Boehringer Ingelheim Research and Development Primed and Ready for the Future

Company announces a research strategy for the 21st Century

Boehringer Ingelheim is currently enjoying a period of unprecedented success with, on average, one major product approval every eight weeks¹. Against this backdrop, Dr. Andreas Barner, Chairman of the Board of Managing Directors, announced a new research strategy that would take Boehringer Ingelheim into the future. With a pipeline that is already filled with around 100 projects, this new strategy seeks to amplify this strong base by building on the expertise of the research organisation in its core research therapeutic areas while also exploring the emerging science and technology of the future.

“Although our company has a heritage of 130 years, our primary goal has been, and always will be, the search for new therapeutic options to improve the lives of the patients we serve both now and in the future. Our new research strategy is geared towards indications and fields with a significant medical need where we seek to ensure that, in the long term, we will be able to develop even more innovative products.”

Dr. Andreas Barner, Chairman of the Board of Managing Directors

The new research strategy is characterised by three elements:

- Four discovery research therapeutic areas: Immunology and Respiratory diseases, CardioMetabolic diseases, CNS diseases and Oncology
- Scientific Platforms: Exploring scientific concepts and mechanisms, with potential in multiple disease areas such as immune modulation, with the aim of creating synergies and building bridges across the research therapeutic areas
- Research Beyond Borders: Harnessing emerging science and technology both within and beyond our research therapeutic areas

Research Beyond Borders and Scientific Platforms are particularly exciting elements of the strategy as Boehringer Ingelheim seeks to be at the forefront of the next wave of scientific and medical innovation. In a rapidly changing scientific landscape, mining knowledge and insights from external colleagues will provide the fuel to drive this engine.

“New research trends and innovative technologies demand a progressive and dynamic research strategy so we can build on our recent series of successes in clinical development. To discover the breakthrough medicines that patients need requires us to bring together the talents and capabilities of our scientists with innovation partners across the world. Both now and in the future, our partners are integral to helping us in this mission.”

Dr. Clive Wood, Corporate Head of Research

Increased Investment in Prescriptions Medicines R&D

In keeping with the Company strategy to drive growth and make a major contribution to healthcare in areas where the need for treatment is high, Boehringer Ingelheim continued its above industry-average commitment to R&D in 2014, namely, investing 23% of prescription medicine net sales in this area. With more than 50% of its early-mid stage pipeline filled with products that are derived from collaborations with external partners, partnering continues to be an essential part of the organisation's R&D strategy.

Reference: 1. Approved by the US Food and Drug Administration and/or the European Medicines Agency, September 2013 – May 2015
Boehringer Ingelheim has established a research alliance with Vanderbilt University to develop new Ras inhibitors for the treatment of cancer. The partnership, announced earlier in 2015, brings together the novel techniques used by Professor Stephen Fesik, PhD – a pioneer in the discovery of small molecules that bind to and inhibit challenging drug target proteins – with the resources and expertise of Boehringer Ingelheim. It is hoped that the combined expertise of these partners will go a long way to addressing this important challenge in cancer.

Boehringer Ingelheim and Eureka Therapeutics, Inc. are working together in a research collaboration to discover novel therapeutic antibodies in oncology.

“We are excited to partner with Boehringer Ingelheim, a leader in oncology research and development, to develop next generation cancer immunotherapies targeting intracellular oncoproteins”, said Dr. Cheng Liu, President and Chief Executive Officer of Eureka Therapeutics. “This collaboration builds upon Eureka’s success in discovery and development of fully human antibodies against intracellular oncoproteins. We look forward to working with Boehringer Ingelheim to advance the immuno-oncology frontier and address some of the most challenging unmet medical needs.”

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Boehringer Ingelheim is looking to expand its access to external innovation, beyond traditional bilateral partnerships, by exploring new ways of harnessing the scientific crowd. Two examples of this where the Company is already seeing success are pre-competitive public-private partnerships, such as its relationship with the Structural Genomics Consortium (SGC) in the field of epigenetics; and secondly, through identifying novel scientific ideas via crowdsourcing by working with partners such as BioMed X and InnoCentive.

As an established member of the SGC, Boehringer Ingelheim has recently synthesised a chemical probe for an important epigenetic protein, bromodomain 9 (BRD9). This will be used by the scientific community, via the SGC, according to its open access principles, to improve the understanding of the role of this protein in cancer.

By working together with the BioMed X Innovation Centre, Boehringer Ingelheim is embarking on an exciting new collaboration model at the interface between academia and industry. An international research team of talented, early-career scientists, will work jointly on novel therapeutic approaches for the treatment of patients with chronic obstructive pulmonary disease.

Together with InnoCentive, Boehringer Ingelheim has also successfully implemented two crowdsourcing challenges in the fields of psychiatry and respiratory diseases.

“The internet and the principles of open innovation have opened up a plethora of new possibilities for accessing exciting scientific ideas in the broader scientific world. As a research-driven organisation that seeks to discover and develop medicines of the future, these new external innovation approaches are ideally suited to help us identify the “secret ingredient” that could be catalyst for the next new medicine.”

Dr. Adrian Carter, Corporate Vice President, Global Research Networking

Sourcing the Scientific Crowd: Boehringer Ingelheim at the Forefront of New Approaches to Open Innovation

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Focus on... Cardiometabolic Diseases

With many years of experience in cardiometabolic diseases, innovation from both our own and external research and development projects has resulted in important achievements for Boehringer Ingelheim and our partners, with three of the top five products for the Company today in this therapeutic area. In 2014, we were able to build on our diabetes franchise and achieve further milestones in our successful global strategic alliance with Eli Lilly and Company, with the launch of empagliflozin (Jardiance®), a sodium-glucose co-transporter-2 inhibitor for the treatment of adults with type 2 diabetes.

