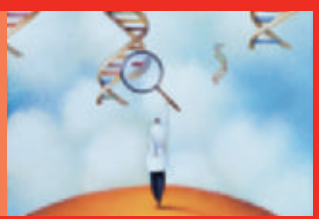
R&D – key to the future

Boehringer Ingelheim



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Introduction

Advancing therapeutic options, contributing to therapeutic progress, treating diseases more effectively and more safely, as well as treating diseases so far untreatable, or insufficiently treatable, form the common denominator of research, development and clinical testing at Boehringer Ingelheim.

It is a fascinating time for research: the human genome has been mapped, the human proteome is being analyzed, though our understanding remains limited; 30,000 to 40,000 genes and about 500,000 proteins may well lead to an unprecedented wealth of research targets. The analysis and description of proteins will become as important and intensive for research as was the human genome only until recently.

Research targets must aim for innovation and anticipate therapeutic progress. In-depth knowledge of the therapeutic area, of basic research by academia and other research institutions, and close interaction with responsible physicians, are prerequisites for successful target selection. Central to success in R&D therefore are scientists who can bridge science in the pharmaceutical industry and basic research outside it while being able to rapidly take up new research projects in response to internal or external scientific progress.

At Boehringer Ingelheim, the bridge between industry and academia is further strengthened by the Research Institute of Molecular Pathology, Vienna and the Virtual Research Institute of Aging, Japan.

Successful discovery also relies on excellent interdisciplinary cooperation and well-functioning medicinal chemistry with state-of-the-art tools: combinatorial chemistry, chemoinformatics, a diversified chemical library and efficient biopharmaceutical development. Technologies such as genomics, proteomics, bioinformatics, e-R&D, high throughput screening and modern galenical and device development are *sine qua non* for successful R&D.

The Corporation's long-term commitment to R&D fosters long-term relationships with academic and corporate partners and it has a track record of good collaboration with biotech companies.

At Boehringer Ingelheim, almost 5,000 biologists, chemists, physicians and support staff conduct research into therapeutic improvement in cardiovascular diseases, central nervous system diseases, immunology and inflammation, metabolic diseases, oncology, respiratory diseases and virology.

Key to success in discovery are good people – people with the best scientific knowledge, flexible thinkers, good communicators, who work well with their peers inside and outside the company.

Dr Andreas Barner
Member of the Board of Managing Directors
Boehringer Ingelheim GmbH

"In today's business environment, R&D productivity has become the focus of the pharmaceutical industry."

Building and improving R&D strengths

Rapid change – social, demographic, technological, economic and political – is having an impact on the pharmaceutical industry. This is opening up, on the one hand, a wealth of opportunities for pharmaceutical R&D while, on the other hand, posing tremendous challenges and risks.

Medical needs are high and even increasing due to the aging population. Growing customer information is raising the demand for more and better health care. The complete sequencing of the human genome is providing unprecedented access to new biological information together with the advent of a new generation of powerful technologies, including quantum leaps in information technology. This is creating opportunities for both improved and totally new drug therapies.

Trying to satisfy high unmet needs however means coping with highly complex diseases, such as Alzheimer's disease or diabetes. Only by gaining more insight into the pathophysiological processes at a molecular level, will it be possible to identify promising targets for pharmacological intervention. In this context the full potential of the technological advances for transforming the R&D process, has still to be unleashed. At the same time, regulatory hurdles are ever-increasing, which is illustrated by the fact that the Food and Drug Administration (FDA) approved only 17 new molecular entities in 2002. Safety in particular has become a critical issue in recent years. Recognizing these unique opportunities and challenges, Boehringer Ingelheim is committed to its goal of discovering, developing and profiling new products which represent high therapeutic value for the patient, the physician and the health care provider.

Increasing R&D productivity - the key

Productivity in R&D means the ability to ensure regular product supply to the pipeline and high-speed, high-quality development to bring competitive products to the market.

In today's business environment, R&D productivity has become the focus of the pharmaceutical industry. Particular emphasis is placed on the research phase delivering compounds which, through their intrinsic properties, define to a large extent the expectations and limits of future product claims. For the coming years, Boehringer Ingelheim has set ambitious goals:

- to bring five innovative and competitive compounds with a high intrinsic quality and a significant sales potential into development each year
- to achieve two successful proofs of principle in clinical research each year

- and to achieve an average duration of development of no longer than 7–8 years.

To meet these targets, R&D has taken a number of strategic measures in recent years:

1. We have implemented, and will continue to implement, key enabling technologies – genomics, proteomics, ultra-high throughput screening, structural research, and combinatorial chemistry. These are influencing every step of the drug discovery process, from the identification of new drug targets and their validation to the identification of new lead structures and their optimization with the goal of creating innovative and developable compounds.
2. We are increasing chemistry capacities at all sites since the impact of medicinal chemistry on drug discovery has possibly been underestimated in pharmaceutical companies and is often the key bottleneck, especially in the phase of lead optimization.
3. We have strengthened the interaction of the research teams with the development disciplines resulting in close collaboration with the goal of jointly selecting optimal drug candidates.
4. We are applying defined selection criteria for all major milestone decisions and perform active portfolio management to further lower the attrition rate in later phases of development.
5. We have implemented, together with Medicine, International Project Management and Operations, a company-wide development strategy with particular focus on the smooth transition between the many disciplines involved in pharmaceutical development.
6. We have strengthened our in-licensing efforts, with a view to early development compounds and new technologies, since no pharmaceutical company can be self-sufficient but needs to acquire outside knowledge, which is specifically emerging from academia and the biotech community. This new venture has been organized within corporate R&D and all of our R&D sites and builds on our reputation as a research-driven company, our researchers' external networks around the globe and our proven capability to successfully launch New Molecular Entities (NMEs).
7. And finally, with our Patent Optimization Project (POP) we believe that we are able to more aggressively protect and defend the Corporation's proprietary assets.

"We are small enough to retain an entrepreneurial spirit, yet large enough to ensure critical mass to drive projects along a fast track."

Our R&D organization

Boehringer Ingelheim has organized its R&D activities in the following way by establishing Centers of Excellence – individual research sites with full responsibility and accountability for specific indication areas.

Biberach, Germany
- central nervous system diseases
- metabolic diseases
- respiratory diseases

Ridgefield, USA
- cardiovascular diseases
- immunology
- inflammation

Laval, Canada
- virology

Vienna, Austria
- oncology

The efforts of our major research sites are complemented by a molecular biology research group in Kawanishi, Japan, with close contacts to Japanese academia, and by a medicinal chemistry center in Milan, Italy, which primarily supports our German research sites.

In non–clinical development a structure with regional responsibility has been implemented. Ridgefield is developing all compounds stemming from the North American sites, with support in formulation development from Farmerit in Buenos Aires, Argentina. Biberach is responsible for the development of all Europe-originated compounds. Respiratory device development will continue to be located in Ingelheim. In addition, the site in Kawanishi is being integrated into our international development activities and takes up defined projects especially in the area of pharmaceutical development. The International Research Review Meeting (IRRM), consisting of the heads of all R&D sites and representitives from medicine and marketing, chaired by the head of Corporate R&D, is steering the worldwide research activities. The International Research and Development Committee (IRDC) develops the corporate research strategies supported by Medicine, sets priorities and allocates capacities in research. The IRDC also defines global standards for carrying out our research and development activities according to best practices and fosters collaboration between the sites.

This collaboration is illustrated by the joint selection and acquisition of key technologies, such as in genomics/proteomics, with a regular exchange of experiences. Potential novel targets are also shared between research sites, for instance in the area of protein kinases, which are relevant for a number of indication areas. Joint research programmes are ongoing, for example, between Ridgefield and Biberach in respiratory diseases, spanning both sides of the Atlantic.

Directing Boehringer Ingelheim's drug development activities is the task of the International Development Committee (IDC), where R&D is joined by Medicine, International Project Management, Marketing and

Operations under the leadership of Dr Andreas Barner. Our international network of development sites facilitates a very flexible use of our worldwide capacities and capabilities.

Bringing forward new ideas

All pharmaceutical companies acknowledge that most of the new ideas, which are the basis for any new drug discovery initiative, come from the outside world, namely academia and the biotech industry. It is therefore essential to establish close links between our in-house researchers and the international scientific community.

We utilize our informal scientific outside contacts around the globe to identify promising new ideas very early on and complement this by introducing a more systematic approach through the R&D Licensing organization, focusing on early development compounds. The company strives to become a preferred partner, which seeks first class in-house research and publications in high-profile scientific journals.

In addition, basic research is conducted within our company through the Research Institute of Molecular Pathology in Vienna, which is world renowned for its research into fundamental cellular growth processes of health and disease. The Virtual Research Institute of Aging was established in Japan to tap into the research potential of the pan-Pacific region.

Thus, new ideas – developed outside or within Boehringer Ingelheim are adopted by the more applied therapy-oriented research groups in order to develop assays and high throughput screenings, to identify and profile promising development candidates.

Targeting our strengths

Boehringer Ingelheim is small enough to ensure a collaborative culture, yet large enough to tap into the scientific reservoir throughout the world. We are small enough to retain an entrepreneurial spirit, yet large enough to ensure critical mass to drive projects along a fast track.

As a family-owned company, we are not solely dependent on short term success stories, yet we are committed to results.

To make R&D work successfully within an international pharmaceutical company, requires a globally managed organization and a performance culture which values and rewards. It needs critical mass and a team-oriented focus. It needs internal openness and communication skills as well as support and understanding from all parts of the company.

Building on, further improving and finally exploiting these strengths, is our ambition.

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The scope of our clinical research

Boehringer Ingelheim has a large, experienced global team managing and conducting clinical research simultaneously in up to 20 countries. With experience in many indication areas, teams can be rapidly assembled to handle either routine or extremely challenging drug development tasks, explains Dr Manfred Haehl, Head of Corporate Division Medicine.

The Corporation has medical departments in over 50 countries, covering North, Central and South America, South Africa, Kenya, Egypt, all of Asia, all of Europe, Australia and New Zealand.

Clinical research personnel working on development programmes for international registration are concentrated in Argentina, Australia, Brazil, Canada, Denmark, Finland, France, Germany, Italy, Japan, Mexico, New Zealand, Norway, Portugal, Singapore, South Africa, Spain, Sweden, the United Kingdom, the USA, and Eastern Europe.

More than 1,100 Boehringer Ingelheim personnel are involved in clinical research including many physicians, statisticians, data managers and field monitors. In some countries external contractors augment to the Corporation's pool as needed.

International clinical research studies are conducted where there is an optimal balance of professional skills and availability of relevant patient groups. Some programmes demand patients in countries outside the primary international clinical structure base and that is readily accommodated using contract organisations, or our own people travelling to those countries.

Because of our R&D infrastructure and in-licensing activities, it is usual for the company to manage up to 40 programmes or more in parallel. Using a team approach, this has proved complex, but manageable. In common with other big pharma companies, Boehringer Ingelheim has worked with many clinical research organizations (CROs), either in single countries, or as part of multi-country studies. Different constructs have been used to facilitate the interactions and this process is carefully overseen to ensure compatibility with our standards of practice (SOP).

All our clinical research staff involved directly with study organization and conduct are trained in good clinical practice (GCP) and SOPs.

Our clinical programmes have been conducted in cardiovascular disease,

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respiratory, neurology, urology, oncology, immunological disease, including arthritis, transplantation and virology, especially HIV. Where an indication area is new to Boehringer Ingelheim's clinical research experience, indication physicians and external consultants enable the new areas to be managed professionally and effectively.

