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Opening the innovation process in research at Boehringer Ingelheim to discover new medicines

AUTHORS
Adrian J. Carter, PhD & Clive R. Wood, PhD

Discovery Research
Boehringer Ingelheim GmbH
Binger Strasse 173
55216 Ingelheim am Rhein
Germany

CORRESPONDENCE
Please address correspondence to
Dr. Adrian J. Carter
adrian.carter@boehringer-ingelheim.com

After a lean period in the first decade of the twenty-first century, the success of the pharmaceutical industry in registering new medicines continues to increase. For example, the United States Food and Drug Administration (FDA) approved a total of 45 new drugs in 2015, the highest number for 19 years[1]. Boehringer Ingelheim has been part of this success story with 11 launches in major markets in 2014 and 2015, including the new medicines Praxbind (idarucizumab) and Ofev (nintedanib), as well as the combinations Synjardy (empagliflozin and metformin), Glyxambi (linagliptin and emplaglifozin) and Stiolto Respimat (tiotropium bromide and olodaterol). In addition, four of our drug candidates have received FDA breakthrough therapy designation since the inception of the programme in 2012. In November 2015, Boehringer Ingelheim announced its new research and development (R&D) strategy and five-year R&D investment programme. The company pledged to invest a total of €11 billion in R&D over five years to develop the next generation of innovative medicines. Boehringer Ingelheim recognizes that open innovation has an essential part to play in the discovery of new medicines. Indeed, our success is dependent on our ability to access innovative ideas for new therapeutic approaches and disease mechanisms, and to combine these with our proven internal strengths in drug discovery and development. Consequently, Boehringer Ingelheim has redefined its research strategy to foster a greater culture of innovation in the organization and, importantly, to more effectively enhance its ability to access breakthrough science from around the world.

Boehringer Ingelheim is pleased to support this Outlook to highlight the variety of open innovation. Open innovation is a term that can be interpreted in many different ways, but all relate to opening the innovation process to access external ideas according to the original suggestion of Henry Chesbrough[2]. We have chosen to define open innovation as the process of innovating with others outside of our organization to create new medicines of the future. Open source is the process of making the knowledge generated by a collaboration freely available to the wider scientific community, not just to the partners in the collaboration, and it takes as its basis the open-source model from the software industry. On the basis of our definition, we have categorized our early-stage, open-innovation approaches into three main areas: (i) bilateral collaborations; (ii) public-private partnerships (PPP); and (iii) crowdsourcing. Bilateral partnerships with leading academic institutions have been the cornerstone of some of our most successful scientific relationships. The reason for these collaborations has, more often than not, been the scientific expertise, background patent rights or recent scientific discoveries of an academic group. Firstly, we should like to introduce our Discovery Research Strategy and highlight some of the many exciting bilateral early-stage collaboration agreements we have entered into to support the implementation. We shall then describe our involvement in PPPs and crowdsourcing initiatives.

Discovery Research Strategy

Boehringer Ingelheim's Discovery Research Strategy is based on three guiding principles: (i) building on our strengths; (ii) creating synergies; and (iii) capturing emerging science (Figure 1). We are building on our strengths by focusing on four core research therapeutic areas, for which we have developed significant expertise over time, and continue to rely upon efficient cross-functional project work at our research sites. The main research therapeutic areas in our new discovery research

