer-Institute, Harvard, Johns Hopkins, Karolinska, Kyoto University, London Imperial College, Max-Planck-Institute, MIT, Moscow and Polish Academy of Sciences, NCI, NIH, Oxford, Princeton, Scripps, Seoul University, Stanford, Technion, Weizmann, Yale. They are CEOs, Board Members or Global R & D Heads of world-class companies, e.g. Amgen, Bayer, Baxter, Berlex, Crucell, DSM, DuPont Merck, Genentech, Genzyme, Invitrogen, Lonza, McKinsey, Mologen, Monsanto, MorphoSys, Novartis, Novo Nordisk, Philips, Roche, SmithKline, Schering – and from FDA.

This profound and balanced mixture of academia and industry was intended to make the book equally appealing to scientists at research institutes, physicians at hospitals, students at universities and laboratory technical staff from areas like medicine, all different areas of LifeSciences, as well as other healthcare professionals. It is my hope that it will serve as an inspiration for all professionals in the field, since it offers a very good framework for understanding the complex nature of biopharmaceuticals, the mainstay of modern medicine.

Of course, some of the breakthrough technologies described need to be treated with caution, e.g., human cloning. The chapter by Hwang et al. impressively demonstrates that we are now able to clone a human being, but this ground-breaking scientific success also has various ethical implications, depending on how it will be applied. These pluripotent embryonic stem cells from somatic cell nuclear transfer of reprogrammed human adult cells can be grown to have an unlimited source of autologous cells for transplantation medicine (some striking examples on organogenesis and organ repair are presented in the section "cell therapeutical approaches"). This is very exciting, because for the first time transplant rejection can be overcome, since the transplant is built from the *patient's own cells* with the *pa-*

tient's own genetic setup. However, this breakthrough for therapeutic cloning could also be misused for evil purposes (as with nuclear power) and this reminds me of a quote from *Jurassic Park*: "Biotechnology is the most powerful force which was ever on the planet. But you play with it like a child, who just found his father's gun". So, whether these powerful biotechnologies are solely (and exclusively) applied in a positive way that is beneficial for mankind really depends on how respectful we as scientists deal with them!

We all know that since the remarkable "debut of modern biopharmaceuticals", the field of pharmaceutical biotechnology has evolved tremendously. By comparison, when I follow how quickly (life) sciences advance, it would make Newton's apple appear to fall in slow motion. I am very happy that people who contributed most to this fast and exciting development of biopharmaceuticals, who helped to usher in a golden age of molecular biology, also contributed to *Modern Biopharmaceuticals – Design, Development and Optimization.* I would like to take the opportunity to thank all of the authors for their excellent contributions and hope that the reader will enjoy this fantastic collection of scientific art.

I also wish to thank the publisher Wiley-VCH for making this project happen – especially Andrea Pillmann and Waltraud Wüst. Both were very supportive from the beginning of this exciting book project – not just in managing the publication itself, but also for managing my ideas. And I guess sometimes it was a tough job to stop my "creativity" in generating new ideas. Another idea which both were in favor of was to also provide a supplementary CD-ROM with a PowerPoint presentation that I have assembled over the years. This I use for educational purposes when I share with students the fascination of (20 000 years of) biotechnology. The CD-ROM also includes some fantastic video animations, e.g., showing the whole process from DNA unwinding in the nucleus through transcription into mRNA to the expression of a biopharmaceutical. By focusing on key aspects, these animations tremendously help in the understanding of such complex processes. Or, as a homage to Albert Einstein (whose theory of relativity would have its 100th anniversary this year): "make it simpler, but not simple".