Boehringer Ingelheim has successfully completed multiple studies in Phase I with its two internal Phase I units in Germany. Development studies have been completed with up to 18,000 patients in acute cardiac intervention. Two-year studies of 6,000 patients, outcome studies of over 20,000 subjects, and long-term studies where data collection has continued over six years are part of our very broad clinical trial experience.

Multiple studies often constrained by tight timelines to meet rigorous regulatory needs have been planned and successfully managed through to registration in the US and Europe.

Data for the decade 1992 to 2001

Over the past ten years, Boehringer Ingelheim has conducted over 1,600 studies for more than 160 substances. Of these 437 were in Phase I, 338 in Phase III, and 407 in Phase IV.

More than 260,000 patients were enrolled in Phase I to IV studies including over 50,000 in North America, 160,000 in Western Europe, 9,000 in Japan, and 9,000 in South Africa.

The distribution by therapeutic area of Phase I-IV patients studied were 49,000 in angina and hypertension, 11,000 in stroke, 33,000 in myocardial infarction, 8,400 in other cardiovascular diseases, 39,500 in COPD and asthma, 15,000 in other respiratory diseases, 15,000 in HIV, 6,000 in oncology, 2,700 in immunological disorders, 11,000 in various CNS diseases such as depression, Alzheimer's and Parkinson's diseases, and 34,000 in rheumatoid and osteo-arthritis.

Clinical research management

All clinical research programmes for registration are conducted under local control but within a global coordinated management to ensure quality, consistency, harmonization and optimal speed to completion.

Each clinical therapeutic area is coordinated by a Therapeutic Area Head (TAH). They supervise the strategic and planning activities and each physician responsible for a single programme reports to the respective

TAH. Currently there is a TAH for each of the following: cardiovascular, respiratory, oncology, virology, neurology, immunology and central nervous system/general medicine.

All operational study tasks are assigned to our operative unit staff whose activities are managed and coordinated on a regional basis, either in North America or Europe, to facilitate harmonization and to move sites rapidly within the region in the event of slow recruitment.

All international programmes are supervised and reviewed at international committees, such as the International Medical Committee (IMC), to ensure consistency, quality and timely delivery. The committees include medical directors of clinical research countries which supply the bulk of the studies.

All programmes are planned on an international basis seeking to satisfy the basic scientific requirements to describe a drug's efficiency and safety, but also to meet the needs of the principal regulatory authorities. From an early stage of development the marketing needs are defined globally and built into overall development plans.

A worldwide clinical trial management system (CTMS) has been developed to provide a single source of data on trials planned and in conduct; timelines, status of patient recruitment, organization, management of budgets and investigator payment, identification of involved sites, countries and investigators. This one-stop information source enables operational people in the group and senior management with global oversights to review different aspects of the same data.

Standards are maintained by international SOPs by full review and release of clinical trial reports from their global perspectives, and by a formal auditing process on a worldwide basis. Each programme is managed by a clinical team headed by the medical team leader. The team includes a statistician, a data manager, a field monitor liaison officer and a DRA representative. Local studies are organized by a similar team structure and liaise closely with the programme's medical team.

Performance

A formal 'Speed to Market' project revisited all process steps involved in clinical trials and regulatory submissions. This clarified all steps in a study's progress and defined the maximal times for each stage of a study's conduct, including time to complete protocol, to initiation, from last patient out to database lock and to finalization of a report. Compliance with these timelines is carefully monitored.

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A recent process initiative called SCOPE (submission chain optimization project) established multiple process improvements with the clear objective of shortening the time to regulatory approval on a global basis by including ongoing label development during late stages of development, early preparation of possible regulatory questions and submitting applications within weeks in most countries.

Eleven new drug applications (NDAs) and supplementary NDAs have been successfully submitted or approved in the US in the past seven years and multiple approvals have been obtained worldwide for products in areas such as hypertension, myocardial infarction, COPD, Parkinson's disease, asthma, HIV infection, non-steroidal anti-inflammatory drugs (NSAIDs) for osteo- and rheumatoid arthritis, benign prostatic hypertrophy, stroke prevention and allergic rhinitis.

DRA support

Drug Regulatory Affairs (DRA) is organized on an international basis. This enables a submission to be navigated by DRA personnel with full international focus. Opinion is supplemented where needed by regional or local regulatory experts.

A technical DRA group focuses on chemical manufacturing control issues with the Food and Drug Administration (FDA) and European Medicines Evaluation Agency (EMEA) to facilitate the comprehensive compliance of drug development with these complex and sometimes troubling aspects of regulatory submissions.

Interaction with the FDA and EMEA over many years helps us maintain a hard-headed approach to drug development, preferring to interact repeatedly with regulators to ensure that development programmes are optimal for success, yet economical and fast.

R&D Germany - Discovery concentrated at Biberach

Our R&D organization in Germany is fully equipped and dedicated to master drug discovery, non-clinical development and enabling technology functions. Since the end of 2002, discovery research is concentrated in Biberach, writes Prof. Dieter Hinzen, Head of R&D Germany.

The goals for Respiratory Diseases are improved treatments for chronic obstructive pulmonary disease (COPD) and asthma. For COPD, we aim to strengthen our position in the field of anticholinergic bronchodilators and to extend our portfolio to treatment of underlying inflammation. In asthma, the goals are to identify mechanisms which allow the replacement of steroids, and the provision of treatments for aspects of the disease with unmet medical need.

In Central Nervous System Diseases the focus is on approaches for the treatment of chronic (neuropathic) pain and neurodegenerative diseases. In neuropathic pain targets are pursued with recently cloned ion channels. It is an accepted hypothesis that the ß-amyloid protein of Alzheimer brains is a causative factor for the disease. Approaches are therefore intended to prevent the generation of this protein.

Metabolic Diseases constitute one of the most important risk factors for cardiovascular morbidity/mortality. Metabolic research will focus on options for the prevention/treatment of diabetes mellitus type II.

Medicinal Chemistry has its important role in drug discovery at the interface between biology and development. Lead Discovery aims at selecting the most attractive options for the start of lead optimization, also taking into consideration potency and selectivity aspects of pharmacokinetics, physicochemical properties and tolerability. Significant effort is dedicated to the design and diversity of the chemical compound pool, which currently encompasses 700,000 molecules. Medicinal Chemistry in Germany works closely with the Chemistry Research Center (Milan), Italy, in support of our research activities and with Chemical Development, which provides scaling-up activities for the early supply of new chemical entities.

High throughput screening (HTS) is successful in identifying compounds that show an interaction with the biological target. In the HTS group a 100-fold increase over the 1995 throughput has been achieved.

The strategic role of drug metabolism and pharmacokinetics has changed. In the past, this discipline was solely involved to retrospectively describe the pharmacokinetic and metabolism

profile of drugs. This function has evolved now as a core discipline in drug design and lead optimization.

Genomics approaches have become a constituent of target identification. Joint activities between genomics and therapeutic areas have proven effective. To date, three expression profiling projects proceeded to the target validation phase (COPD, Alzheimer, diabetes). Proteomics focus will be on new developments, such as improved mass spectrometry techniques or even protein chip technology. Toxicogenomics and its significance for drug development is advancing. We plan to analyze gene expression patterns of blood samples with the objective of identifying surrogate markers of toxicity.

A R&D Licensing unit enriches our portfolio by bringing in promising projects and early development compounds. Representatives of the non-clinical development functions at Boehringer Ingelheim Pharma KG are integrated in multi-disciplinary teams led by project leaders from the department Project Management R&D. They bear responsibility for the professionally competent and timely advance of all European products from discovery to registration. In Chemical Development this means generating an efficient way of synthesis, with regard to future manufacturing requirements too, starting at a laboratory size and evolving up to kilogramme scale.

The goal of Pharmaceutical R&D is to critically determine developability of substances, and to optimize feasible dosage forms embracing all relevant technologies. Development of a manufacturing process for the drug product has to be established. Especially drug substances with poor solubility or stability problems require special know-how and establishment of innovative dosage forms. Analytical sciences work in close cooperation with Pharmaceutical R&D and our Special Drug Delivery department, as development of dosage forms demands analytical test methods for characterization of drug substance, degradation products and impurities, as well as determination of quality and stability of the drug product.

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“This focusing at a single location is bringing valuable synergy effects.”

Research Campus Biberach

Germany, with its two big sites at Ingelheim and Biberach, is of central importance to the whole Corporation’s R&D operations and product pipeline.

In Biberach, a top quality research campus is being established in which Boehringer Ingelheim’s German R&D capacities are being concentrated, as has already been the case with medicine and biotechnology. This focusing at a single location is bringing valuable synergy effects.

The current discovery research work in Germany is focused on the therapy areas central nervous system, metabolism and respiratory. Even after the centralization of oncological research in Vienna, Germany will remain the development center for this field of therapy in Europe. Furthermore, activities in modern special drug devices will continue to be one of the central operations.

No less important for Boehringer Ingelheim are the services that Medicine provides in Germany. On the one hand, Clinical Research is of central importance for the planning, conception and implementation of clinical studies of Phases I-IIIb. It is also at the important interface between pre-clinical and clinical development. Here, the first applications to humans (Phase I) of all new drug substances in the Corporation are carried out in our Human Pharmacological Centers in Ingelheim and Biberach. On the other hand, the Medical Data Services assume central functions such as biostatistics and data management and other services for the whole of Europe.

Biopharmacy is also of singularly great significance in the company. This sector controls the whole biopharmaceutical process chain from genetic engineering to international registration and marketing. Close cooperation between R&D and Medicine is essential in developing

new therapy principles. Products that are manufactured on the basis of mammalian cell cultures in Biberach, or microorganisms in Vienna, come not only from the company's own R&D but also from cooperations with other biotech and pharmaceutical companies. On account of its highly successful development, biopharmaceutical active compound production will be doubled at the Biberach site – Boehringer Ingelheim's greatest capital expenditure project to date. The complex is due to come into operation at the end of 2003, creating 400 new jobs.

The course for the central objective of conducting research into innovations with considerable therapeutic benefits for the Boehringer Ingelheim product pipeline, and developing them to market launch, has been set by concentrating German operations in R&D, Medicine and Biotechnology at Biberach. Implementation is at an advanced stage. The physical proximity and close links between Research and Development and Medicine and important parts of Biotechnology of the company at a single site will lead to considerably shortened development times through improved communication, greater flexibility and increased efficiency.

Biberach will also increasingly assume the character of a research campus as a result of the infrastructural measures being carried out in connection with these projects. New buildings have been, or are being, erected for toxicology, pharmacology and pharmacokinetics, analytics and chemical development, chemical research and lead discovery and biology, as well as a technical center for Pharmaceutical R&D. A new Human Pharmacological Center is being planned for the site. These buildings, supplemented by the new building for biopharmaceutical active compound production and adjacent new laboratory wings, make Biberach considerably more attractive for new employees, a most important factor on the road to innovation.
In parallel, a top-quality technological research platform is being created that includes the ultra high throughput screening and combinatorial chemistry as well as the future-oriented subjects of genomics and proteomics. This innovative environment is rendering the Biberach research campus fit for the future and underlines its importance for the Corporation's future success.

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"Strategic partnering within the bioscience network also provides a great opportunity for research and development."

R&D USA - Key player in immunology and inflammation

Ridgefield, Connecticut is home to 650 scientists in our North American R&D Center. Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) also supports Boehringer Ingelheim (Canada) Ltd. in compound development, drug discovery support and ultra-high throughput screening and is assisted by Boehringer Ingelheim Argentina in analytics and pharmaceutics.