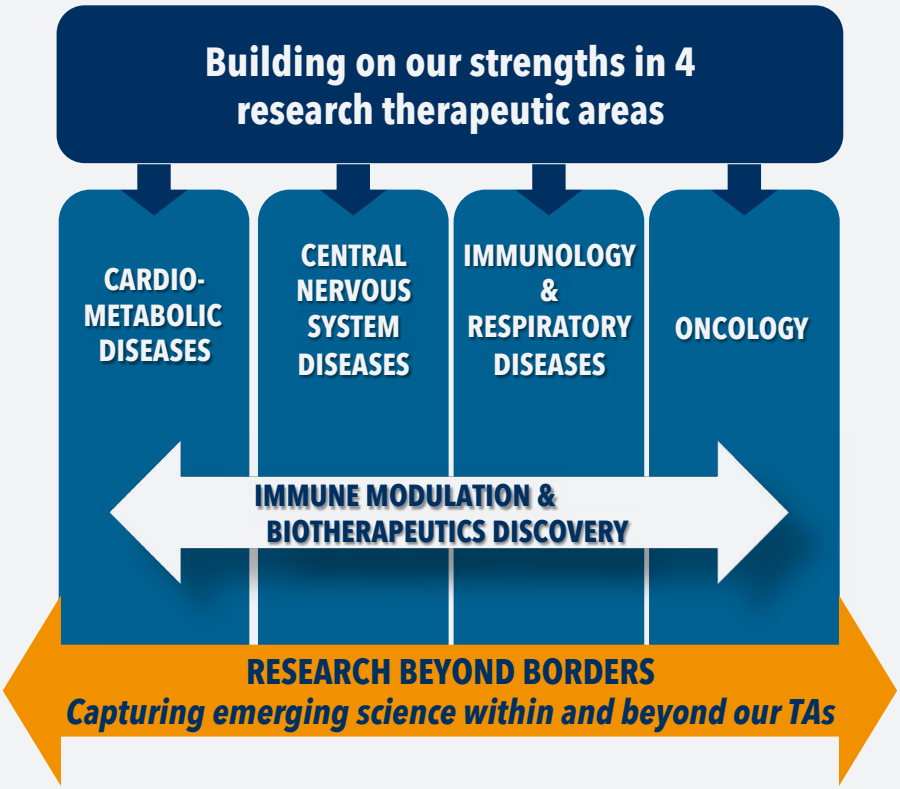

Figure 1 | **Boehringer Ingelheim's Discovery Research Strategy.** Boehringer Ingelheim's new discovery research strategy is based on three guiding principles: (i) building on our strengths in four core research therapeutic areas; (ii) creating synergies with a scientific platform for immune modulation in which we want to identify new mechanisms with potential therapeutic applications across different indications such as inflammatory diseases and oncology; and (iii) capturing emerging science with Research Beyond Borders from the next wave of scientific and medical innovation for the benefit of patients.

organization are: (i) Central Nervous System Diseases Research; (ii) CardioMetabolic Diseases Research; (iii) Immunology and Respiratory Diseases Research; and (iv) Oncology Research. Despite the fact that we defined four separate research therapeutic areas, we believe that it is imperative to create synergies and build bridges in different areas, especially where they have common disease mechanisms. We decided to create a global CardioMetabolic Diseases Research function from two previously separate departments (the Cardiovascular and the Metabolic Diseases research departments) because of the fundamental importance of cardiovascular complications in disease outcome for metabolic diseases. In addition, we also created a single global research therapeutic area of Immunology and Respiratory Diseases Research from two separate departments (Immunology/ Inflammation Research and Respiratory Diseases Research) because of the importance of understanding immunological mechanisms to find new treatments in these disease areas. Here, we profile our research therapeutic areas in turn to highlight our areas of interest and illustrate the different specific approaches taken with respect to open innovation.

Research therapeutic areas

The Central Nervous System Diseases Research therapeutic area, located in Biberach, Germany, focuses on psychiatric diseases and aims to discover distinct treatments that address specific symptoms of different patients. Following an approach that accords well with the National Institutes of Mental Health Research Domain Criteria Initiative (RDoC) (https://www.nimh.nih.gov/research-priorities/rdoc) we have decided to focus on key symptom domains of a multitude of mental illnesses, such as cognitive impairment, impulsivity or anhedonia as manifestations of maladaptive brain circuits. Consequently, we systematically investigate these brain circuits functionally with electrophysiological, imaging and optogenetic methodology to link them to behaviour using quantifiable and translatable operant tests. Within this framework, we are investigating glutamatergic pathways in cortical areas, modulation of GABAergic interneurons, monoaminergic modulation, principles of synaptic plasticity as well as neuroinflammatory and epigenetic mechanisms as possible entry points for drug discovery. For example, we have been working with Circuit Therapeutics (Menlo Park, CA) since 2013 to use optogenetics to identify and characterize drug targets from brain circuits involved in psychiatric disorders. In addition, in January 2016 we announced an exclusive licensing deal with Arena Pharmaceuticals, Inc. (San Diego, CA) to conduct joint research to identify drug candidates targeting an undisclosed G protein-coupled receptor (GPCR), which belongs to the group of orphan receptors.

