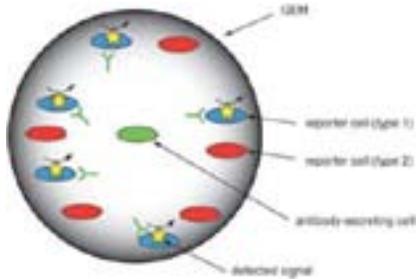




## Discovery & Development. Direct.

R&D Partnerships with Boehringer Ingelheim

### Boehringer Ingelheim Extends Commitment to Biotherapeutic Research



**Gel Encapsulated Microenvironment (GEM) Assay.**  
Courtesy of Crystal Bioscience Inc.

Boehringer Ingelheim's growing commitment to biotherapeutic drug discovery is demonstrated by the announcement of a new partnership in this important and growing area of research and development. Crystal Bioscience Inc., will apply its proprietary gel encapsulated microenvironment (GEM) and chicken immunisation platforms to discover therapeutic antibodies to multiple targets selected by Boehringer Ingelheim. These platforms provide the ability to isolate monoclonal antibodies from immunised chickens, and can screen simultaneously for specificity and biological activity. The depth of screening provided by the GEM assay in combination with the breadth of the antibody repertoire in immunised birds provides access to an extensive source of affinity-matured antibodies with therapeutic potential.

*"We appreciate the confidence that Boehringer Ingelheim has placed in our team and technology following on the success of our prior work together. We are very pleased to have a partner with the depth and breadth of experience of Boehringer Ingelheim in the development of therapeutic products"* commented Robert J. Etches, President and CEO of Crystal Bioscience.

*One of the pillars of Boehringer Ingelheim's research and development is the discovery and development of new biological entities. As our understanding of human disease improves, it has become clear that multiple pathways contribute to disease pathogenesis. Thus molecules that target multiple pathways offer the support to deliver superior benefits for patients. To achieve this goal, multi-specific molecules capable of modulating different biological pathways are beginning to emerge as a core platform for the next generation of NBE products.*

#### New discovery and development partnership announced with Crystal Bioscience Inc.

Boehringer Ingelheim's growing commitment to biotherapeutic drug discovery is demonstrated by the announcement of a new partnership in this important and growing area of research and development. Crystal Bioscience Inc., will apply its proprietary

#### Boehringer Ingelheim and Athera partner on novel therapy for atherosclerosis

A second announcement that Athera Biotechnologies and Boehringer Ingelheim have entered into an option agreement for a novel preclinical antibody programme is further demonstration of Boehringer Ingelheim's growing commitment to biotherapeutics. Boehringer Ingelheim was a pioneer in the field of biotechnology and is now one of the leading companies for the development and manufacture of biopharmaceuticals.

Athera's fully-human monoclonal antibody is intended for the treatment of patients with cardiovascular disease, who are at an increased risk of secondary events and death. Athera will conduct preclinical development and a Phase I study for the lead antibody following which Boehringer Ingelheim will have an exclusive option to acquire Athera's assets and rights relating to the programme. Athera is 65% owned by Karolinska Development – a public biotech investor company which originates from the Karolinska Institute, one of Europe's largest medical universities.



**Torbjörn Bjerke,**  
CEO and President  
at Karolinska  
Development.

*"We are confident that Boehringer Ingelheim, with its vast experience and resources within the cardiovascular field, is the ideal partner for this innovative program", said Torbjörn Bjerke, CEO and President at Karolinska Development.*



## Boehringer Ingelheim's Long-term Commitment to Partnering



Michel Pairet,  
Corporate Senior Vice President  
R&D Non-Clinical

The Boehringer Ingelheim R&D organisation is committed to increasing its access to breakthrough science – fuelled by external therapies. To achieve this goal, we are building on our drug discovery excellence in the fields of new chemical entities (NCEs, small molecules) and new biological entities (NBEs, therapeutic proteins), combined with a strong focus on external innovation for novel mechanisms and new therapeutic modalities.

Over the last 10 years, our R&D organisation has demonstrated its ability to harness external innovation by instigating several key research partnerships and licensing deals with academic institutions and biotech companies. These collaborations are significantly contributing to our early development pipeline.

This activity supports Boehringer Ingelheim's own successful track record of building up a noteworthy development pipeline. Several important prescription medicines have been brought to the market, which have helped millions of patients and secured significantly above industry average growth for the company. These medicines include tiotropium (Spiriva®),

dabigatran etexilate (Pradaxa®), linagliptin (Trajenta® also known as Tradjenta® in the U.S.) and afatinib (Giotrif® also known as Gilotrif™ in the U.S.).