BIPI's R&D, surrounded by three major Pharma companies and 27 biotech companies, faces enormous competition in terms of science, technologies and qualified workforce. However, strategic partnering within the bioscience network also provides a great opportunity for research and development in our Ridgefield R&D Center.

Our scientists are engaged in the discovery and development of innovative therapeutic agents to treat immunological and inflammatory diseases, such as rheumatoid arthritis (RA), psoriasis, inflammatory bowel disease (IBD) and multiple sclerosis.

Discovery efforts are mechanistically driven and founded on significant advances in molecular and cell biology that have accelerated our understanding of the immune system. This also provides potential new avenues for the generation of new medicines in the fields of cardiovascular diseases, oncology, respiratory diseases and virology. Among allergic disorders, we focus on asthma.

Our key research programmes include regulation of immune cell activity, cell trafficking and adhesion, antigen presentation and intracellular signalling processes attributed to inflammation.

"We are harnessing new, world class technologies for drug discovery and development."

Recent discoveries include a novel class of molecules that specifically disrupt the protein-protein interaction of the cell adhesion molecules LFA-1 with ICAM-1 in humans and thereby suppresses inflammatory responses. Pro-inflammatory molecules – cytokines – play a key role in enhancing the destructive effects of autoimmune diseases. By interfering with intracellular signalling pathways linked to the production of those cytokines, our scientists have discovered promising new therapeutic agents now being studied in patients with RA, psoriasis and IBD.

The recent discovery of steroid mimetics opens new gates to treat a broad band of inflammatory diseases.

Cardiovascular research is being implemented as a further therapeutic area to strengthen our drug discovery. Modern immunological concepts offer new ways to address the unmet medical need in coronary heart disease and heart failure. Ridgefield scientists already focus on creative approaches in the fields of therapeutic angiogenesis (arteriogenesis) and vascular protection to identify novel and effective therapeutics beyond current treatment regimes.

With strategic licensing in and out we leverage internal and external knowledge to further strengthen our R&D portfolio. We are harnessing new, world class technologies for drug discovery and development and approaching the genomic/proteomic revolution with targets that will significantly improve immunology and inflammation medicine in the 21st century. Our commitment to the former is the Lead Discovery Technology (LDT) building, which houses the ISLAR (International

Symposium on Laboratory Automation and Robotics) award winning 'ALLEGRO' ultra-high throughput screening system. Knowledge management and information sharing are also key competitive advantages for us. Rapid conversion of huge data volumes to valuable knowledge – especially in the fields of bioinformatics, chemoinformatics and chip array experiments is supported by first rate IT technology and personnel and first rate scientists.

External partners, such as Gene Logic, Lexicon Genetics and Lion Biosciences, leverage our capabilities.

In collaboration with the National Institute of Environmental Health Sciences (NIEHS) Phase I Molecular Toxicology and the University of Connecticut, R&D has established a leading position in toxicogenomics and – proteomics. This allows us to evaluate the toxicity potential of new compounds based on gene and protein expression profiles and support lead optimization programmes in medicinal chemistry.

High throughput crystallography and chemgenetics approaches strengthen our medicinal chemistry department. The strong involvement of development disciplines into early drug discovery phases helps to identify improved drug candidates and lower the late phase attrition rate.

State-of-the-art non-clinical development functions and integrated processes guarantee professional development for all American drug products along the entire R&D value chain.

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R&D Canada - Center for virology research

The development of effective treatments for viral infections remains a major challenge for the management of infectious diseases today. It also represents a tremendous opportunity for Boehringer Ingelheim, according to Dr Paul Anderson, Head of R&D Canada.

The antiviral therapeutic area has been, and is projected to remain, one of the fastest growing pharmaceutical market segments. Recent advances in biomedical research are the drivers of this growth. The discovery of new viruses associated with human disease, and a knowledge and understanding of the pathogenic processes underlying viral diseases, have permitted the development of innovative antiviral drugs for previously untreatable viral illnesses.

In 1995, the research center of Boehringer Ingelheim (Canada) Ltd., in Laval (near Montréal), Québec, was given a new strategic direction and mandate as the Corporation's center of excellence for antiviral drug discovery. Research in Laval, one of Canada's largest pharmaceutical research centers, now focuses on chronic and acute viral diseases for which no vaccine exists, current therapy is either lacking or unsatisfactory and a significant unmet medical need exists. These include hepatitis C virus (HCV), human immunodeficiency virus type 1 (HIV-1), human papillomaviruses (HPVs) and respiratory syncytial virus (RSV).

The development of effective treatments for such viral infections is a significant scientific challenge. Viruses are intracellular parasites; they replicate within cells and exploit the cellular machinery to carry out many of the processes essential for their growth and reproduction. Since different viruses are genetically distinct and employ diverse and

"The development of effective treatments for such viral infections is a significant scientific challenge."

complex strategies to subvert the cell's machinery to their own needs, it is difficult, if not impossible, to develop "broad-spectrum antiviral agents" analogous to the antibiotics commonly used today to treat the myriad bacterial infections. Rather, antiviral agents must be specifically developed to target individual viral pathogens. Moreover, in common with other infectious agents, viruses possess the capability of developing resistance to therapy.

The antiviral research programmes in Laval focus on the discovery of drug molecules which inhibit the functions of specific viral gene products. These approaches are facilitated by a detailed knowledge of the genetic composition of most viruses of medical importance and offer the advantage of providing targets specific to the virus and hence limited in their potential for mechanism-based toxicity.

Nevertheless, the remarkably small genomes of viruses encode a limited repertoire of viral gene products, which are potential targets for therapeutic intervention. A small number of viral enzymes and viral protein-protein or protein-nucleic acid interactions, whose functions are essential for virus reproduction are thus the focus of antiviral drug discovery research.

From their inception in 1995 the virology research programmes in Laval have now matured and our most advanced programmes are yielding promising and novel candidate antivirals targeted to the key replicative enzymes of these important viral pathogens.

The HCV programme is exploiting both rational design and screening approaches to identify inhibitors of key viral enzymes responsible for the proteolytic maturation of viral proteins and for the replication of the viral genome. These approaches may lead to the development of novel classes of antiviral for the treatment of chronic hepatitis C.

HIV research in Laval aims to complement Boehringer Ingelheim's portfolio of antiretrovirals, which include our marketed non-nucleoside reverse transcriptase inhibitor, VIRAMUNE®, and the protease inhibitor tipranavir, currently in clinical development. The most advanced programme seeks to identify reverse transcriptase inhibitors with improved safety and efficacy, which will add to the armamentarium of drugs available to infected individuals, particularly those who have failed prior therapy due to the development of drug resistance.

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"The time for drug discovery in oncology has never been better."

R&D Austria - Drug discovery for cancer medicines

Have you ever tried to imagine high-calibre pharmaceutical drug discovery in the heart of one of Europe's most attractive and culturally rich capitals, surrounded by a thriving academic and biotech environment, and using state-of-the-art facilities run by highly-motivated and talented people from a dozen countries spanning the globe? Dr Wolfgang Rettig, Head of R&D Austria, replies.

This is more than a dream at Boehringer Ingelheim Austria in Vienna. Since its inception 40 years ago, the Vienna R&D unit – operating under the company name Bender until 1998 – has earned a reputation for pharmaceutical innovation, including pioneering work on interferons, cytokines and other biologic agents in the 1980s, high throughput screening, gene therapy, and genomics. The drive to enhance drug discovery processes has remained a key element of the Vienna R&D effort, but in recent years the site has also evolved into Boehringer Ingelheim's dedicated Drug Discovery Center for Oncology, charged with adding new cancer medicines to the product pipeline.

For this enlarged role, substantial investments have been made to provide a world-class infrastructure, resources, and expertise across a broad range of disciplines. As a result, the entire drug discovery chain from genomics to molecular and cell biology, biochemistry, structural research, assay robotics, medicinal chemistry, pharmacology, drug discovery support (pharmacokinetics, analytics) and immunology are in place in Vienna. Already, the Center works closely with Boehringer Ingelheim Development Centers and corporate functions, such as Medicine and Marketing, to achieve its goals.

The importance of finding new cancer treatments can hardly be over-emphasized. In the western world alone, one in every two women and one in every three men is afflicted by malignant cancer in their life-times. Worldwide

there are over 12 million new cases and seven million cancer deaths per year. A cure is possible today in a proportion of patients, especially if the disease is detected early. But far too many patients eventually succumb to their disease in spite of sometimes debilitating surgery, chemotherapy or radiotherapy.

Fortunately, the time for drug discovery in oncology has never been better. The revolution in genomics has benefitted cancer researchers tremendously, and the first detailed blue-prints of what causes cancer have been drawn up. These blue-prints point the scientists in Vienna in the direction of better cancer drugs. There are almost too many opportunities to be handled by any one company: drugs that can halt the cell division clock, oppose signals that drive cancer growth, block blood vessels needed to sustain the disease, affect the cell aging programmes, or inhibit the invasive and metastatic spread of cancer cells into healthy tissue. Then add to this cancer vaccines and antibody-guided drugs.

In light of the strengths of Boehringer Ingelheim in both classical drug development and biopharmaceuticals, it is no surprise that several leading European and US biotech companies and academic groups working in the cancer field have entered into cooperations with the Vienna R&D Center.

Big is not always better in research and in drug discovery. For Austria R&D, the focus on interdisciplinary teamwork and a fine balance between creative independence, rigorous science, and prudent resource management promise to deliver results and improve the lives of patients with cancer.

www.boehringer-ingelheim.at

R&D Japan - Our Asian research arm

Kawanishi Pharma Research Institute (KPRI), founded as an independent entity has continued to expand and flourish since it was merged with Nippon Boehringer Ingelheim Co. Ltd. in 1980. Today, KPRI has nine departments and 131 personnel.

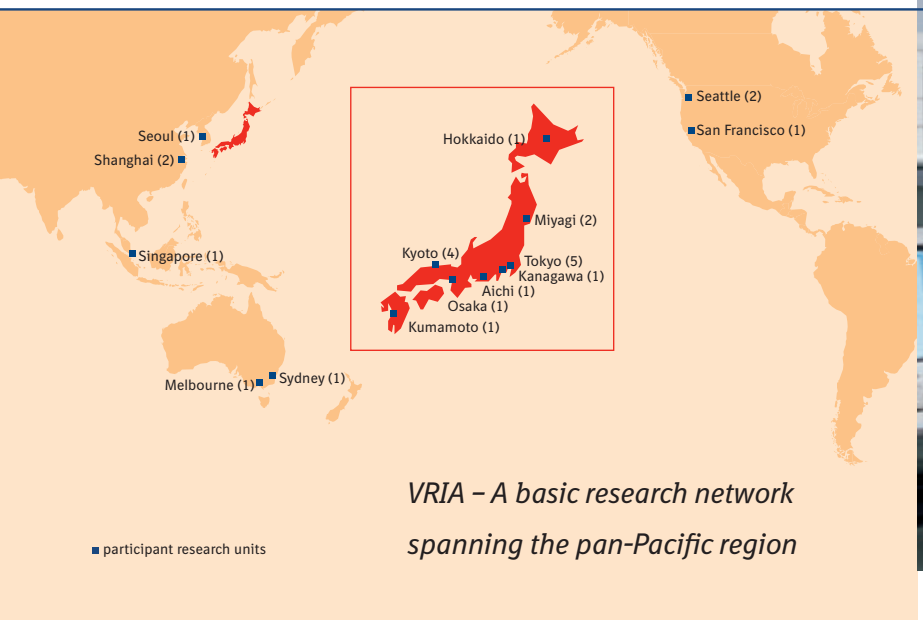
KPRI's Department of Molecular and Cellular Biology (MCB) has state-of-the-art molecular biology know-how and supports drug discovery work in other Boehringer Ingelheim R&D Centers. It provides a variety of tools for high throughput drug screening, such as mammalian cells expressing human ion channels or receptors and recombinant human enzymes.