Having said that, if you have any valuable educational video animations that I could incorporate into the presentation on the supplementary CD-ROM, I would be very grateful if you could contact me. Also, if you identify any areas, topics or technologies which you feel are not yet captured, please let me know. In addition, I would appreciate any comments which will help to keep the topics/content up to date and make the next edition of *Modern Biopharmaceuticals* (which is in preparation already) even more comprehensive. Pleast visit our biotechnology hub at www.get-gps.net to discuss current trends with the respective Global Pharma Specialist from our worldwide competence network. And this will help all of us in the LifeScience community, because as we all know: *knowledge is power – shared knowledge is success.*

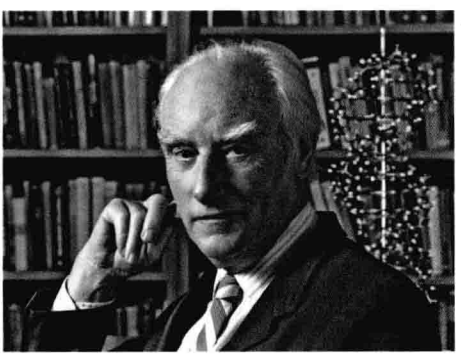
Thank you very much in advance and enjoy reading *Modern Biopharmaceuticals*!

Jörg Knäblein
Scientific Advisor
Executive Boardmember
and designated President
of European Association
of Pharmaceutical Biotechnology
Berlin
May 2005

Dedication

My family and loved ones for their continuous support and patience

Modern Biopharmaceuticals – Design, Development and Optimization is dedicated to the man who made all this possible:
Francis Crick (1916–2004).



Francis Crick (courtesy of Marc Lieberman, Salk Institute, La Jolla, CA)

Francis Harry Compton Crick was born on 8 June 1916 in Northampton, England. He studied physics at University College, London, where he obtained a BSc in 1937. He then started his PhD in physics, which was interrupted in 1939 by the outbreak of World War II. Crick worked as a scientist for the British Admiralty until he left in 1947 to study biology in Cambridge, where he worked at the Strangeways Research Laboratory.

Two years later, he joined the Medical Research Council Unit at Cambridge University's Cavendish Laboratory, headed by Max F. Perutz, to study X-ray diffraction by the helix. The work of Perutz laid the groundwork for his interest in protein structures (as it did for my teacher, Robert Huber, and later for myself as well). Thus, he became a research student for the second time and was accepted in 1950 as a member of Caius College, Cambridge. Crick's career was then critically influenced by his friendship with James D. Watson, which in April 1953 led to the ground-breaking proposal of the double-helical structure for DNA and its mechanism of replication published in *Nature*: "We wish to suggest a structure for the salt of deoxyribose nucleic acid (DNA). This structure has novel features which are of considerable biological interest".

Crick obtained a PhD in 1954 on his thesis entitled "X-ray diffraction: polypeptides and proteins" and in 1959 became a Fellow of the Royal Society for his work on DNA as well as for his study of the structure of proteins. Finally, in 1962, Watson and Crick, along with their colleague Maurice Wilkins, were awarded the Nobel Prize in Physiology or Medicine.

After his work on the double helix, which changed the face of modern-day

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science and medicine, Crick collaborated with Sydney Brenner at Cambridge to develop the adaptor hypotheses about protein synthesis and the genetic code. Between 1966 and 1976, Crick worked on embryology until he moved to the Salk Institute for Biological Studies in San Diego, CA. There, he began to work on the understanding of the brain and neural correlates of consciousness, which he continued for the rest of his career.

"Darwin has interested us in the history of nature's technology" (Karl Marx), and Watson and Crick paved the ground for modern biotechnologies: all the work described in this book only became possible through the elucidation of the structure of DNA – the greatest scientific accomplishment of the 20th century. This fascinating work on DNA revolutionized science, and enabled molecular genetics, biotechnology and the development of modern biopharmaceuticals.

When I was asking Francis Crick for his contribution to my book, on 4 November 2003, he replied that he very much appreciated this endeavor of creating such a comprehensive book: "...Nice of you to ask me to contribute to your book on biopharmaceuticals ... Unfortunately I am in very poor health so do please excuse me. Apologies, Francis Crick".

Francis Crick, the DNA code-breaker, died after a long battle with cancer at the age of 88 years on 29 July 2004, at Thornton Hospital of the University of California in La Jolla.