Additionally, we are excited to look to the future with research projects such as volasertib, a polo-like kinase inhibitor, which is being investigated for the treatment of acute myeloid leukaemia. Volasertib has been granted a Breakthrough Treatment designation by the US Food and Drug Administration (FDA), intended for any drug that "treats a serious or life-threatening condition and preliminary clinical evidence indicates that the drug may demonstrate substantial improvement on a clinically significant endpoint(s) over available therapies."

Innovations such as these depend on our scientists – they are our greatest assets. It is they who create the environment in which research partnerships, across scientific disciplines and cultures succeed.

If you have a project and are seeking a research or development partnership opportunity, contact us to find out more.

For more information on research and development partnerships with Boehringer Ingelheim please visit our websites:  
<http://sincerelyyours.boehringer-ingelheim.com/> or <http://discoveringtogether.boehringer-ingelheim.com/>

## Focus on... Immunology and Inflammation

Partnering activities at Boehringer Ingelheim are focused on our research areas of interest and have one theme in common: a continuing need for new and/or better medications for patients.

One area of significant medical need is in the autoimmune diseases. There is tremendous need for safe and effective therapies in chronic inflammatory diseases such as rheumatoid arthritis and Crohn's disease, in which aberrant immune responses significantly impact patients' quality of life.

Our fully integrated research centre of 200 scientists in Ridgefield, CT, USA has extensive capabilities in small molecule and biotherapeutic drug discovery, and works with both academic and industry partners in their efforts to discover new therapeutic options to treat these chronic progressive disorders.

Research focus: rheumatoid arthritis; systemic lupus erythematosus; inflammatory bowel diseases such as Crohn's disease and ulcerative colitis; graft-vs.-host disease and transplantation; multiple sclerosis; systemic sclerosis.



The five major areas of focus for Boehringer Ingelheim research and development

### Specific opportunities for partnering include:

- Building deep expertise in core pathways and targets associated with disease-relevant processes:
  - Adaptive immunity and co-stimulation (e.g. effector cells and autoantibodies)
  - Innate effector function (e.g. macrophages and dendritic cells)
  - Tissue regulation (e.g. epithelial-immune interactions)
- Translational concepts that facilitate precision medicine
  - Access to samples from well-annotated patient cohorts to link molecular signaling pathways with patient segments
- Therapeutic programmes
  - In-licensing and collaborative opportunities, at both pre-clinical and clinical stages, for therapeutic programmes within our identified research focus areas

If you have a project outside these specific areas and would like to explore opportunities to partner please contact us with more information.

## Biotherapeutics – Medicines for the Future



Cell culture cultivation. Biopharmaceuticals,  
Biberach, Germany.

### Boehringer Ingelheim Research and Development of New Biological Entities

The innovative potential of biotechnological products is a significant driver of medicinal progress and is a pillar of research and development at Boehringer Ingelheim. The portfolio of biotherapeutic projects has grown steadily in both preclinical and clinical stages, helping to realise our vision of producing innovative medicines by implementing new technologies and developing differentiated NBEs with superior efficacy profiles.

To strengthen our research portfolio and expertise in developing NBEs binding to two targets (bispecific therapeutics), we have established partnerships with Ablynx NV, MacroGenics, Inc., and f-star Ges. m. b. H. Additionally, we work together with Micromet, Inc., (now part of Amgen) to develop and commercialise a BiTE® (bispecific T-cell engager) for the treatment of multiple myeloma.

This is an exciting time for NBE Research and Development at Boehringer Ingelheim. While much progress has already been achieved, even greater mutual cooperation, innovation, and dedication will be the key for success for the development of these medicines for the future.

## Boehringer Ingelheim Partnering Team Open for Business



Dr Paola Casarosa,  
Corporate Vice President,  
Therapeutic Alliances and  
Strategic Partnerships

"We believe working as equal partners in an open, trusting and fun environment is the best way to convert today's science into tomorrow's cures," commented Dr. Paola Casarosa in a recent interview with Biopharma Dealmakers.