Five specialized departments comprised of 15–20 people each, and the Quality Assurance Department (QA) and a project coordination group work on drug development. Until recently the Japanese authorities requested various kinds of Japan-specific studies for New Drug Application (NDA) approval and such departments were obliged to undertake them. However, a recent International Conference on Harmonization (ICH) agreement has reduced the necessity for such studies. Even so, KPRI has continued to carry out studies for some international projects and the results have been used as a part of international submissions. Boehringer Ingelheim also chose the strategy of worldwide and simultaneous submission of new drug applications (NDA).

Given this status, KPRI has launched a drive to improve itself so that it can generate more data that is acceptable internationally and strengthen the interface with international drug development teams.

In September 1999, integration of Nippon Boehringer Ingelheim into the international drug development system was approved by the International Steering Commitee (ISC). In 2000, KPRI was acknowledged as one of the Corporation's drug development centers. Now the ratio of international work versus national work exceeds 80 per cent and will increase further. As its next step, KPRI will particularly be involved in the development of formulations for international projects.

www.boehringer-ingelheim.co.jp



VRIA – A basic research network spanning the pan-Pacific region

Virtual Research Institute of Aging (VRIA)

Life expectancy has increased steadily over the last century. Where it was around 45 years in 1900, today, only four or five generations later, we expect to live for 80 years on average. Japanese women are in the lead worldwide with a life expectancy of 84 years. What are the biological mechanisms that control the aging process and, above all, what makes the aging body so susceptible to disease? Professor Rudolf Hammer, Nippon Boehringer Ingelheim, describes the corporation's innovative research approach.

With the VRIA, Boehringer Ingelheim has embarked upon a completely new direction. This is a basic research network of 25 academic groups selected by a Scientific Advisory Board of renowned Japanese professors and representatives of the Boehringer Ingelheim management (see map). The focus is on Japan and the key countries of the pan-Pacific region. Moreover, Boehringer Ingelheim is also investing in countries such as China, Korea and Singapore, where the scientific facilities at the universities are currently being sponsored and developed intensively. With this initiative the company takes account of the significant progress in biomedical science in this region in recent years.

The research is to be sponsored for a period of three years. Boehringer Ingelheim has given the researchers considerable leeway in return for being notified immediately of the research results. This affords the company access to new, potentially patentable findings from basic research before they are made public. Should this cooperation give rise to patents that are later granted, Boehringer Ingelheim can assert the right of first refusal.

The VRIA research projects can be divided into five main areas:

- genomic instability
- signal transduction
- proliferation and cell death
- developmental mechanisms
- disease related animal models

In Japan the call for the country to open up and introduce trenchant reforms is becoming ever louder. This applies to both the natural sciences and medical research. The founding of the VRIA by Nippon Boehringer Ingelheim can serve as an excellent example of how Japanese institutions are opening up, intensifying communication with the rest of the world, and entering into promising alliances at international level.

IMP - The life science think-tank

If you are looking for the highest density of creative, imaginative – perhaps even eccentric – scientists within the Boehringer Ingelheim world, you will probably find it at the Research Institute of Molecular Pathology (IMP), Vienna, Austria, where Prof. Tim Hunt, Nobel Prize winner for medicine in 2001, has for seven years been on the IMP Scientific Advisory Board. Prof. Kim Nasmyth, Director of the IMP reports.

At the IMP, around 120 biologists, biochemists and MDs from 27 countries work towards understanding fundamental principles of life and mechanisms of disease.

The IMP's role within the company is to carry out basic research in the field of developmental biology, cell cycle regulation and molecular genetics. Boehringer Ingelheim provides about 80 per cent of the institute's budget, the rest is financed through grants. In return, the intellectual property created by IMP is at Boehringer Ingelheim's disposal. Probably the most valuable contributions from the IMP's research are new drug targets for innovative therapies. Among those identified so far are cell cycle targets and chromatin modification targets. IMP researchers have also developed efficient gene transfer methods. A number of projects have been chosen for further development by the company – mostly under New Chemical Entities Oncology Projects.

These include recent discoveries by IMP Director Kim Nasmyth and Senior Scientist Jan-Michael Peters on the molecular mechanisms of cell division, which have yielded two new drug targets. Thomas Jenuwein, another Senior Scientist, revealed details of the epigenetic regulation of genes which resulted in a drug screening project. Hartmut Beug, a Senior Scientist who collaborates intensely with Boehringer Ingelheim researchers in Ingelheim, Biberach and Ridgefield, identified a target which has already shown promising results in a high throughput compound screen. Jan-Michael Peters and his team are collaborating closely with the Corporation on the characterization of cell cycle inhibitors whose molecular targets are as yet unknown. Such targets are likely to be useful in oncology.

Through its quasi-academic character and intense international exchange, the IMP also serves the company as an "antenna" for the scientific community. Researchers travel frequently and keep close contact with their peers. This enables them to spot the hottest topics in science at an early stage and get a

"The IMP also serves the company as an 'antenna' for the scientific community."

good overview of current research projects elsewhere. Information of this kind can give Corporation projects a headstart.

Established in 1988, the IMP has gained a worldwide reputation in biomedical research. Its success is documented in 80-90 publications per year in high impact scientific journals. In addition, 79 patent applications with the potential to be exploited commercially have been filed so far.

Recognition of the quality of research at the IMP also manifests itself in a number of awards and honours every year.

The most prestigious Austrian prize in science is the Wittgenstein prize, awarded by the government. Since the prize was established in 1997, three IMP scientists have been among the laureates: Erwin Wagner, Kim Nasmyth and Meinrad Busslinger. Two new research groups have been funded by Wittgenstein money.

Awards in 2001 included the Novartis Research Prize for Biology which went to Jan-Michael Peters for his work on cell division. Three group leaders were elected EMBO members and three students received a prize for their theses.

The productivity of IMP scientists also received recognition in a study carried out by the Austrian Science Fund. In a survey of publications in leading journals during a five year period, it was found that the IMP had turned out more papers than any other research institution in the country, including the universities.

www.imp.univie.ac.at

IMBA

The Institute of Molecular Biotechnology (IMBA) combines forces with the IMP in the "IMP-IMBA Genome Research Center", a joint research initiative by Boehringer Ingelheim and the Austrian Academy of Sciences. IMBA research foresees the use of mice and other model organisms to investigate how they develop and function, and to explore the molecular basis of human diseases. It is located next door to the IMP at the Campus Vienna Biocenter, Austria, a center of excellence in molecular biology and genetic research. IMBA activities started in 2003.

www.imba.oeaw.ac.at

nature MILESTONES

Constructive cooperation with Nature

The Nobel Prize for Physiology or Medicine was awarded in 2001 for research into the control mechanisms behind cell division. To confirm its commitment to this field of research, with its strong impact on oncology, Boehringer Ingelheim decided to support the internationally renowned scientific journal Nature in publishing a special edition, "Milestones in Cell Division", and producing a dedicated website.

That the 100th Nobel Prize for Medicine was awarded for work in precisely the field of cell division was an enormous surprise and the best conceivable promotion for the Boehringer Ingelheim project.

The prize went to the British scientists R. Timothy Hunt, Sir Paul M. Nurse and the American Leland H. Hartwell for their research into cell growth and division. The scientific papers submitted by the three laureates represented a major contribution to understanding what has "gone wrong" in cancer patients. In their studies in yeasts and sea urchins, Hunt, Nurse and Hartwell uncovered the genetic and molecular biological key regulators of the cell cycle. And the key molecules controlling the cell cycle in yeast and sea urchins function in exactly the same way in all other eukaryotic organisms, including animals and people. Defects in the control of cell growth and division can lead to chromosomal changes and hence to the development of tumour cells. Thus the cell cycle discoveries are beginning to help in the diagnosis of cancer and may in the long term open new possibilities for treatment.

Several factors link Boehringer Ingelheim's own basic science center, the Research Institute of Molecular Pathology (IMP) in Vienna, with the research rewarded by the Nobel Prize committee. The IMP has an excellent reputation in the elucidation of cell cycle controls. Moreover, Hunt served on the nine-member Scientific Advisory Board of the IMP from 1995 until the end of 2001.

The results obtained by Hunt, Nurse and Hartwell are also of major importance to the pharmaceutical industry – for instance for Boehringer Ingelheim's oncology research in Vienna, Austria. Boehringer Ingelheim arranged for over 30,000 scientists, institutes and other interested parties worldwide to receive a copy of this journal free of charge.

A well-visited website sponsored by Boehringer Ingelheim also provides details on cell division with free access to more than 100 full-text research papers, reviews, news, historical perspectives, etc. that were published by the Nature Publishing Group. It also contains original papers that formed the basis of Milestones in Cell Division and includes biographies and photographs of the 55 milestones advisers. There are also hyperlinks to cell division websites and Nature journals.

www.nature.com/celldivision

"R&D Licensing has evolved into a strong and agile global team."

R&D Licensing

Dr Klaus K. Wilgenbus is head of R&D Licensing. He summarizes the challenges and success of coordinating and steering of world-wide in-licensing activities for R&D.

What has been the greatest challenge and achievement for R&D in-licensing?

KW: Within the first month it became clear that specializing on in-licensing compounds in research and early development as well as in-licensing of enabling technologies requires a high level of scientific competence and a wide screen to identify and successfully approach potential licensors. Luckily, within the global R&D organization we hold a promising and impressive array of competence. The initial challenge of integrating this diversity of knowledge and skills spread over different sites to operate as one team was turned into success. R&D Licensing has evolved into a strong and agile global team.

Can you comment on your current tasks and describe even early results?

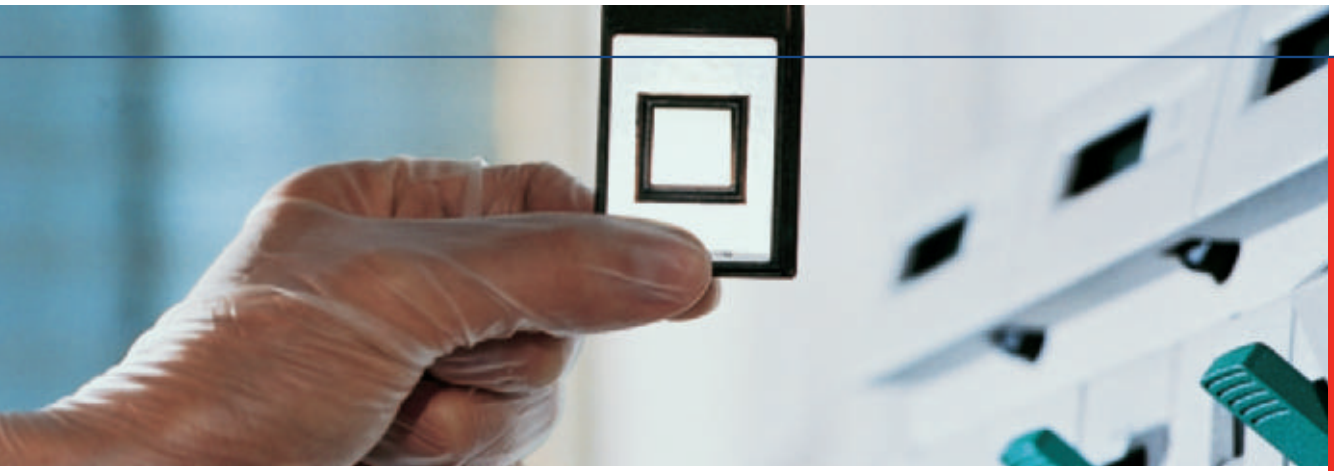
KW: In contrast to more advanced projects in clinical development, early in-licensing opportunities are often not overt and only minimally described. This requires extensive networking among scientific circles and mining of various information sources, particularly scientific and competitor data to grasp the potential, risks and ultimately the value of an early stage in-licensing opportunity.