"I will always remember Francis for his extraordinarily focused intelligence and for the many ways he showed me kindness and developed my self-confidence", says

James Watson and Jörg Knäblein, October 2004 during Watson's visit at the Charité in Berlin, Germany

his long-time colleague and friend James D. Watson, whom I had the honor of spending an evening with in October 2004 during the Faculty Meeting at Charité, Berlin. I am very grateful that I had the opportunity to discuss recent trends in biotechnology and his view on "Modern Biopharmaceuticals". "He treated me as though I were a member of his family", Watson says. "Being with him for 2 years in a small room in Cambridge was truly a privilege. I always looked forward to being with him and speaking to him, up until the moment of his death. He will be sorely missed."

Francis Crick made an enormous contribution to science, and our understanding of biology and the health of mankind. His death is a sad loss to science and especially to modern biotechnology.

Dr. Jörg Knäblein
Head of Microbiological Chemistry
Schering AG
Berlin
May 2005

Foreword

History of Modern Biopharmaceuticals: Where Did We Come From and Where Will We Go

It is a pleasure to write the Foreword to this unusual and excellent biotech book! *Modern Biopharmaceuticals – Design, Development and Optimization* gives a comprehensive overview of the status of pharmaceutical biotechnology today, but also looks ahead and shows future trends with an outstanding collection of very recent results. It presents a comprehensive overview on breakthrough achievements with state-of-the-art biotechnologies, demonstrating that Life-Sciences are nowadays shaped by amazing and ground-breaking discoveries.

When James D. Watson and Francis Crick elucidated the structure of "the molecule of life" in 1953, it was compelling in its sheer beauty. However, more importantly, the three-dimensional structure of DNA led to the mechanisms of replication and "was the first three-dimensional Xerox machine" (Kenneth Boulding). Three years later, Arthur Kornberg isolated the enzyme that synthesizes the molecule of life: DNA polymerase.

Around that time, scientists were also working on the more complex structures of proteins: John C. Kendrew and coworkers described the structure of myoglobin in *Nature* in 1958 (A three-dimensional model of the myoglobin molecule obtained by X-ray analysis, *Nature 181*, 662–6), and shortly after that Max F. Perutz and coworkers described the structure of hemoglobin (A three-dimensional Fourier synthesis of reduced human haemoglobin at 5.5 Å resolution, *Nature* 199, 633–8). Both shared the Nobel Prize in Chemistry in 1962 for their "studies on the structures of globular proteins".

In the field of DNA, one important discovery was followed by the next: the first plasmid was isolated in 1959, 1 year later François Jacob and Jacques Monod defined mRNA as the carrier for the blueprint of the entire protein, and in 1961 Marshall W. Nirenberg started decoding the genetic alphabet by identifying that at the mRNA level the codon UUU encodes the amino acid phenylalanine. The respective phenylanalyl-t-RNA was later discovered by Aaron Klug (see his quote for "Modern Biopharmaceuticals"). Now the mystery of transcription and even of translation is solved, and, in 1962, Watson (see his quote for "Modern Biopharmaceuticals") and Crick, along with their colleague Maurice Wilkins, were awarded the Nobel Prize in Physiology or Medicine. In 1968, "gene scissors", discovered by Werner Arber, revolutionized molecular biology, since these restriction enzymes are capable of specifically cutting bacterial DNA. This enabled

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scientists for the first time to prepare recombinant DNA. Two years later the "central dogma" of biochemistry, i.e., that the genetic flow is unidirectional from DNA via mRNA to protein, was proven wrong: Howard Temin and David Baltimore discovered the enzyme reverse transcriptase, synthesizing cDNA from mRNA. This breakthrough discovery eventually allowed the expression of eukaryotic genes, as the untranslated segments in the genome are spliced out by this process.

At Brookhaven National Laboratory, New York, the Protein Data Bank (PDB) was established in 1971, and has become a repository for protein coordinates which are shared between scientists worldwide. The PDB is a very important tool and the basis for rational, structure-based drug design – a prerequisite for the development of modern biopharmaceuticals.