Our CardioMetabolic Diseases Research therapeutic area, based in Biberach and Ridgefield, CT, is interested in understanding the role of ß-cell regeneration, insulin resistance, adipose tissue inflammation in type 2 diabetes, how energy expenditure, fat-cell browning, feeding and reward systems contribute to obesity, mechanisms of diabetic retinopathy and diabetic macular oedema,

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non-alcoholic steatohepatitis (NASH) and the role of podocyte biology, inflammation and fibrosis in chronic kidney disease and diabetic nephropathy. The team has successfully brought three new molecular entities to the market, Trajenta (linagliptin), Jardiance (empagliflozin), and Praxbind (idarucizumab) in the past five years, and is also working on various projects in different stages of discovery and development. To further broaden our presence in the field, and on the basis of several already existing collaborations, we have entered into a series of new partnerships. In August 2015 we announced a second research collaboration agreement with Circuit Therapeutics in which we work with Circuit's proprietary optogenetics technology platform, but this time to investigate metabolic disorders with the aim of developing novel medicines to improve the treatment of obesity and associated diseases. Furthermore, we recently signed an option and asset purchase agreement with Pharmaxis (Sydney, Australia) for PXS4728A, an inhibitor of the enzyme amine oxidase, copper containing 3 (AOC-3), for NASH. In 2015 we also entered into a second worldwide research collaboration and license agreement with Hydra Biosciences, Inc. (Cambridge, MA) to identify small-molecule inhibitors of ion channels for the treatment of renal diseases. Finally, in an effort to improve the quality of life for people with diabetic nephropathy we are working together with a team of investigators at the universities of Michigan and Minnesota as well as the intramural research branch of the National Institute of Health in Phoenix to seek to identify new mechanisms and disease drivers underlying this debilitating disorder.

The Immunology and Respiratory Diseases Research therapeutic area has departments located both in Ridgefield and Biberach. Our teams are focused on the discovery and development of new therapeutic concepts that will radically alter the progression of chronic inflammatory and autoimmune diseases. Our scientific expertise includes mechanisms and targets that underpin chronic obstructive pulmonary disease (COPD), inflammatory bowel disease (IBD), pulmonary fibrosis, systemic sclerosis, systemic lupus erythematosus, asthma and spondyloarthritis. The core of our research is centered around four central themes: (i) mucosal barrier injury and repair; (ii) aberrant tissue remodelling; (iii) dysfunctional innate immune effector function; and (iv) immune checkpoint modulation. To bolster our efforts to drive innovation in key disease areas, we have recently signed several new collaboration agreements to enrich research and development of novel therapeutic approaches for patients with IBD. These include partnerships with the Icahn School of Medicine at Mount Sinai, Massachusetts General Hospital, Scripps Research Institute and Weill Cornell School of Medicine. Our goal is to work together with leading academic experts to identify and validate potential therapeutic targets and biomarkers that will result in better treatments for patients with Crohn's disease and ulcerative colitis. Furthermore, in conjunction with the BioMed X Innovation Center, located on the campus of the University of Heidelberg in Germany, we announced an innovative crowdsourcing approach to gain insight into the epigenetic regulators of COPD pathogenesis. We have now successfully established an interdisciplinary team of outstanding scientists in Heidelberg to identify therapeutic targets in this arena. Our ambition is to address epigenetic mechanisms that may underscore cellular senescence and dysfunctional repair pathways that could ultimately lead to disease modifying therapies for the treatment of this devastating disease.