With all of the compounds and most therapeutic approaches being novel, the risks involved are significantly higher compared to late stage candidates, however the return will also be significantly higher. Recent important results of our efforts were the completion of licensing agreements with Kissei and Sagres Discovery.

What challenge do you see ahead?

KW: In an even more rapidly changing environment, we need to further increase Boehringer Ingelheim's visibility as a competent partner for in-licensing of early stage compounds. We need to demonstrate our commitment by fast execution of decision processes and fair and successful deals. This requires even better networking and integration within our own organization as well as with potential partners. Here we learn from our competition that R&D in-licensing is best executed by showing support and competence even at very early stages. Scientifically as well as commercially competent licensing managers help to crystallize ideas into opportunities, help to increase its commercial value by providing expertise and fair risk sharing and catalyze intense partnerships with industry as well as academia-based science at all levels.

licensing@ing.boehringer-ingelheim.com



Targeting new territory – Genomics, proteomics, bioinformatics

The complete set of genetic instructions for the generation of an organism is contained in its genome. In the past decades, the methods of classical and molecular genetics have been applied widely to examine portions of human, animal and other species' genomes in a piece-meal fashion, characterizing "a gene at a time", writes Dr Klaus Ebert, Chairman of the Genomics Strategy Team.

The situation changed dramatically with the emergence of genomics and proteomics as new fields of research. Genomics aims to study in a systematic and comprehensive fashion entire genomes in different species. Proteomics is an emerging field in the analysis of biological systems and comprises the large-scale study of the complete protein complement of the genome, the proteome.

Although genomics and proteomics draw heavily on concepts derived from classical and molecular genetics and protein biochemistry, they add an element of sheer size and, therefore, require a unique technology base.

Allowing an "unbiased approach" to biology, these technologies are providing a wealth of opportunities as well as challenges for drug discovery and development.

In research, the essential starting point for any new drug discovery initiative is a validated target for pharmaceutical intervention. The availability of the complete human genome sequence will allow – as the quality of both the sequence and its annotation improves – comprehensive access to genes and proteins and thus potentially to all hitherto unknown drug targets. However, the real challenge is to develop a thorough understanding of the function of a gene product, i.e. a protein, in both health and disease, to explore its full utility as a suitable novel target.

Therefore, in order to be most effective, Boehringer Ingelheim's approach to genomics/proteomics in research utilizes selected technologies in very close collaboration with the therapeutic area expertise to link genomic information to pathophysiology.

As a major direction, the identification of gene expression patterns and their association with disease is being pursued. This is done via large scale expression profiling using DNA microarray chips, a very reliable and robust technology. Affymetrix DNA microarray instruments have been installed at most of our research sites.

Genomics is complemented by proteomics approaches in those cases where gene expression profiling is not biologically meaningful. Moreover, "interaction proteomics" technologies are applied to identify specific protein interaction partners. Proteomics technologies as such are not yet as mature as genomics, particularly regarding high throughput applications. We are therefore exploring technological advances and expertise both internally and externally.

We are carrying out genomics/proteomics projects in all Boehringer Ingelheim therapeutic areas, i.e. respiratory and autoimmune diseases, diseases of the central nervous system, metabolic, cardiovascular and viral diseases as well as oncology.

"We are carrying out genomics / proteomics projects in all Boehringer Ingelheim therapeutic areas."

Due to the progress made in these target identification efforts, we will, in the future, place more emphasis on technologies that enable us to expeditiously advance genomics project initiatives to validated targets. For this reason, collaborations have been established with GeneLogic, enabling us to quickly identify *in silico* the expression pattern of a candidate target in a multitude of different healthy and diseased tissues; and Lexicon Genetics, provides access to specific mouse models for *in vivo* target validation.

The application of high throughput technologies leads to unprecedented data volumes in biology. The challenges of raw data processing, data mining and data interpretation gave rise to the new scientific discipline of bioinformatics, which quickly became an integral part of all genomics and proteomics approaches. High performance computing, intelligent software programmes (e.g. the BioScout in licensed from Lion Biosciences) and highly skilled personnel are mandatory for properly conducting *in silico* analyses.

Altogether, these initiatives have already resulted in interesting target candidates and patent applications for Boehringer Ingelheim.

Besides the use of genomics/proteomics in early stages of drug discovery, there is growing interest in employing these technologies in the drug development disciplines too, which has given rise to the field of pharmacogenetics/pharmacogenomics. In toxicology, the genetic basis of organ-specificity of certain drugs is addressed. In pharmacokinetics, genes involved in drug metabolism are investigated. And in clinical development, genotyping data may allow early identification of those patients who respond best to a drug or patients at highest risk for toxic side effects.

In order to ensure effective communication on a strategic basis between Boehringer Ingelheim's individual research sites in the area of genomics and proteomics, the Genomics Strategy Team was established in 1997, comprising members from Boehringer Ingelheim's R&D in Germany, the USA, Canada, Austria and Headquarters. This team has formulated Boehringer Ingelheim's strategy in the field of genomics/proteomics. As a consequence it has the task of identifying and evaluating key technologies of company-wide interest and of initiating the integration of such technologies within Boehringer Ingelheim research.

In addition, it is the task of the Genomics Strategy Team to continuously evaluate changes in the environment and discuss the implications for Boehringer Ingelheim, to adapt our strategy accordingly.

"It is still wholly unjustified to harbour hopes of a world free from sickness and death."

Genome research – The challenging road ahead

Dr Andreas Barner, Member of the Board of Managing Directors of Boehringer Ingelheim and member of the Steering Committee for Germany's National Genome Research Network discusses with Kerstin Felix, Corporate Division Communications the pros and cons of genome research, embryonic testing and the ethical limits of science at Boehringer Ingelheim.

The DNA sequence of the human genome has been almost fully decoded. Does this pave the way for a world free from sickness and death with so-called designer children?

Dr Barner: Our knowledge of the genome is currently only a little more than knowledge of an alphabet. But, unfortunately, we are still largely unable to read this alphabet. For that reason it is still wholly unjustified to harbour hopes of a world free from sickness and, of course, death.
The question of creating designer children actually has little to do with understanding the human genome. Rather, it has more to do with our approving pre-implantation diagnostics while condoning that embryos are selected at this stage according to particular features. And if one embraces quite extreme visions that instil a certain fear, it is conceivable that attempts might be made to modify the genes in a move to create the "ideal" child.

However, this last point is technically so complicated that I do not assume it is an issue we shall be facing in the near future. However, these are all basically questions which society in general and the company will in certain aspects in particular have to examine and find answers to.

As a result of the current criticism of research in genetic technology, the scientific achievements in this field are not readily apparent. Where do you see the opportunities for genomic research and biotechnology?

Dr Barner: These questions have to be separated into areas which have already brought enormous benefit for many years, for instance the biotechnical production of proteins or antibodies. It is now undisputed that genetically engineered protein production does offer an alternative to extracting proteins from donor plasma or donor blood, for example, in view of the enormous risk of infection with serious diseases, such as hepatitis B or C or HIV.

The second area of biotechnology is research into the human genome. The opportunities emerging include our being able to identify considerably more goals in research that can then be pursued. That is, we improve our understanding of sickness and health, of metabolic processes and pathophysiological processes; and this opens up considerably more opportunities in research. At present we are still in a phase in which the questions we have to ask continue to outweigh the answers we have. And if you look at everything published following research using the methods of molecular biology, it is immediately clear that molecular biology and genetic engineering have made, and will continue to make, major contributions to scientific progress.

"One has to distinguish between adult stem cells on the one hand and embryonic stem cells on the other."

Another issue that is currently the subject of heated public debate is stem cell research, which apparently promises to revolutionize therapy. What is the potential here?

Dr Barner: One has to distinguish between adult stem cells on the one hand and embryonic stem cells on the other. Great hopes are harboured here. Embryonic stem cells are taken from very early animal or human embryos and can express a large number of tissues, while adult stem cells in many adult tissues from mature animals or humans can be extracted by taking tissue samples and cultivating these later in cell cultures in the lab. However, no one yet knows if they are as versatile and as effective as embryonic stem cells. From the research results to date only certain cell types appear to be expressed. More recently, however, a remarkable potential of adult stem cells has been identified. For this reason, the aim of a new and extremely interesting area of research, the so-called trans-differentiation of adult stem cells, investigates whether, under certain circumstances, adult stem cells can express different tissues to those assumed to date. This is, as many hope, an alternative to the use of embryonic stem cells and therapeutic cloning, which are the subject of ethical concern.

What are the special benefits of therapeutic cloning?

Dr Barner: Therapeutic cloning is the idea of incorporating the genetic material from an adult animal, or conceivably from a human adult, into an egg cell, obtained in advance, and modifying it to correspond to that of an embryo. The problem here is that it involves the production of identical animal or human tissue which for many reasons, not least of all ethical reasons, raises a number of questions. The incentive, or attraction, is naturally being able to produce tissue with the same genetic material, in theory at least. This may also thus avoid rejection, as the transplant tissue has been produced largely from the patient's own genetic material. Allow me to point out again that here too I believe, at least going by recently published results, that adult stem cells may offer the more viable solution.

In your opinion, how great is the therapeutic potential of stem cell research, that is which diseases could be eradicated once and for all?

Dr Barner: One can only speculate when answering this question. Stem cell research in cells extracted from adult human tissue, or research in embryonic stem cells, is probably more useful to furthering our understanding of cell differentiation. We could learn much from basic research as to how embryonic stem cells can be modified or influenced such as to produce the desired tissue, which would then be used to replace tissue in the body, for instance heart muscle cells following infarction, islet cells in diabetes, nerve tissue in the presence of Parkinson's disease or even nerve lesions. Stem cell research also plays a key role in answering questions in oncology. Yet, the ultimate therapeutic potential still remains unclear. We must first produce evidence that stem cell research can bring revolutionary success in therapy, ultimately eradicating certain diseases from the face of the earth. Perhaps one day we will actually be able to say that stem cells have brought about a cure for diseases that are still incurable today. However, as things stand, we should today not invest too much hope in the possibilities for therapy. We are probably still years from achieving anything like that. The most likely case is that we will understand more about cell differentiation and the development and production of body tissue.

When do you think the first treatments using stem cells could be on the market?

Dr Barner: Perhaps in ten years, perhaps twenty. But I very much hope, when such time comes, that similar treatments will be possible with adult stem cells rather than with embryonic stem cells. It could be that we embark upon quite different courses because by then we will have a better grasp of the pathophysiology and the processes enabling tissue differentiation.

Will such treatments be affordable?

Dr Barner: I assume so, yes, because ultimately this involves methods which we already understand, that is to say molecular biology and related disciplines.