In 1973, a new era in biotechnology started with the advent of gene technology, when Allan Maxam and Walter Gilbert (Harvard) and Frederick Sanger (Cambridge) developed a "DNA sequencing method". Combining all these fascinating findings, Stanley Cohen (see his quote for "Modern Biopharmaceuticals") and Herbert Boyer re-combined *in vitro* DNA pieces to form a new gene for the first time.

At the same time, Georges J.F. Köhler and César Milstein were working together at the Medical Research Council Laboratory of Molecular Biology in Cambridge, where in 1975 they discovered a technique to produce *monoclonal* antibodies. Previously, to prepare substantial quantities of antibodies, scientists had to inject an antigen into an animal, wait for antibodies to form, draw blood from the animal and isolate (a mixture of different types of) antibodies. The only way to obtain monoclonal antibodies was to clone lymphocytes, secreting one form of antibody molecules. Lymphocytes, however, are short-lived and cannot be cultivated easily. By fusing lymphocytes with myeloma cells, Köhler and Milstein obtained hybrid cells synthesizing a single species of antibody while perpetuating themselves indefinitely. Together with Niels K. Jerne, they received the Nobel Prize in Physiology or Medicine 1984. Most present biopharmaceuticals (i.e., therapeutic and diagnostic proteins) are antibody-based molecules, and this is why the development of monoclonal antibodies revolutionized medicine and paved the way for new, target-specific approaches, where pure, uniform and highly sensitive protein molecules can be used as biopharmaceuticals for diagnosis and therapy.

The recombinant DNA technology of Cohen and Boyer enabled them to generate the first commercial product in 1978: human insulin expressed in *Escherichia coli*. These efforts also led to the first biotech company: on 15 October 1980 Genentech went public on the New York Stock Exchange. Fascination about this modern biopharmaceutical and the huge potential of the new biotechnology caused the stock price to jump from US $ 35 to 89 in the first 20 minutes; by the evening of the same day, the market capitalization was US $ 66 million!

The year 1984 is another landmark: the first transmembrane protein, the photosynthetic reaction center (RC) from *Rhodopseudomonas viridis*, was solved. The challenge in solving the structure of this huge (150 kDa) protein was that it consists of 11 membrane-spanning, hydrophobic α-helices. Solving the RC structure was a major breakthrough, since many of the most interesting drug targets are membrane-bound proteins. In 1988, my colleagues Johann Deisenhofer and Hartmut Michel and myself were awarded the Nobel Prize for Chemistry for this work.

Then there was the advent of a surprisingly simple tool that readily revolutionized molecular biology and heavily influenced modern biotechnology. In 1983, Kary Mullis invented a process he called the polymerase chain reaction (PCR), which solved a core problem in molecular genetics, i.e., gene amplification. In other words: how to make copies of a strand of DNA that you are interested in? PCR turns the job over to the very biomolecules that nature uses for copying DNA as well. Two "primers" flag the beginning and end of the DNA stretch to be copied and an enzyme called polymerase "walks" along the segment of DNA, reading its code and assembling a copy. To complete the PCR cocktail, a pile of DNA building blocks is added, which the polymerase needs to make that DNA copy *in vitro*. Kary Mullis won the 1993 Nobel Prize in Chemistry for this discovery (see his quote for "Modern Biopharmaceuticals"). Exactly 10 years later another breakthrough for modern medicine was awarded: Paul Lauterbur received the Nobel Prize for his pioneering work in imaging technique. This enabled early diagnostic and enhanced earlier treatment leading to high success rates (see his quote for "Modern Biopharmaceuticals").

Another quantum leap for modern biotechnology was the first cloned mammal by Ian Willmut in 1996 (see his quote for "Modern Biopharmaceuticals") by means of somatic cell nuclear transfer (SCNT) – the sheep "Dolly". Then, in 2004, the first human embryo was cloned by a team led by Woo Suk Hwang, who was able to obtain pluripotent embryonic stem cells by SCNT of reprogrammed human adult cells. The highly differentiated genetic program of the nucleus from an adult cell can be completely reprogrammed after being introduced into an enucleated oocyte from a donor, so that these embryonic stem cells can be grown to produce an unlimited source of autologous cells for transplantation medicine. This experiment, together with some striking examples of how one can apply this new source of stem cells for organogenesis and organ repair, is also presented in this book.