Our Oncology Research, based in Vienna, Austria, has two major focus areas: (i) cancer cell-directed therapies including growth signalling, regulation of apoptosis, epigenetic regulation and regulation of protein homeostasis; and (ii) immune cell-directed therapies based on priming of tumour-specific T cells, cancer vaccines, immune cell re-activation, checkpoint control, natural killer cell activation, immune cell re-direction and T cell engager approaches. At the end of 2015, we announced a new collaboration with the University of Texas MD Anderson Cancer Center focused on developing innovative medicines for pancreatic ductal adenocarcinoma (PDAC). The new collaboration combines the MD Anderson Cancer Center's exceptional understanding of potential drivers of PDAC with our experience in drug discovery and development. In 2015 we also announced that we had established a research alliance with Vanderbilt University and the cancer drug discovery laboratory of Stephen Fesik. The aim of the collaboration with Vanderbilt University is the research and development of small molecule inhibitors of oncogenic RAS for the treatment of cancer. The RAS genes are critical oncogenic drivers that are activated by point mutations in about 20% of human malignancies with KRAS being the most commonly mutated form occurring in pancreatic, colorectal and lung adenocarcinomas. KRAS has been a particularly difficult oncoprotein to target despite more than three decades of effort by academia and industry since its discovery[3]. The collaboration with Stephen Fesik further strengthens our focus on fragment-based drug discovery for seemingly intractable drug targets. In addition, we have signed an agreement with Eureka Therapeutics Inc. (Emeryville, CA) for the discovery of novel therapeutic antibodies in oncology. Eureka Therapeutics will apply its human sequence antibody libraries and its unique technology platform to identify antibodies recognizing intracellular proteins, which represent approximately 90% of cancer-specific targets. Cancer-specific peptides that can be displayed using the MHC-complex (major histocompatibility complex) on the cell surface will be selected to develop better therapies for people with cancer and for whom existing treatment options are inadequate or non-existent.

Immune Modulation and Biotherapeutics Discovery

We also established a scientific platform for immune modulation (IM) in which we wish to identify new mechanisms with potential therapeutic applications across different indications such as inflammatory diseases and oncology in alignment with our core themes of creating synergies and building bridges. The scientific platform is combined with biologics discovery functions as Immune Modulation and Biotherapeutics Discovery (IMBD). The leading areas of scientific interest relate to fundamental mechanisms by which immune responses are controlled and especially manipulating those pathways that are down modulators of immunity. We take an agnostic view in our initial assessments of potential therapeutically relevant pathways and targets, thereby preferring to move in a particular therapeutic direction as the science and biology dictates and after we better understand what direction is best. This has efficiencies of being able to look at both up and down modulation and also avoids the risk of narrowing focus too early by being biased by a particular disease type that may have rather narrow relevance. One important area relates to lymphocyte and myeloid cell regulation and boosting or blocking immune inhibitory or activating (checkpoint) receptors to achieve this. We believe that while the field is exciting and has shown substantial benefit in cancer

with its focus to boosting T cell function, there is much to discover, especially how to apply these same concepts to switching off versus switching on immune responses.