Genetic researchers across the world are rapidly moving the ethical and legal goalposts. Where are the limits to freedom of research, which is ultimately one of our basic rights?

Dr Barner: The spiral of perfectionism will end when we have made irreversible changes to the human germ line, as we have no way of knowing where manipulations to the germ line will lead. We must also firmly reject all unethical use of embryos.

In some countries, human embryonic stem cells are being produced exclusively for research – do you consider that justified?

Dr Barner: No. We should never create life specifically for research purposes, simply to destroy afterwards, not even if this might hold the promise of subsequent therapeutic progress. That is our clear ethical obligation. It is likely that in certain areas, for instance in oncology, greater significance will be attached to the differentiation of cells and for that reason research in human stem cells might well be required. It is conceivable in such a case that animal stem cells might offer a suitable alternative. However, as regards human embryonic stem cells, these are issues for basic research, that is the basic mechanisms of cell differentiation, which do not necessarily have to be investigated within the pharmaceutical industry. Above all, as this involves highly specific issues, "surplus" embryos from *in vitro* fertilization ought to be sufficient. In my view, there is no justification for going beyond this; consequently, I reject all consumptive stem cell research which creates embryos simply to kill them off again later. This applies, not only to oncology, but to every field of therapy.

The are other sources of stem cells such as the umbilical cord. Scientists have discovered that the cord contains valuable stem cells for tissue types such as the nerves, muscles, and bones. Do you see this as an alternative to research with human embryonic stem cells?

Dr Barner: An alternative to such research it certainly is not. But quite possibly an alternative to therapeutic options, as much research is still required to understand how this tissue could be put to use. The stem cells in the blood of the umbilical cord are probably intermediate cells somewhere between embryonic and adult stem cells. Intensive research will have to produce evidence here to indicate the full extent of the therapeutic opportunities. However, I do consider it worthwhile and acceptable to freeze blood from the umbilical cord at birth as a prophylactic measure.

How important is stem cell research for the research and development of new drugs at Boehringer Ingelheim?

Dr Barner: At Boehringer Ingelheim we apply many elements of human genome research, molecular biology and genetic engineering, but no research methods involving human embryonic stem cells. We have always opposed any manipulation of the germ

"We must firmly reject all unethical use of embryos."

line, that is gene therapy with germ line cells. As far as one can say today, human stem cells are not required for conventional pharmaceutical research. The therapeutic possibilities are investigated in animals. On the other hand, human embryonic stem cell research is more relevant to highly specific issues of basic research. For the time being, only in basic research can we accept embryonic stem cell research under clearly defined conditions for experiments in which animals cannot provide the answers. This could include research in specific areas such as oncology. However, here again we should only use stem cells from unused embryos from *in vitro* fertilization.

Boehringer Ingelheim is already conducting embryonic stem cell research in mice. Will this research with mammal embryonic stem cells pave the way for research with human embryonic stem cells?

Dr Barner: Quite the opposite. Everything that can rationally be done in animal studies should be done in animal studies. That includes, of course, stem cells from mice and other animals and the research in the resulting animals. In other words: creating transgenic animals in order to develop disease models undoubtedly makes sense. Creating transgenic humans would be unacceptable.

Embryonic stem cell research is still the subject of much debate in Germany, while some other countries have set the scene for research, for instance the United Kingdom. Does not this put Boehringer Ingelheim under massive pressure to avoid lagging behind its pharmaceutical competitors?

Dr Barner: This debate, which we accept in the interests of ethics, is a necesssity. I would consider stem cell research in human embryonic stem cells a wise move in the interests of basic research. However, this should be under strictly controlled conditions. It is also important that we do not use embryonic stem cells from embryos that have been created specifically for this purpose. Our company has a responsibility and takes it very seriously. It must certainly not be the case, that we conduct research into therapies which involves destroying human life. We will have to think of a more intelligent approach.

What are your own personal feelings when you think about the possibilities of these new methods? Fear? Hope?

Dr Barner: Primarily scientific curiosity, but also concern and hope. The question "What can we learn from this and what are the therapeutic opportunities that will emerge". Like any other technology, this can be abused, but it can also be put to worthwhile use. And I am confident that this technology too will be applied sensibly. Yet, we will undoubtedly encounter cases of misuse and have to consider how this should be handled both in Germany and at international level. The possibilities open to nations that do not maintain democratic structures are extremely worrying.

On the whole, however, I feel the most positive aspect is that new findings can be obtained and therapeutic options provided. This in turn opens up new and interesting areas of research for Boehringer Ingelheim from which drugs can ultimately be developed.

Glossary of terms

Adult stem cells
Stem cells taken from the tissue of adults by biopsy . These are pluripotent, i.e. they can develop into different cells and tissue of an organism but not into a new individual.

Cloning
Identical reproduction used in connection with e.g. cells and animals.

Differentiation
Process by which pluripotent cells, initially without specific function, develop into specific tissue, i.e. heart muscle tissue, liver tissue, etc.

Embryonic stem cells
Stem cells taken during early embryonic development. These are totipotent, i.e. they can form a complete individual with all cells, tissues and organs.

Genome research
Research into the complete genome DNA sequence, etc. of an individual person.

Germ line manipulation
Irreversible, deliberate change made to the genetic information in a germ line cell through which the altered genetic material is passed on to successive generations.

In vitro
(literally “in glass”) in a test tube, outside the living body.

***In vitro* fertilization**
Creation of embryos in a test tube, e.g. for artificial insemination.

Pluripotent cells
Cells which can develop into specific tissue and organs.

Pre-implantation diagnostics
Cells taken from embryos created *in vitro* and tested for possible genetic defects prior to artificial insemination.

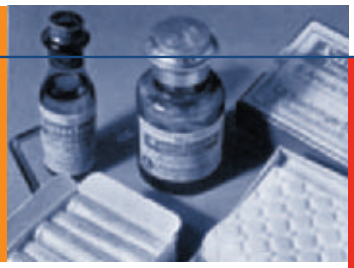
Stem cells
Cells with the potential to reproduce themselves an unlimited number of times through cell division (“immortal cells”) and able to develop into cells of different specialization (differentiation).

Therapeutic cloning
Cell core, e.g. from a patient, is injected into an empty egg (with nucleus removed) to recreate a complete egg (with nucleus) which can be developed into an early embryo *in vitro*. From this, embryonic stem cells can be obtained. Transplant tissue from these stem cells is not rejected by the patient’s immune system.

Totipotent cells
Cells which can form all tissues, organs or even a complete organism.

Transgenic animals
Animals (and their offspring) that can develop new, specific characteristics through gene transfers. Used in pharmaceutical studies as animal models, or in basic research to study the specific diseases the animals develop after the genetic transfer.

Albert Boehringer (1861–1939)



1912
LAUDANON®
launch

1948
THOMAPYRIN®
packaging

Highlights from the past

1885
Albert Boehringer founded a factory in Ingelheim/ Germany, producing cream of tartar from wine yeast with 28 employees.

1886
Tartaric acid production started.

1906
Morphine and codeine production started.

1910
Semi-synthetic manufacture of codeine started.

1915
Close research cooperation between Boehringer Ingelheim and Heinrich Otto Wieland, a relative of Helene and Albert Boehringer.

1917
First “Scientific Department” set up in Ingelheim

1927
Heinrich Wieland receives the Nobel Prize for Chemistry.

1933
Citric acid production started.

1941
The sympathomimetic drug ALDURIN®, first in a series of anti-asthmatic agents, introduced.

1942
Large-scale synthetic manufacture of caffeine started.

1946
Dr. Karl Thomae GmbH, whose products included the analgesic THOMAPYRIN®, founded in Biberach, Germany.

1971
Boehringer Ingelheim Pharmaceuticals, Inc. founded in USA.

1975
ATROVENT®, recommended standard treatment for COPD, introduced.

1978
Boehringer Ingelheim Vetmedica GmbH founded.

1983
Boehringer Ingelheim Fonds foundation set up to promote basic research in biomedicine.

1985
The Institute of Molecular Pathology (IMP) founded in Vienna/Austria as joint venture of Boehringer Ingelheim and Genentech, Inc., USA.

1986
Biopharmaceutical production started in Biberach.

1987
ACTILYSE®, the biotechnology product, licensed for the treatment of acute myocardial infarction and marketed worldwide.

1989
J. Michael Bishop together with Harold E. Vamus receives the Nobel Prize for Medicine.

2001
Nobel laureate
Tim Hunt

2002
SPIRIVA®
launch

2003
Biopharmaceutical
plant, Biberach

1990
ALVEOFACT®, a natural surfactant, launched.

1992
J. Michael Bishop starts advisor function on the IMP's Scientific Advisory Board.

1993
The IMP owned 100 per cent by Boehringer Ingelheim.

1994
Tim Hunt starts advisor function on the IMP's Scientific Advisory Board.

1995
Boehringer Ingelheim's worldwide R&D expenditure reached more than DM 1 billion for the first time.

COMBIVENT® launched in first countries.

1996
MOBIC®, the antirheumatic agent, launched.

1997
SIFROL® (pramipexole), for symptomatic treatment of idiopathic Parkinson's disease and VIRAMUNE® (nevirapine), the antiretroviral treatment for HIV-1 launched.

1998
Boehringer Ingelheim KG and Dr Karl Thomae GmbH merged under Boehringer Ingelheim Pharma KG.

1999
The Institute of Molecular Biotechnology (IMBA) founded in Vienna/ Austria by Boehringer Ingelheim and the Austrian Academy of Sciences.

MICARDIS®, for the treatment of high blood pressure, launched.

2000
New headquarters building, the Boehringer Ingelheim Center, inaugurated in Ingelheim/Germany.

2001
Tim Hunt, Paul Nurse and Leland Hartwell receive the Nobel Prize for Medicine.

Boehringer Ingelheim's first virtual research institute, the VRIA, founded in Japan with academic institutes in the pan-Pacific region.

Boehringer Ingelheim takes over responsibility for the Heinrich Wieland Prize.

Foundation stone laid for the expansion of biopharmaceutical production in Biberach/Germany – the corporation's largest single investment to date (€255 million) for further leadership in biotechnological production with mammalian cell cultures.

SPIRIVA® (tiotropium), the first once-daily bronchodilator for the treatment of COPD, registered. Global co-promotion agreement reached with Pfizer.

2002
Inauguration of the active ingredient plant in Ingelheim/Germany (€180 million investment).

Boehringer Ingelheim FENS Research Award is awarded for the first time.

SPIRIVA® launched in initial countries.

Boehringer Ingelheim and Lilly signed a long-term agreement to jointly commercialize duloxetine for the treatment of stress urinary incontinence worldwide (excluding Japan).

e-R&D - Mastering the data flood

Terms like "e-R&D" or "in silico" (analogous with in vitro or in vivo) have been around for a while. There is, however, no clear definition of these terms, which basically mean, that information technology is applied in more and more areas of research and development. Dr Helmut Hofer, Dr Manfred Reiffen and Dr Jim Stevenson explain.

The internet and intranet today play an increasing role in sharing information among researchers. Processes are changing from manual to automated, as in the case of the preparation, compilation and submission of a dossier for registration, which is now done electronically with Documentum. The submission of SPIRIVA® in the USA was the first example of this new document management system being applied. Another example is the preparation of clinical trial supplies, that will in future be supported by new software, which among other functions handles incoming materials, manages the manufacturing process, creates clinical labels, and administers the shipping of patient kits.