This collaborative attitude is perfectly in step with the rapidly changing world of drug discovery and development. Boehringer Ingelheim recognises that with the increasing scope and speed of emerging scientific concepts and technologies, expertise exists beyond its own boundaries. Alliances with academic institutions, nonprofit research centres and external industry partners stand shoulder-to-shoulder with in-house initiatives at Boehringer Ingelheim. Every partnership is based on mutual

trust, understanding of each other's needs and – perhaps most important – enjoyment.

Boehringer Ingelheim seeks innovation regardless of its source or stage of development. This philosophy has led the company to partner on developing internet-based tools and therapies still in lead optimisation. Teaming up early in development encourages the truest form of collaboration, one shaped equally by the expertise and experience of the partners. "This harnessing of the collective, complementary capabilities of two partners in a flexible collaboration is a powerful force," Casarosa said.

Now, as Boehringer Ingelheim looks at the scientific challenges that will define the coming decades, the need for equal, mutually rewarding collaborations is greater than ever.



## Building the Boehringer Ingelheim Biotherapeutic Pipeline with our Partners

### Bi-specific antibody therapeutic candidate selected for pre-clinical development

Boehringer Ingelheim and MacroGenics have been working in a global alliance since 2010 to discover, develop and commercialise antibody-based therapeutics with the potential to span multiple therapeutic areas including immunology, oncology, respiratory and cardiometabolic. The selection of a candidate for pre-clinical development marks an important landmark in this partnership.

Scott Koenig, M.D., Ph.D., President and CEO of MacroGenics, commented: "We are pleased that the lead candidate in this research programme achieved this milestone. Over the past three years, we have greatly enjoyed our relationship with Boehringer Ingelheim and look forward to

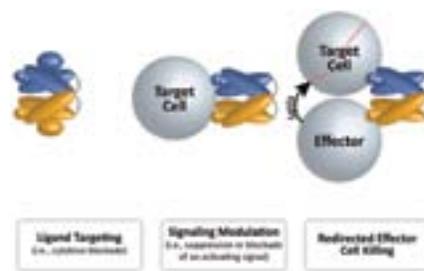
our continuing collaboration on additional DART research candidates."

The dual-affinity re-targeting (DART) platform technology is focused on dual specificity "antibody-like" therapeutic proteins capable of targeting multiple different epitopes with a single recombinant molecule.

The DART platform has been specifically engineered to accommodate virtually any variable region sequence in a "plug-and-play" fashion with predictable expression, folding, and antigen recognition.

A key technological advancement and distinguishing feature of DART is a covalent

linkage which results in a molecule having superior stability, optimal heavy and light chain pairing and predictable antigen recognition.



DART modalities. Courtesy of MacroGenics.

### Key milestone in ongoing 6-year partnership as Boehringer Ingelheim initiates Phase I study in Alzheimer's disease with Ablynx's Nanobody®

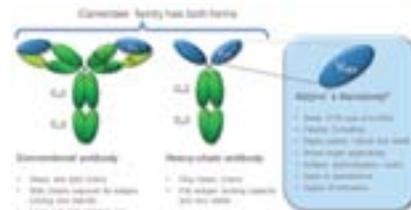
Boehringer Ingelheim has recently commenced a Phase I clinical study in healthy volunteers to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of Ablynx's Nanobody® for the treatment of Alzheimer's disease. The single-centre, partially randomised, single-blind, placebo-controlled study is expected to recruit 80 subjects and results are anticipated during 2014.

Nanobodies are a novel class of therapeutic proteins based on single-domain antibody

fragments, for a range of serious human diseases, including inflammation, haematology, oncology and pulmonary disease.

"We are very pleased that Boehringer Ingelheim has dosed the first healthy volunteers as part of our collaboration in Alzheimer's disease which we started in 2007. The Nanobody's progress into the clinic demonstrates their belief in its potential as a valuable treatment option for patients suffering from this complex

disease for which no adequate drugs are currently available" commented Dr. Edwin Moses, Chairman and CEO of Ablynx.



Understanding nanobodies. Courtesy of Ablynx.

## Discover our team

More than 7,400 staff in research, development and medicine working around the world in our R&D centres of excellence are looking forward to listening to your ideas and sharing their own experiences with you.

Our experienced partnering team has extensive knowledge of our strategic therapeutic areas and, as scientists themselves, recognise the importance of your project to you and want to work with you to nurture your idea so together we can make it grow and flourish.

Please visit our websites to find out more:

<http://discoveringtogether.boehringer-ingelheim.com> <http://sincerelyyours.boehringer-ingelheim.com>