We have signed a research collaboration agreement with Yale University with the goal of researching novel therapeutic targets in the field of immune modulation for oncology, autoimmune and respiratory disorders. Harnessing IM-based mechanisms provided by regulatory T cell pathways is still in its infancy but the now-recognized contribution of this mechanism of action to the anti-cancer activities of ipilimumab, an anti-CTLA4 monoclonal antibody versus a standard checkpoint mechanism only, validates the importance. Moreover, the side effects of dysregulated inflammation experienced by many treated patients also provides valuable insights into the importance of effective regulatory T cell (Treg)-mediated immune regulation, and thus the potential therapeutic value of manipulating these cells for cancer or inflammatory diseases. A collaboration agreement with scientists at the US National Institutes of Health has also been established to discover additional pathways to modify human Treg function. Finally, in cancer, the importance of 'releasing the brakes' on the immune system is now clear, but the means through which the immune response can be primed to recognize and fully respond to tumours is much less well understood and developed, especially clinically, despite years of active work in the area. Boehringer Ingelheim is especially committed to testing and developing new drugs in this area and has set up bilateral collaborations in mRNA vaccine approaches with CureVac AG (Tübingen, Germany) as well as with Oxford BioSciences (Oxford, UK) and Eureka Therapeutics, Inc (Emeryville, CA). This will enable the discovery of novel tumour antigens to help feed a future portfolio of vaccine and T cell redirection modalities of relevance to the treatment of solid tumours.

Research Beyond Borders

The Research Beyond Borders (RBB) function in the Discovery Research organization explores emerging science and technologies for and beyond our core research therapeutic areas to create new approaches and capabilities for drug discovery and development. This allows us to capture breakthrough opportunities and prepare timely paths to entry for our therapeutic areas of today and the future. High priority areas include new target spaces and therapeutic approaches such as the gut microbiome, hearing disorders, regenerative medicine and technologies such as gene therapy. To accomplish this, RBB is integrating both internal and external insights as well as exploring new models for collaboration to bring together the talents and capabilities of our scientists most effectively with the strengths of scientists around the world. RBB is now in the process of extending its global scientific network by locating teams at strategic innovation hot spots around the world and by partnering with successful incubators such as LabCentral (Cambridge, MA). RBB builds on the success of the Boehringer Ingelheim Venture Fund (BIVF) that was established in 2010 to invest in biotech and start-up companies that provide new therapeutic approaches and technologies to help drive innovation in medical science. In addition, the BIVF, as a strategic investment fund, has the potential to work with Discovery Research to build our pipeline.

We provide here two recent examples to illustrate the approach of RBB. Firstly, we believe that the organisms in the gut microbiome have profound effects on the mucosal immune system because they are able to shape anti-inflammatory as well as pro-inflammatory aspects of mucosal function and may play important parts in diseases such as inflammatory bowel disease[4]. Through a unique multi-institute, collaborative research model, RBB will bring together the expertise and capabilities of leading experts in the microbiome field to study intestinal barrier disruption and enhanced permeability through an iterative process of presentation of bacterial stimuli from a pathogenic microbiome, activation of host immunity, and exacerbation of chronic tissue damage. The programme benefits from having postdoctoral research fellows from these expert laboratories working together with scientists from Boehringer Ingelheim at our research site in Ridgefield. Although the initial emphasis will be on IBD, we anticipate extending this to other areas such as oncology and psychiatry by engaging additional leading experts. Secondly, hearing loss is the most common form of sensory impairment in human beings[5]. We are convinced that understanding the molecular pathways that regulate the development and function of the auditory system will help us to provide new starting points for drug discovery projects. RBB has recently launched a project with experts in regenerative medicine from Kyoto University (Japan) to explore this further.

Public-private partnerships

We have also seen an increase in pre-competitive PPP in which several pharmaceutical companies, including ourselves, work with one or more public institutions in defined areas and share all results with a wider audience. We have been active partners in 27 different projects as part of the first phase of the Innovative Medicines Initiative (IMI), Europe's largest PPP initiative that aims to speed up the development of better and safer medicines, covering a breadth of topics, including discovery of biomarkers across a number of indications, initiatives aimed at improving drug safety, and engagement of patients in the drug discovery process. Our overall committed in-kind and cash contribution to these projects exceeds €33 million. As is evidenced by our participation in the second phase of IMI we will continue to support such projects, especially those that we believe address important research and development topics, and which take advantage of leveraging the intrinsic advantages of such PPPs.