The exponentially increasing amount of data coming from different R&D disciplines requires a paradigm shift from pure data collection towards data integration, analysis and interpretation. Researchers will want to explore the multi-parametric space with visual tools (i.e. Spotfire), rather than with tables and numbers. An additional challenge is to extract useful knowledge from this mass of information by data mining. Here, large amounts of information are distilled using clustering and classification, so that one can deal with a manageable number of classes and then "drill down", and examine a particular class in detail.

For example, we may have hundreds of thousands of data points from an ultra-high throughput screening (uHTS) campaign that will be narrowed down to a few thousand interesting active compounds. However, even this number can be difficult for the scientist trying to extract a potential lead from this information. By clustering compounds according to their structural classes, and classifying them according to assay results, one can get a higher level view of the data and focus on specific sets of compounds. Computers are also applied in the structural design of new active molecules and first steps are being made to undertake virtual screening without even synthesizing or testing the molecules in real experiments.

"Time to market of new products will be reduced and our competitiveness will be strengthened."

Today, Boehringer Ingelheim increasingly uses many new information tools, such as the compound database (combining compound structural information and biological testing results), biological data systems (including bioinformatics and genomics data) and ELAB, which is an electronic laboratory notebook for chemists.

Bioinformatics is the application of computers, for instance in the analysis of genome sequence data, which are stored in ever growing databases in a global network in order to exploit the potential for new therapeutic target discovery.

In engineering, for instance in the aircraft industry, software is successfully applied to make simulations of what happens in reality. This can save considerable cost and development time compared to real experiments. In research and development in the pharmaceutical industry the possibility for simulations has recently become more realistic. Computers have been applied to simulate effects of therapeutic interventions in man or to predict *in vivo* experiments based on *in vitro* data. *In silico* prediction in drug metabolism and toxicology promises to identify potentially ineffective or harmful drugs even before animal studies or clinical trials begin. Models of biological systems, like the "e-cell", tissues or organs are becoming commercially available.

The Boehringer Ingelheim R&D community is to start a new initiative in order to further evaluate the potential of *in silico* approaches and to identify areas where pilot projects appear to yield promising results.

Applying advanced methods of information technology to the R&D process at Boehringer Ingelheim is likely to shorten development times by improved communication, an increased level of automation, efficient integration and analysis of large quantities of data from multiple sources and reducing a number of expensive and time consuming experiments by predictive computer simulations. Thus, time to market of new products will be reduced and our competitiveness will be strengthened.

"The databases will replace traditional paper records in a way that meets all regulatory, legal and patent requirements."

R&D - The IT Strategy Project

The computer systems under implementation in this important project provide support for the complete R&D cycle beginning with the identification of biological targets and compounds active against these targets and optimization of the chemical and biological properties of these active compounds, as Tom Blahovici and Dr Mireille Cartier explain.

The project, has over 70 scientists and IT professionals worldwide involved in gathering requirements and developing and implementing the necessary solutions. It consists of three sub-projects, each dealing with a different set of systems optimized for various phases of research.

Biology Database System

Recent technological advances in the fields of genomics and proteomics are revolutionizing the way scientists look at biological processes, giving them the opportunity to simultaneously survey the expression of thousands of genes or proteins in a living system. Such a "large-scale biology" approach generates increasingly large quantities of data, giving rise to an urgent need for data storage, management, and mining tools.

The Biology Database System (BDS) project was established in 2000 to facilitate the storage and subsequent analysis of biological data by all Boehringer Ingelheim scientists. In collaboration with the Genomics Strategy Team members, the BDS project team is implementing a platform of databases and software tools that are required for biologists and bioinformaticians to analyze large data sets and obtain appropriate information from the public domain.

Up to now the priority of the BDS project team has been to evaluate and implement the appropriate software and database (HybDB) for storage and analysis of gene expression profiling data that is being generated in Boehringer Ingelheim research laboratories worldwide. In addition, the BDS project team has been striving to integrate numerous bioinformatics platforms and allow biologists to access biological information generated in house or available in the public domain seamlessly, with just a few "mouse clicks".

The BDS promises to provide important and necessary tools for all processes of drug discovery from target identification to drug development.

Compound database

This database system links chemical structures and test results during lead identification and optimization and plays a key role in determining structure activity relationships of compounds. It provides storage and worldwide replication of data generated from many sources such as ultra high throughput screening, secondary biological testing and physicochemical analysis. This new database system also provides for the documentation of general laboratory methods as well as a registration interface to allow the connection of external laboratory systems and instrumentation.

The roll-out of the first version of the Compound Database was successfully completed in 2001.

Electronic notebooks

This sub-project is involved in providing systems for the storage and searching of laboratory generated physical, chemical, biological and developmental data. The databases created will replace traditional paper records in a way that meets all regulatory, legal and patent requirements. As a result of the efforts to date in this sub-project, electronic notebooks have been installed in medicinal chemistry laboratories in all of the Boehringer Ingelheim research centers thus providing access to the synthetic methodology of each of our research compounds.

"HandiHaler® and respimat® meet the challenge of future drug development."

Activities in drug delivery

Drug delivery is defined as a physical technology to deliver the drug into the body to improve efficacy, safety, patient compliance and convenience. Considerable advances have taken place in the pharmaceutical industry in drug delivery during the past 20–30 years. Most remarkable are the development of inhalation devices and sustained release systems, writes Dr Jürgen Nagel, Head of Drug Delivery.

Our aim in drug delivery is to face these growing challenges and to focus on development of innovative devices for inhalation. The inhalative route is gaining importance for a variety of indications, as in some cases it is possible to reduce side-effects.

Development of complex drug delivery systems such as inhalers requires close co-operation in interdisciplinary teams of engineers, pharmacists, chemists and physicists. Our Drug Delivery Department meets these needs by assembling expertise in the different disciplines involved.

The main focus at present is on three technological platforms: dry powder inhalers (HandiHaler®), soft mist inhalers (respimat®) and the conventional metered dose inhaler (MDI). The HandiHaler® is a robust breath-actuated dry powder inhaler which is easy to use. It was developed for application of the inhalets – capsules containing a premetered dose of drug with lactose as carrier. Inhalation through the device releases the drug substance and disperses it in the airstream.

The first product to be launched with HandiHaler® will be spiriva® which is predicted to represent a major advance in the respiratory therapy.

respimat® is a hand-held propellant-free nebulizer for inhalation of drug solutions which is compact and easy to use. The main principle is to force the drug solution with high pressure through a nozzle with two channels. The jets of the liquid strike each other at high velocity generating a soft mist.

When compared with conventional metered dose inhalers, respimat® leads to an improved lung deposition of the drug which could result in lower doses and therefore reduced adverse effects.

HandiHaler® and respimat® offer Boehringer Ingelheim a very competitive platform in inhalation therapy and meet the challenge of future drug development.

Boehringer Ingelheim's strategy is to fully integrate Operations into the development process.

Managing the interface between R&D and Operations

Boehringer Ingelheim's goal is to complete product development within seven years, ensuring R&D's internal customers products of the highest quality for minimum cost with maximized supply security, according to Dr Joachim Wenzel, Head of the SPIRIVA® *Launch Department.*

Managing the interface between R&D and Operations is a specific challenge during development: the main burden lies with the development team (the core team) and various subteams. Minimizing "time to market" is the target, but a production process should provide the balance between "minimum cost, necessary quality and sufficient supply security".

Operations normally had to live with manufacturing processes for the life of products, as reformulation is expensive, and a change in registration often hard.

Today, Boehringer Ingelheim's strategy is to fully integrate Operations into the development process. The interface between Operations and R&D is not a "one-off" handover, where R&D simply halts its activities, with Operations taking over from one day to the next. Today, the interface is a smooth transition, where production increasingly takes over responsibility.

In the early phases of development Operations' input is also extremely important, as here decisions are made that determine product costs. If the final formulation has been fixed, every additional test of alternate exipients or material for packaging has a direct impact on the development timeline. The seven-year target will not be met, if Operations later wants to use a less costly or more easily available compound. A major task for Operations representatives in development teams is to make sure that all cost avoidance measures are built into a product.

The R&D subteam, which includes Operations, must also make sure, that the appropriate quality can be produced, when scaled up. Process robustness needs to be evaluated at this phase: what impact does varying compressing speed have on the tablet, can the shipping carton for the capsules be exposed to sunlight, or how long can an intermediate be stored.

Basic decisions on supply security are also made in a very early state of development, when the final formulation is being developed. A most important question is the long-term availability of components used for product development, packaging, or device development. In this development phase, Operations must ensure that long-term supply security is built into the product.

After the Production Reallocation Projects, the research sites lost their production capabilities on site. Managing the interface between R&D and Production is therefore also a question of managing communication and cultural differences. Personal contact, and even more so, common manufacture of batches and analysis are essential for transfer processes.

In future, due to the higher complexity of new chemical substances, more non-standard technologies will potentially be required to bring compounds to market, requiring even closer interaction between R&D and Operations. Moreover, after seven years of development a product has not necessarily achieved 100 per cent maturity for ordinary production. Both aspects are much easier to take care of, if product launches are always made from the same plant. A launch site concept could further optimize the interface between R&D and Operations by easing communication, resulting in the closest cooperation to overcome technical hurdles.

The production paradigm

There is a fine balance which Operations must seek to establish in the production process from the earliest stage of product development.

"Nothing benefits society more than when capable young people can develop their performance skills freely. Accordingly, the B.I.F. deserves not only thanks from the many hundreds of Ph.D. students it has supported, but from all of us."

[Prof. Hubert Markl, former President of the Max Planck Society]

Dr Hermann Fröhlich, Managing Director B.I.F.

B.I.F. - Building trust in the scientific community

The Boehringer Ingelheim Fonds (B.I.F.), founded by C. H. Boehringer Sohn and Boehringer Ingelheim International in 1983, conducts its business from the Schlossmühle in Heidesheim, Germany. The purpose of the B.I.F. is the exclusive and direct promotion of basic research in biomedicine. The B.I.F. is a public foundation subject to German civil law – an independent, non-profit-making organization. Dr Hermann Fröhlich, Managing Director of the B.I.F. explains.

What were the objectives underlying the foundation of the B.I.F.?

HF: By virtue of B.I.F.'s orientation towards basic research, the donors made it clear from the very beginning that they were not interested in pursuing short-term, self-centred goals. Their intention is to emphazise that, as a research-driven pharmaceutical enterprise, they recognize an important partner in academic institutions from whom they can seek advice, in whose well-being they take an active interest and from whose scientific progress mankind might profit one day. This commitment discriminates between donors and sponsors.

How exactly does B.I.F. promote basic research?

HF: With an annual budget of € 3.6 million the foundation cannot possibly cover the whole range of expensive requirements of basic research in biomedicine. We therefore concentrate on three programmes. At the heart of the B.I.F. are the long-term scholarships for Ph.D. students. Over 100 scholars are supported at any one time. We surely cannot allocate the funds entrusted to us more sensibly than in supporting young, upcoming scientists during this decisive time in their careers. Secondly, we provide travel allowances for Ph.D. students and post-doctoral scientists who wish to learn new techniques in laboratories or scientific courses further afield. Finally, we organize the International Titisee Conferences (ITC) for established scientists twice a year. And we are proud that the list of scientific organizers of the ITC reads like a "Who's Who" of science.

What has gained B.I.F. such a high reputation in the scientific community?

HF: The high standards of the Board of Trustees, the reputation of the trustees themselves and their stringent selection criteria. The board consists of seven internationally renowned scientists and a representative of the Deutsche Forschungsgemeinschaft (Germany's central public funding organization for academic research) as a permanent guest. They work in an honorary capacity and decide upon all matters of fundamental importance.

