

„Modern Biopharmaceuticals - Design, Development and Optimization“ (Wiley-VCH) is dedicated to Francis Crick (1916 – 2004) ISBN 3-527-31184-X

PROLOGUE

Jörg Knäblein: Head of Microbial Chemistry, Schering AG & Executive Board Member of the European Association of Pharmaceutical Biotechnology; *”Mens sana in corpore sano”* - rationale for *”Modern Biopharmaceuticals”*

FOREWORD

Robert Huber: Nobel Prize laureate & Board Member of Proteros Biostructures; History of Modern Biopharmaceuticals: where did we come from and where will we go

PREFACE

Günter Stock: Senator of German Research Society, Board Member and Head of Research of Schering AG; Modern Biopharmaceuticals – A Primer: Stem Cell Research and Very Recent Breakthroughs

EXECUTIVE SUMMARY

Jörg Knäblein: Head of Microbial Chemistry, Schering AG & Executive Board Member of the European Association of Pharmaceutical Biotechnology; Modern Biopharmaceuticals – A New Era in the New Millennium

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Gary Walsh: Industrial Biochemistry Programme, University of Limerick; "Current status of Biopharmaceuticals: approved products and trends in approval"

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Thomas R. Cech: Nobel Prize laureate, Howard Hughes Medical Institute; Beginning to understand the end of the chromosome

Shiew Mei Huang: Deputy Office Director, CDER / FDA; "The Role of Pharmacogenetics /Pharmacogenomics in Drug Development and Regulatory Review"

Jörg Geistlinger: CEO of Array-On GmbH, Gatersleben, Germany; Large-scale detection of genetic variation – the key to personalised medicine

Bonnie E. Gould Rothberg, Carol Pena, Jonathan Rothberg: CEO of CuraGen & Yale University; A systems biology approach to target identification and validation for human chronic disease drug discovery and development

Thorsten Gutjahr: Program Leader, Herceptin, Hoffmann-La Roche Ltd, Basel, Switzerland: The development of Herceptin®: Paving the way to individualized cancer therapy

siRNA – the magic bullet & other gene therapeutical approaches

Gabor Rubanyi, Michael McCaman: Berlex Biosciences; "Adenovirus-based Gene Therapy: Therapeutic Angiogenesis With Adenovirus 5 Fibroblast Growth Factor-4 (Ad5FGF-4) in Patients with Chronic Myocardial Ischemia"

Burghardt Wittig: CEO of MoloGen & Free University; "MIDGE vectors and dSLIM immunomodulators: DNA-based molecules for gene therapeutic strategies"

Maciej Szymanski, Jan Barciszewski, and Volker A. Erdmann: Polish Academy of Sciences & Free University; Non-protein-coding RNAs and their potential as biopharmaceuticals

Andreas Wagner, Heiko von der Leven: CEO / CSO of AVONTEC GmbH; "Double stranded decoy oligonucleotides as new biopharmaceuticals"

Queta Boese, Anastasia Khvorova: Director Dharmacon, Lafayette: Rational siRNA design for RNA interference: Optimization for therapeutic use and current applications

Mobilis in mobile – human embryonic stem cells & other sources for cell therapy

Woo Suk Hwang: Professor of Seoul National University: The first cloned human embryo: an unlimited source of stem cells for therapeutic cloning

Izhak Kehat, Oren Caspi, Lior Gepstein: Department of Cardiology, Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel: Myocardial Regeneration Strategies Using Human Embryonic Stem Cells.