We have also been an active member of the Structural Genomics Consortium (SGC), a PPP that supports the discovery of medicines through open-access research, for several years and have supported the establishment of the ChemicalProbes.org site[6]. We have experienced at first hand the way that open access chemical probes can transform drug discovery with JQ1, a selective probe for BET bromodomains[7]. We have worked with our colleagues at the Institute of Molecular Pathology in Vienna to understand the role of such BET bromodomain 4 (BRD4) inhibitors in acute myeloid leukaemia[8,9]. Indeed, we are currently testing our own proprietary compound, BI 894999, in Phase I clinical studies for cancer[10]. BRD7 and BRD9 are related proteins containing a single bromodomain that form a small sub-branch of the bromodomain family tree. Both proteins have been implicated in chromatin remodelling. Boehringer Ingelheim has worked with the SGC to develop a specific inhibitor of BRD9/7 called BI-9564. This probe was discovered through fragment-based screening and optimized by structure-guided design[11]. Boehringer Ingelheim is a member of the Division of Signal Transduction Therapy (DSTT), a PPP involving the United Kingdom's Medical Research Council, the University of Dundee, and six major pharmaceutical companies. The DSTT aims to further the development of new drug treatments for major global diseases by targeting kinases and the ubiquitin system.

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And in 2015 our company became a member of the GPCR Consortium, an international, nonprofit, open-source collaboration that comprises academic research institutes in the United States and China and major pharmaceutical companies from around the world. The GPCR Consortium was initiated in 2014 with the purpose of helping coordinate and manage the generation of high-resolution structure-function studies of medically important proteins known as G-protein coupled receptors (GPCRs) while making all data publically available. The SGC and the GPCR Consortium are good examples of the open-source approach.

Crowdsourcing

Finally and more recently, we have become involved in the third and newest type of open innovation, crowdsourcing, in which we have worked with broker organizations to access potential problem solvers. Crowdsourcing is a term that was coined for the first time by Jeff Howe in an article in Wired magazine titled 'The Rise of Crowdsourcing'[12]. He subsequently defined the term in his blog as the "the act of taking a job traditionally performed by a designated agent and outsourcing it to an undefined, generally large group of people in the form of an open call", or more simply, "the application of open source principles to fields outside of software"[13]. Many pharmaceutical companies have become adept at defining problems or questions that need to be solved and they reach out to the wider scientific community for solutions. The pharmaceutical company either establishes its own Internet portal to solicit solutions from potential solvers or works together with the help of brokers who have defined platforms such as InnoCentive or Kaggle[14, 15]. We have pursued several different crowdsourcing projects with InnoCentive covering a wide range of different topics. Examples include studying the new translational models of psychiatric diseases, antidepressant effects of ketamine, new approaches for *in vivo* modulation of gene expression in lymphocytes, novel hypotheses on the contribution of mast cell phenotypes to respiratory diseases and asthma, and mimicking airway smooth muscle re-modelling in severe asthma. As previously mentioned, we are already working with the BioMed X Innovation Center, as both broker and incubator, in the field of epigenetic approaches to COPD and have recently extended the collaboration in an attempt to define a team to discover novel therapeutic concepts for the treatment of psychiatric diseases.

In summary, our Discovery Research Strategy is based on three guiding principles: (i) building on our strengths, (ii) creating synergies, and (iii) capturing emerging science. The success of this endeavour will depend on our ability to access innovative ideas for new disease mechanisms and therapeutic approaches from around the world, and combine these with our proven internal strengths in drug discovery and development. Opening the innovation process is a fundamental part of our drug discovery activities. We believe open innovation is the best way of nurturing trust within the drug discovery community, which in turn fuels even more creativity and exchange. Please join us in celebrating the many exciting ways that scientists all over the world are lighting up the discovery of new medicines.

ACKNOWLDGEMENTS

We are very grateful to our colleagues at Boehringer Ingelheim who are working together with us, not least of which the teams in Business Development and Licensing that help us to find and build our alliances in the open innovation environment.

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