"The B.I.F. scholarship contributed in many ways to my professional development. Most importantly, it gave me confidence always to strive for the best in research and to embark repeatedly on entirely new research endeavours."

[Dr Detlef Weigel, Director at the Max Planck Institute of Developmental Biology, Tübingen – former B.I.F. scholarship holder]

Furthermore, the board constitutes an impartial body of experts, who meet three times annually to scrutinize the applications and select the scholarship holders and chairmen of the ITCs.

What distinguishes the B.I.F. from other public and private institutions involved in the promotion of research?

HF: The B.I.F. supports people, not projects. More importantly, we have always made a point of providing our scholarship holders with more than just the monthly cheque, supporting them in word and deed whenever problems arise. Our experience tells us that the best young researchers, in particular, will accept financial support from non-academic institutions only if the following two criteria are met: scientific freedom is guaranteed and personal care is offered. The latter generally results in a relationship of mutual trust between the fellows and the foundation. I think the figures speak for themselves: almost all of our 726 fellows are in contact with the foundation and an impressive network has developed between the scholars themselves.

Whom do you support with the scholarships?

HF: The B.I.F. focuses on biologists and biochemists, in particular on those practising methods derived from molecular biology, reflecting the worldwide trend which has changed the face of basic research in biomedicine over the past three decades. Since 1990, B.I.F. has assumed an international dimension. At present, half of our scholarship holders conduct their research outside Germany – a quarter in the rest of Western Europe and in North America respectively. Every fourth scholarship holder is of non-German nationality.

How are the scholars selected? How do you separate the wheat from the chaff?

HF: Independent scientific experts evaluate every application – notably without receiving financial benefit. In addition, if at all possible, members of the secretariat visit the applicants and submit a record. Two members of the Board of Trustees examine the application and present it to the whole board, whereupon a final decision is made. The decisive criteria are: the applicant demonstrated talent and creativity, inquisitiveness and determination, motivation and perseverance during his/her training; the proposed project is imaginative and promising; the methods are sophisticated, the work schedule is realistic; the laboratory in which the project is to be pursued has an international reputation and is equipped to the highest standard.

www.bifonds.de

Prof. Ernst-Ludwig Winnacker

Dr Martin Teitel

"The modification of the human germline, either on purpose or inadvertently, is a social problem of historic proportions."

[Prof. Ernst-Ludwig Winnacker]

Ethics in biotechnology

Biotech research is at the centre of Boehringer Ingelheim's R&D programme for the 21st Century. Amid widespread unease over ethical and safety issues, we contrast the views of an eminent researcher and a prominent activist.

Prof. Ernst-Ludwig Winnacker, one of Germany's foremost gene researchers, President of the Bonn-headquartered Deutsche Forschungsgemeinschaft (DFG), Germany's central public funding organization for academic research.

Dr Martin Teitel is President of the Council for Genetic Research, a non-profit/non-governmental organization based in Cambridge, Massachusetts, USA, devoted to fostering public debate about the social, ethical, and environmental implications of the new genetic technologies.

Where do you see the main questions of morality in medicine and scientific research based on biotechnologies and genomics?

E-L W: The main questions were ever that the distance between the human being as a scientist and the human being as an object of research has become too close. As an example, I would say genomic diagnostics, genome analysis, which creates difficulties, say, when we diagnose diseases we cannot treat. Huntington chorea is a disease which leads inevitably to death at the age of around 50. It can now be diagnosed. It is a difficult decision how to communicate this to an affected patient. In such cases, we have to have the right not to know. Another example connected with gene analysis is the interest of third parties involved in the knowledge of hereditary disease, for example life insurance or health insurance companies. Again here we have to honour privacy and the close relationship between the patient and his or her doctor.

MT: As with other powerful, transformative technologies, we are challenged to adjust basic concepts of ethics and policy. Biotech-based medicine raises some very basic questions, such as what a person is – "could your clone get a passport?", can life and the substance of life be owned products, and what constitutes a fair return on the investment in basic R&D. There are many other questions arising from biotechnology, such as issues of genetic privacy and genetic discrimination, near-monopoly control over portions of humanity's food supply, and who is competent to make decisions about public health and safety – as well as environmental safety – in an era of new scientific development.

"Prudence is good public policy, good science, and good business."

[Dr Martin Teitel]

Do you see any areas of current or proposed research in which the moral barriers are in danger of being breached?

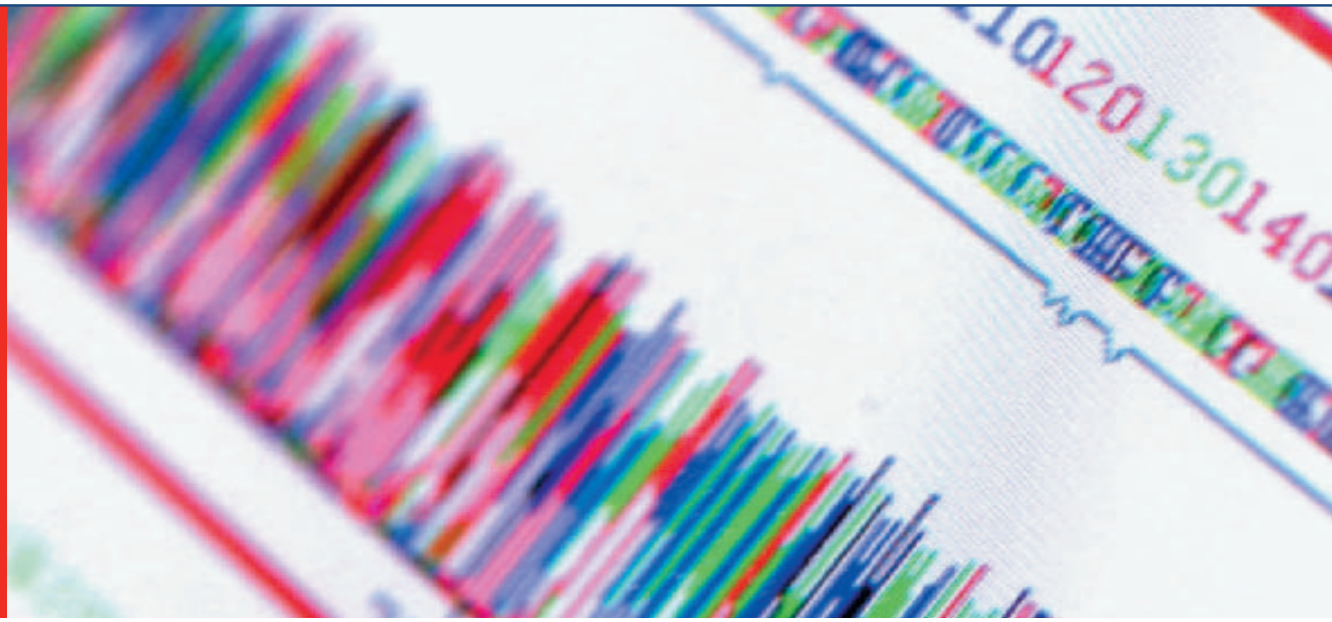
E-L W: The two major areas I see at the moment are for example reproductive cloning, that is the cloning of human beings. I have not heard any good reason why it should be done and there are many good reasons against it. Another example is therapeutic cloning – here we have the same issues where the donation of egg cells from female patients could be regarded as a human rights violation. But there are others, for example, modification of the human germline which should be studied very carefully, if used in therapeutic approaches.

MT: There are a number of areas that are at or even over the ethical line. In the USA, people are compelled to purchase genetically engineered ingredients in about two-thirds of their food, which they cannot avoid since these ingredients are unlabelled. Clearly embryo splitting, nuclear cell transfer and other techniques associated with cloning disturb many citzens. And the cost of patents on thousands of molecules and DNA fragments, when added to the price of new medicines, raises troubling issues in spiralling health care costs. Finally, the modification of the human germline, either on purpose or inadvertently, is a social problem of historic proportions.

Is this just a question of morality – or are there real safety issues here that need to be addressed?

E-L W: It is peculiar that you say "just" morality, because academic freedom or freedom of research can never be separated from the responsibilities in performing science and in recognizing moral boundaries of science. An example of where real physical safety issues are involved is therapeutic cloning. Here the experiment is nucleus transplantation into egg cells the nuclei of which have been removed. These experiments have been shown in the model of the sheep Dolly to be extremely dangerous. Only one in 277 sheep was born. Many pregnancies were aborted and I consider it impossible to do such experiments in a human context. I even think that in the case of therapeutic cloning, where we are not only dealing with human beings but with cell types or organs, that even there the stochastic nature of the process is unacceptable for application with human patients.

MT: Well, as a philosopher I am not sure I can subscribe to the characterization of "just" morality, since morality is an essential human consideration; also, real safety issues are inseparable from moral and ethical issues. In any event yes, there are huge safety issues. In our organization, we are not occupied as much with opposing



biotechnology as we are in asking that the process of developing this technology be accomplished in a careful and responsible manner. We want to see scientists and government regulators leading the way, not investment bankers and attorneys.

Where should we strike the balance between prudence and progress in medical research?

E-L W: Well, it is always wise to be prudent in everything you do. But I think that only those who recognize the limits in science can make progress. A good example that comes to mind is gene therapy. Gene therapy experiments started more than a decade ago and promises were being made which could never be fulfilled because at the time the complexities of the human genome were not understood. And they are not understood even now. And therefore progress will be slow. There will be diseases that will be amenable to treatment with gene therapy and there are hundreds of gene therapy protocols now in clinical trials. Some of them will work. I am quite optimistic about this. But it will take time and shows the intricacies of the networks and interactions between proteins in living cells which are not yet understood.

MT: This is an easy question. We should always put prudence first. Today's idea of progress can look like a blind alley next week, but we will never regret having been careful. Prudence is good public policy, good science, and good business.

The Boehringer Ingelheim world of R&D

For a global player in the pharmaceutical industry it is no longer sufficient to develop drugs that simply match products already on the market. As a research-driven group of companies, Boehringer Ingelheim is committed to discovering and developing substances which represent substantial therapeutic progress.

Front-line research and development projects are the means by which we achieve our therapeutic goals. Demonstrating its commitment to innovation, in 2002 Boehringer Ingelheim invested over EUR 1.3 billion in R&D, corresponding to about 17 per cent of the Corporation's net sales. In Prescription Medicines, the R&D percentage amounted to about 22 per cent.

We maintain five R&D centers worldwide, employing some 3,000 scientists, technicians and support services in all. This number is complemented by 1,800 clinical monitors, statisticians and data managers working in clinical development.

Our two human pharmacological centers investigate new chemical entities for safety, tolerability and initial pharmacodynamic properties.

www.boehringer-ingelheim.com

Boehringer Ingelheim's R&D Centers

R&D Centers

1 **Biberach (Germany)**
- Research in central nervous system, metabolic, respiratory diseases
- Special drug delivery devices
- Non-clinical development

2 **Ridgefield/Connecticut (USA)**
- Research in cardiovascular, immunological, inflammatory diseases
- Non-clinical development

3 **Laval/Quebec (Canada)**
- Research in virology

4 **Vienna (Austria)**
- Research in oncology
- Research Institute of Molecular Pathology

5 **Kawanishi (Japan)**
- Research in molecular biology
- Non-clinical development
- Virtual Research Institute of Aging

Support Centers

6 **Milan (Italy)**
- Chemical synthesis

7 **Buenos Aires (Argentina)**
- Non-clinical development

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