Abeel Mangi: Harvard Medical School: "Repair of infarcted myocardium by genetically enhanced mesenchymal stem cells"

Elke Reissig, Hermann Graf, Joachim-Friedrich Kapp: SBU Head of Schering AG: "Spheramine: a cell therapeutic approach against Parkinson disease "

Yair Reisner: Weizmann Institute of Science, Israel: "Applying human cells for organogenesis and transplantation – how to create an artificial kidney"

PART II: BIOPHARMACEUTICALS AND THEIR MODE OF ACTION

Quid pro quo – lysis vs. coagulation in the fine-tuned balance of the clotting cascade

Rainer Friedrich: Max-Planck-Institute: Mechanisms of serine proteinase activation: insights for the development of biopharmaceuticals for coagulation and fibrinolysis

Luis Moroder: Max-Planck-Institute: Application of the Principle of Polyvalency for Protease Inhibition

Friedrich Dorner, Norbert Riedel: Board Member of Baxter & MIT: A new technology standard for safety and efficacy in FVIII replacement therapy: Designing the advanced category rFVIII concentrate ADVATE®

Errare humanum est – what causes cancer & how to selectively fight tumors

David Newman: Division of Cancer Treatment and Diagnosis, National Cancer Institute, Bethesda, Maryland: Nature's role in developing potent biopharmaceuticals

Raymond M. Reilly: General Hospital & University of Toronto: Biomolecules as targeting vehicles for in situ radiotherapy of malignancies

Rolf Kalhammer, Hartmut Hampf, Clemens Unger: CEO Medical Enzymes, Director Klinik für Tumorbologie, University of Freiburg: "New directions in tumor therapy – amino acid depletion"

Mundus vult decipi – high mutation rates of HIV & new paradigms for treatment

Francisco Luque Vázquez: Universidad de Jaén: AIDS gene therapy: A vector able to selectively destroy latently HIV-1 infected cells

John Rossi: Director City of Hope National Medical Center, Duarte: Combinatorial RNA Based Therapies for the treatment of HIV infection

PART III: IMPROVING THE DEVELOPMENT OF BIOPHARMACEUTICALS

Citius, altius, fortius – acceleration by high throughput & ultra-HT

Markus Rarbach, Ulrich Kettling, Manfred Eigen: Nobel Prize laureate & Board Member of DirEvo: Design of modern biopharmaceuticals by ultra-high throughput screening and directed evolution

Jon Chesnut: Head of Research, Invitrogen: "Learning from Viruses: High throughput cloning using Gateway® to transfer genes without restriction enzymes"

In vivo veritas – early target validation in knock-out mice & more

Christoph Bagowski: University of Leiden: Target validation an important early step in the development of novel biopharmaceuticals in the postgenomic era

Cord Brakebusch; Max-Planck-Institute; "Knock-out mice as disease models and to discover true physiological gene functions"

Ilse Zündorf, Thomas Winckler, Theodor Dingermann; Institute for Pharmaceutical Biology/ Biozentrum, Frankfurt; „An NIH model organism for biopharmaceutical and biomedical research: the lower eukaryote *Dictyostelium discoideum*“

Revolution by evolution – rational design for desire & the scientific art of optimization

Hans Brandstetter; Proteros Biostructures; "Releasing the spring: Cofactor- and substrate-assisted activation of factor IXa - Triple mutant of Factor IXa shows 7000 times increased activity"

Harald Sobek, Zhixin Shao; Roche; Accelerating Diagnostic Product Development Process with Molecular Irrational Design and Directed Evolution

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The industry's workhorses – mammalian expression systems

Florian M. Wurm; Swiss Federal Institute of Technology;

Manufacture of recombinant biopharmaceutical proteins by cultivated mammalian cells in bioreactors

Volker Sandig; Head of Research, ProBioGen; "Humanized mouse cell line: human glycosylation combined with high protein expression"

Bram Bout; VP Production, Crucell; "PER.C6: Development of a high yielding human cell line for production of biopharmaceuticals"

John Birch, Andrew Racher, David Mainwaring; Chief Scientific Officer, Lonza Biologics, UK; "Use of the glutamine synthetase (GS) expression system for the rapid development of highly productive mammalian cell processes"

Vivat, crescat, floreat – a ripe & blooming market for transgenic animals & plants

Julio Baez; R&D Manager, FibroGen; "Transgenic expression of Biopharmaceuticals in plants and animals"

Victor Klimyuk, Sylvestre Marillonnet, Jörg Knäblein, Michael McCaman and Yuri Gleba; CEO of Icon Genetics & Academy of Sciences of Ukraine; Production of recombinant proteins in plants