Our cardiometabolic diseases research was also recognised for its innovation with a breakthrough therapy designation being conferred in 2014 by the US Food and Drug Administration (FDA) for idarucizumab – a specific reversal agent to dabigatran etexilate (Pradaxa®) – which is now under accelerated review for approval by the US FDA, the EMA and Health Canada.

Equally, innovation is our priority in partnering, where we seek projects with differentiating features especially in established indications, with a preference for early-stage programmes specifically in:
- Type 2 diabetes
- Obesity
- Micro and macrovascular complications of diabetes and the metabolic syndrome such as chronic kidney disease, pathologies in the cardio-renal axis, diabetic retinopathy and diabetic nephropathy
- Liver diseases (non-alcoholic steatohepatitis (NASH), liver fibrosis, cirrhosis).

“The year 2014 was an exciting time for us in cardiometabolic diseases research. We were pleased to have the opportunity to explore new therapeutic avenues in type 2 diabetes through our partnership with Connexios Life Sciences as well as augmenting our existing partnership with Zealand Pharma, with a second collaboration, exploring novel therapeutic approaches for patients with cardiometabolic diseases. We look forward to building on this success in 2015 in our new research collaborations with Hydra Biosciences and the University of Michigan.”

Dr. Michael Mark,
Vice President, Head of Cardiometabolic Diseases Research

“The search for new therapeutic options with the potential to help patients with liver diseases is a key priority for us. We are especially pleased to have recently strengthened our pipeline in this area with the acquisition of PXS4728A from Pharmaxis as a potential treatment for NASH; and look forward to building our portfolio, with our partners, in this and other challenging cardiovascular and metabolic disease areas.”

Dr. Johannes Zanzinger,
Head Global Licensing Cardiometabolic Diseases

Our research and development centres for cardiometabolic research are located at sites in Biberach, Germany and Ridgefield, CT, USA; we are constantly expanding our network of partnerships in this field to discover new treatments that seek to address continually evolving unmet medical needs.

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**Our CardioMetabolic Diseases Partners**

**Pharmaxis**

- **Indication:** NASH
- **Development stage:** Clinical
- **Agreement and year:** Asset purchase agreement, 2015

**Hydra Biosciences**

- **Indication:** Renal disease
- **Development stage:** Discovery
- **Agreement and year:** License and research collaboration agreement, 2015

**Zealand Pharma**

- **Indication:** Cardiometabolic diseases
  - Type 2 diabetes and obesity
- **Development stage:** Pre-clinical/Clinical
- **Agreement and year:** License, research and development collaboration, 2014; License and collaboration agreement, 2011

**ETH Zürich**

- **Indication:** Diabetes
- **Development stage:** Pre-clinical
- **Agreement and year:** Research collaboration, 2012

**Technische Universität Dresden**

- **Indication:** Diabetes
- **Development stage:** Pre-clinical
- **Agreement and year:** Research collaboration, 2012

**MircrobiomeMx**

- **Indication:** Diabetes
- **Development stage:** Discovery
- **Agreement and year:** Research collaboration, 2015

**Connexios Life Sciences**

- **Indication:** Diabetes
- **Development stage:** Pre-clinical and clinical
- **Agreement and year:** License and research collaboration, 2014

**ETH Zürich**

- **Indication:** Diabetes and obesity
- **Development stage:** Discovery
- **Agreement and year:** Research collaboration, 2012

**Lilly**

- **Indication:** Metabolic Diabetes
- **Development stage:** Clinical
- **Agreement and year:** Global strategic alliance, 2011
Boehringer Ingelheim Pursues Novel Treatments and Targets with New Cardiometabolic Diseases Agreements

Acquisition of worldwide rights to potential treatment for non-alcoholic steatohepatitis from Pharmaxis deepens research portfolio

Boehringer Ingelheim has brought an innovative addition to its clinical development portfolio in cardiometabolic diseases, by exercising its option and thereby acquiring the global ownership of Pharmaxis’ investigational anti-inflammatory drug candidate PXS4728A, including the associated intellectual property rights.

PXS4728A is a semicarbazide-sensitive amine oxidase/vascular adhesion protein-1 (SSAO/VAP-1) inhibitor, discovered by Pharmaxis, that works by blocking leucocyte adhesion and tissue infiltration in inflammatory processes that have shown activity in pre-clinical investigation in non-alcoholic steatohepatitis (NASH). Pharmaxis has developed the compound through to phase 1 clinical studies and demonstrated oral bioavailability, long-lasting target inhibition and good tolerability and safety.

Type 2 diabetes and obesity can lead to NASH, which is the progressive form of non-alcoholic fatty liver disease (NAFLD), the most common liver disorder in Western industrialised nations. It is regarded as a major cause of fibrosis and cirrhosis of the liver and is considered an area of high unmet clinical need.

“We have ambitious strategic goals in diabetes and metabolism and this phase 1 asset acquisition fits well into our development portfolio. We are pleased to have achieved access to Pharmaxis’ research excellence and innovative approach to treatments for NASH and will continue to build our portfolio through both internal and external innovation to bring much needed medications to the patients we serve.”

Glyn Parkin, Corporate SVP and Metabolism Head at Boehringer Ingelheim.