An unusual feature of *Modern Biopharmaceuticals – Design, Development and Optimization* is that, for a book with so many facts, it is a delight to read. Whilst being easy to read, it is a guide to both broad surveys and key papers, which are provided in convenient, but at the same time comprehensive, reference lists and Internet links. Implementing this structure, the reader can easily begin to explore the very extensive literature on all the relevant topics and also has a guide to navigate through the World Wide Web as well. On top of this comes a very educational CD-ROM with impressive video material.

I am convinced that my student Jörg Knäblein has done a great job in compiling a cutting edge and comprehensive book on modern biopharmaceuticals – written by knowledgeable experts from academia and industry. I wish this extraordinary book a numerous and broad readership, and I hope the reader will enjoy this collection of scientific art as much as I did!

Professor Robert Huber
(Nobelprize in Chemistry, 1988)
Max-Planck-Institute for Biochemistry
Martinsried
May 2005

Foreword

Modern Biopharmaceuticals – A Primer: Stem Cell Research and Very Recent Breakthroughs

The opportunities and challenges of an aging population make it mandatory to rethink our attitude towards medicine. With the advent of genomics and proteomics and with the entire new field of molecular medicine, we now have the means in our hands to cope with the challenges lying ahead of us.

More diseases than ever are likely to be treated with innovative and completely new therapeutic approaches. And above all early precise diagnostic procedures at the molecular level will allow us to get a better understanding of the underlying processes. Today, the so-called molecular imaging allows already for a functional diagnosis as well as for diagnostic measures at the molecular level.

At the same time the refinement in our ability to diagnose *in vitro* genetic and protein alterations will eventually lead to a much better understanding of our predisposition to develop certain diseases or will give us a clue as to what types of treatment will be most appropriate for certain groups of individual patients.

Pharmaceutical and biopharmaceutical research hence is a perfect application oriented continuation of what is going on in laboratories of biomolecular research. Probably for the first time in biomedical research there is not only an opportunity but also an irrevocable necessity for public private partnerships in order to fully exploit the potentialities in the field of biomedicine. If predisposition towards genetically influenced diseases can be detected early and if specific molecular imaging diagnostics allowing for a precise and early detection of diseases becomes feasible, it is more than likely that the borderline between secondary and primary prevention will be shifted towards earlier timepoints of preventive intervention. Primary prevention either with lifestyle changes or with pharmaceutical means, will become a routine measure in many forms of early and even very early disease states as well as in those cases where only statistical probability gives a hint towards upcoming diseases.

Taken together, this will allow for a much better and more rational employment of preventive medicine than today. Of course, this can be regarded as utopia, probably also wishful thinking, but there is no doubt that in certain areas and under certain circumstances this will become reality provided that the ways in which we educate and inform patients and potential patients properly change adequately.

Cell biology including stem cell research has become a very exciting new field of

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molecular biology, since this new science offers a much better understanding of elementary processes holding out the prospect of understanding why certain cells e.g. become tumor cells. Making use of the knowledge gained with this research and the cells being produced has another dimension: the so-called Regenerative Medicine. Human embryonic stem cells and adult stem cells are of prime interest for these new fields of biomedical research.

For me there is no doubt that to fully understand the possibilities of stem cells, the mechanism of cell differentiation and hence a basic mechanism of life, we must not concentrate on adult stem cells only, but rather include embryonic stem cells, too.

The question to what extent stem cells – be it embryonic or be it adult – will be used and have to be used in medical and clinical practice later on is still a very open one. There is at least hope that the *in vivo* activation of existing adult stem cells could be a fascinating dimension of research work, resulting from the current work in embryonic and adult stem cells. It is obvious that we still have different legal frameworks for working with embryonic stem cells. It is also true that we are in the middle of a major ethical debate. However, for me it is equally important that the progress to be expected and the advantages to be envisaged from research in stem cells are so fundamental that eventually we will find a regulatory framework within which this type of research can be performed worldwide. If this turns out not to be the case, it could easily happen that the major breakthrough for this type of modern biopharmaceutical research will be achieved in Asian countries, which are already at the forefront in this field.