Gilbert Gorr, Sabine Wagner; CEO of greenovation; Humanised glycosylation - production of biopharmaceuticals in a moss bioreactor

Ning Huang, Scott Deeter; CEO of Ventria; "Transgenic expression of Biopharmaceuticals in seeds"

Stefan Schillberg, Rainer Fischer, Richard Twyman; Fraunhofer-Institute for Molecular Biology, IME, Aachen, Germany; Biopharmaceutical production in cultured plant cells

Shimon Gepstein, Anil Grover, Eduardo Blumwald; Faculty of Biology, Technion-Israel Institute of Technology, Haifa, Israel; Producing biopharmaceuticals in the desert: Building an abiotic stress tolerance in plants for salt, heat and drought

Harry Meade; Head of Research, GTC Biotherapeutics; "The first biopharmaceutical from transgenic animals: ATryn® – antithrombin III from goat milk"

Alea non iacta est – improving established expression systems

Heiner Apeler; Bayer HealthCare AG, Elberfeld, Germany; Preparing for success - the Bayer experience with a broad range of expression systems

Ivan Verner Diers, Asser Sloth Andersen; Head of Insulin Engineering, Novo Nordisk, Denmark; Advanced Expression of Biopharmaceuticals in Yeast at Industrial Scale: the Insulin Success Story

Wilfried Weber, Martin Fussenegger; Institute of Biotechnology, ETH Zürich, Switzerland; Insectcell-based expression systems: boosting product yields while reducing time and costs

Luke Anthony Miles; St. Vincent's Institute of Medical Research, Victoria 3065, Australia; Robust, cost-effective and highly efficient cell-free expression of biopharmaceuticals: *E. coli* and wheat embryos

When success raises its ugly head – outsourcing to uncork the capacity bottleneck

Jan Carsten Hempel; **Chemengineering AG, Managing Director Biotechnology**: “Contract Manufacturing of biopharmaceuticals”

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From hunter to craftsman – engineering antibodies with nature’s universal toolbox

Uwe Gottschalk, Kirsten Mundt; **Amgen and Sartorius AG**; 30 Years of Monoclonal Antibodies: A long way to Pharmaceutical and Commercial Success

Andreas Plückthun, Simon Moroney; **CEO of MorphoSys, University Zurich**: Modern Antibody Technology: The Impact on Drug Development

Constanze Breithaupt; **Max-Planck-Institute**: Molecular Characterisation of Autoantibody Responses in Autoimmune Diseases – Implications for Diagnosis and Understanding of Autoimmunity

Find, fight & follow – target-specific troika from Mother Nature’s Pharmacopoeia

Joke Orsel, Tobias Schaeffter; **Philips**: Molecular Imaging and Applications for Drug Discovery

Eric Aboagye; **Imperial College London**: Design and development of probes for *in vivo* molecular and functional imaging of cancer and cancer therapies by positron emission tomography (PET)

Dario Neri; **CEO of Philogen & ETH Zurich**: “Ligand-based *in vivo* targeting of disease: from antibodies to small organic (synthetic) ligands”

Andreas Briel, Peter Hauff, Matias Mäurer; **Research Laboratories, Schering AG and Julius Maximilians-University Würzburg**: Ultrasound Theranostics: Antibody-based microbubble conjugates as targeted *in vivo* contrast agents and drug delivery system

Getting insight – sense the urgency for early diagnostics

Andreas Wiesner; **Ciphergen Biosystems**: Development of multi-marker based diagnostic assays with the ProteinChip® System

Jörg Ingo Baumbach; **Director Department of Metabolomics, ISAS - Institute for Analytical Sciences**: Early detection of lung cancer: metabolic profiling of human breath with ion mobility spectrometers

PART VI: ADVANCED APPLICATION ROUTES FOR BIOPHARMACEUTICALS

Getting inside – quest for the best & how to improve delivery

Gesine Hildebrand, Stephan Harnisch; **Schering AG**: “Advanced Drug Delivery Systems for Biopharmaceuticals”

Pathfinder – new ways for peptides, proteins & Co

Michael D. Bentley, Mary J. Bossard, Kevin W. Burton, Tacey X. Viegas; **Nektar Therapeutics, Huntsville, USA**: Poly(ethylene) Glycol Conjugates of Biopharmaceuticals in Drug Delivery

Alexander von Gabain, Christina Michaelis, Katharina Wieser; **CEO Intercell AG, Wien**: Novel adjuvants based on cationic drug delivery systems: a therapeutic vaccine against Hepatitis C

Pankaj Modi; **VP R&D, Genex**: The Evolving Role of Oralin® (oral spray insulin) in the Treatment of Diabetes using a Novel RapidMist™ Diabetes Management System

Akira Yamamoto; **Kyoto Pharmaceutical University, Kyoto, Japan**: Improvement of transmucosal absorption of peptide and protein drugs

Via mala – the stoney road of DNA delivery: back-pack, feed-back & pay-back

Robert Langer, Hermann Eisen, Chun Wang and Jorge Heller; **MIT, Cambridge, Massachusetts, USA**: “DNA Delivery from Poly(Ortho Ester) Microspheres”

Shigeru Kawakami, Mitsuru Hashida, Fumiyoshi Yamashita: Department of Drug Delivery Research, Graduate School of Pharmaceutical Sciences, Kyoto University: "Liposomal *in vivo* gene delivery"
Kentaro Kogure, Hidetaka Akita, Hiroyuki Kamiya and Hideyoshi Harashima: Laboratory for Molecular Design of Pharmaceutics, Hokkaido University, Japan: "Programmed Packaging" - A New Drug Delivery System and Its Application to Gene Therapy"

Getting beyond – rocket science & science fiction

Oliver Kayser: University of Groningen, GUIDE, Farmaceutische Biologie, Groningen, The Netherlands: "BioNanotechnology and its role to improve biopharmaceuticals"

PART VII: FROM TRANSCRIPTION TO PRESCRIPTION

Dosis facit venenum – the therapeutic window between systemic toxicity & lack of efficacy

Michael Hildebrand: Head of Corp. Pharm. Dev., Schering AG: Analytics in quality control and in vivo

Tom Blundell, Harren Jhoti, Pamela Williams: CSO, Astex Technology Ltd, Cambridge: Crystal structures of drug-metabolizing human cytochrome P450s

Mike Murray: Associate Vice President, BioPharmaceuticals Business Unit, BTG International Ltd: Mettox™: A Suite of Predictive In Silico and In Vitro Assays for Metabolic and Genotoxicological Profiling of Preclinical Drug Candidates

Happy end – claim to fame & approval

Kurt Brorson, Marjorie Shapiro, Patrick G Swann: CDER / FDA: "Regulatory aspects of approving Biopharmaceuticals in the US – the FDA perspective"

Axel F. Wenzel: EMEA: "The Regulatory Environment for Biopharmaceuticals in the EU"

PART VIII: FROM BENCH TO BEDSIDE – THE AFTERMATHS

Think big & dealmaking for growth – global changes in the health-care sector

Alexander Moscho, Markus A. Schäfer, Kristin Yarema: McKinsey and Company: "Health-care trends and their impact on the biopharmaceutical industry"

News & views – quo vadis, biopharmaceuticals?

Dorian Bevec: CSO, mondoBIOTECH Group, CH - 6925 Gentilino:

Science meets business: Innovative biopharmaceuticals for rare and yet unattended diseases

James Harris: Vice President, Dragon Pharmaceuticals, Canada: Biogenerics and the emergence of healthcare economics: G-CSF and bioequivalence

Light at the end of the tunnel or back to the roots?

Paul Wrede: Charité: Bioinformatics – from peptides to profiled compounds: Pep2Lead and Prediction of ADMETox Properties

Chaitan Khosla, Martha Lovato Tse: Stanford University, Genentech: Engineering and Overproduction of Polyketide Natural Products

EPILOGUE

Quod erat demonstrandum – modern biopharmaceuticals are key
Preparing the next volume of "Modern Biopharmaceuticals"

Knowledge is power & shared knowledge is success – www.get-gps.net
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