In summary, modern biopharmaceutical technologies offer enormous opportunities and are a great intellectual challenge for our imagination and for our daily research work. The field is highly dynamic, it is expanding, and it offers great opportunities for enthusiastic young people. And above all, this exciting field of new science is giving and will give us a much better basis for understanding human life and for adding a new quality of life.

The present book "Modern Biopharmaceuticals" is a good primer to interest young scientists in this multidisciplinary field of modern biotechnology. It is comprehensive, touches most of the currently available modern trends in LifeSciences, and it is written for a broad and cross-disciplined audience. Jörg Knäblein's "Modern Biopharmaceuticals" provides the window into biopharmaceutical research, developments and applications of today and tomorrow, and I hope that readers from academia as well as from industry will appreciate this collection of outstanding contributions from world class researchers working in both fields.

Professor Günter Stock
Senator of German Research
Foundation (DFG)
Board Member and Head of
Research of Schering AG
Berlin
May 2005

Quotes

"The making of pharmaceutical and diagnostic agents in cells has moved from edge to the center of their respective commercial development.

With '*Modern Biopharmaceuticals*', Jörg presents an outstanding collection of articles from groundbreaking scientists, comprehensively describing the many novel ways cells so are being deployed toward human good."

Professor James D. Watson,
"DNA code-breaker" and Nobel Prize laureate (Physiology or Medicine, 1962)
COLD SPRING HARBOR LABARATORY, New York

"The new book" '*Modern Biopharmaceuticals*' has an impressive list of authors drawn both from world-renowned academic research laboratories and also from the world's leading biotech and pharmaceutical companies. The experts from this coalition of world-class companies, institutes and universities have direct experience of the cutting edge technologies described and understand the various needs, met and unmet. This fantastic line up of authors make it a truly world class book – a four-volume educational platform covering the full spectrum of science from discovery to applications.

It is hoped, that there will also follow (an inexpensive) student edition, which would be more widely accessible."

Professor Sir Aaron Klug,
"Discoverer of the Phenylalanyl-t-RNA"
and Nobel Prize laureate (Chemistry, 1982)
MRC LABORATORY
OF MOLECULAR BIOLOGY
Cambridge, United Kingdom

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"The comprehensive coverage provided in '*Modern Biopharmaceuticals*' by eminent investigators should stir the imagination of all scientists interested in possible medical applications of their own research. I wish you best of luck in your endeavors with this excellent biotech book."

Professor Stanley Cohen,
"Designer of the first cloning vector"
and Nobel Prize laureate
(Physiology or Medicine, 1986)
VANDERBILT UNIVERSITY
SCHOOL OF MEDICINE
Nashville, Tennesee

"We always seem to be right on the edge of solving all our health problems, just like we always seem to be on the verge of ultimately discovering the physical mysteries of the universe. It does seem like we are about to understand cancer, genetic diseases, infectious diseases – all the things that bring us discomfort on the personal level.

Gunther Stent decided in the late Sixties, in his wonderful lectures at Berkeley entitled the Rise and Fall of Molecular Biology, that all the interesting stuff in molecular biology had already been figured out. Only the boring details remained – just then biotechnology exploded. Our latest shocking advance, the ease of reading and manipulating DNA, is what is responsible, I suppose for our latest bout of thinking we know almost everything important. It turns out though, that there are always new things to discover.

You need to keep up on what is known already and you always need to know what's already known. So, read this book '*Modern Biopharmaceuticals*' and you will get a very good overview of what is currently known in the exciting field of Life-Sciences."

Professor Kary Mullis,
"Inventor of PCR" and Nobel Prize laureate
(Chemistry 1993)
Newport Beach, California