

# HuCAL Technology – The Road to Industry Standard

Understanding of the causes of diseases, as well as opportunities for early detection, diagnosis and treatment are improving daily. This progress is driven by basic research conducted at universities and research institutes worldwide, and by application-specific research carried out by the pharmaceutical and biotechnology industries. However, the improved knowledge of the most suitable strategies for attacking relevant target molecules increases the demands placed on antibodies and on the suppliers of antibody technologies. Although a few systems are capable of producing fully human antibodies, only the HuCAL GOLD technology provides more flexibility and greater potential for optimization to enable researchers in the pharmaceutical industry to meet these requirements. Therefore, we believe it is the most advanced technology available to meet the constantly growing demands of the life sciences industry.

## **MorphoSys Antibodies Enter the Clinical Phase**

MorphoSys's main sources of revenues in 2005 were collaborations in therapeutic applications with partners from the pharmaceutical industry. At the end of 2005, MorphoSys had 29 active antibody programs with its partners in various phases of development. In February 2005, the drug candidate 1D09C3, resulting from the collaboration with GPC Biotech, became the first HuCAL antibody to enter a phase 1 clinical study. At the beginning of 2006, MorphoSys's partner Roche followed with an antibody intended for treatment of Alzheimer's disease. This means that two projects based on MorphoSys's technology are currently approved for testing

in human patients. The launch of clinical studies is an important step for MorphoSys: investors measure the maturity and value of a drug pipeline on the basis of the number of projects in the clinical phase, as these projects involve products that are closer to being marketed. Furthermore, attractive, success-dependent clinical milestone payments are made to MorphoSys at the beginning of the clinical phase.

#### **Most Recent Clinical Study: Antibody Against Alzheimer's Disease**

A therapeutic candidate developed by the Roche pharmaceutical group to treat Alzheimer's disease is the second antibody from the HuCAL library to enter clinical development. Alzheimer's disease is one of the greatest threats facing aging industrial societies. Estimates suggest that around one million people in Germany alone are living with this form of dementia. In the U.S.A., this figure is close to five million. There is currently no cure for Alzheimer's disease, only the possibility of slowing its progression. In 2005, the memantine class of drugs currently used for treatment of Alzheimer's disease generated revenues of around US\$ 660 million, and this category of treatment alone is forecast to achieve a market volume of US\$ 1 billion over the next few years. However, memantine drugs have poor selectivity in their mode of action, so their use is associated with severe side effects. They can therefore only be administered in small doses, which limits the benefits of the treatment. The antibody identified during the collaboration with Roche attacks the abnormal build-ups of the amyloid beta protein in the cerebral tissue that are characteristic of Alzheimer's disease. The international Alzheimer's research community has identified the breakdown of these deposits as a promising starting point for treatment. Removal of the amyloid beta deposits has been linked to improved cognitive functioning.

The HuCAL-based antibody, 1D09C3, is intended to improve the therapy of various types of leukemia and lymphoma. Each year, more than 50,000 people in the U.S.A. and approximately 65,000 in Europe are diagnosed with non-Hodgkin's lymphoma. After GPC Biotech received approval for clinical studies in Switzerland in December 2004, the MorphoSys partner undertook a first phase 1 study at the Oncology Institute of Southern Switzerland. This was followed in August by approval for a second center in Italy and the launch of a study in Milan's Istituto Nazionale dei Tumori. In November 2005, GPC Biotech was granted approval for clinical studies in Germany. The study to be carried out at the University Hospital in Cologne is intended to determine the safety of and tolerance to the antibody in patients, as well as providing recommendations concerning dosages and the application scheme to be used in more extensive phase 2 studies. Thus, the phase 1 study program involving approximately 28-43 patients has been successfully launched in three countries.

For more information regarding Alzheimer's disease and MorphoSys's collaboration with Roche please see also the interview with Dr. Andrew Sleight, Head of Central Nervous System Research at Roche on pages 30-33



**Stephen S. Yoder**  
Senior Counsel,  
Head of Licensing and  
Intellectual Property

## Intellectual Property Secure

It is extremely important for research companies such as MorphoSys to be able to protect their own inventions. MorphoSys is constantly involved in patent protection and is steadily strengthening its position with new patent applications in order to consolidate the legal protection of its technology. In an industry as competitive as biotechnology, patent disputes are inevitable. In September 2005, MorphoSys settled its latest patent dispute with Applied Molecular Evolution (AME), a wholly owned subsidiary of the pharmaceutical group Lilly, under attractive terms. With the settlement, MorphoSys is not involved in any patent infringement claims from any party for the first time in its history as a public company.

### Patent Dispute Settled and New Partner Acquired

The settlement secures MorphoSys the right to develop and investigate certain recombinant peptide and protein collections using the AME technology, as well as the right to market all resulting products. At the same time, Lilly received a four-year license to use HuCAL GOLD technology in their research and development projects. For all therapeutic antibodies developed by Lilly within the scope of the agreement, Lilly is to pay exclusive license fees, milestones and royalties on end products. Therefore, in settling the patent dispute, MorphoSys also acquired a new partner in Lilly, which is one of the world's 20 largest pharmaceutical groups. Ten of these companies, including Lilly, are now working with MorphoSys's technologies.

The unchallenged patent position means that MorphoSys now also enjoys greater flexibility in planning future generations of the proprietary HuCAL antibody library. This is because the settlement also includes the future use and marketing of all versions of the HuCAL libraries by MorphoSys or its partners.

### First Patent for CysDisplay in Australia

In addition to settling the final pending patent dispute, MorphoSys has further consolidated its patent position by obtaining new patents for the Company's proprietary technologies. MorphoSys has been granted a patent in Australia as well as a new patent for the HuCAL technology in the U.S.A. The patent granted by the Australian patent office in May 2005 protects the CysDisplay technology – a fundamental component of MorphoSys's proprietary HuCAL GOLD antibody library. As a result, MorphoSys has been granted a total of 14 patents, with more than 40 applications currently being processed worldwide.

## Systematic Further Development of Technology

The field of antibody generation and development is characterized by ongoing technological progress. MorphoSys's HuCAL GOLD technology is currently the most advanced technology in this sector and its market share is growing steadily. However, it is strategically important for the Company to defend its technological advantage over competitors in the future. For this reason, MorphoSys tracks all innovations and seminal technological trends with the aim of continually expanding and modernizing its technology.

**Dr. Armin Weidmann**  
Director R&D

**Dr. Margit Urban**  
Senior Director R&D

**Dr. Markus Enzelberger**  
Senior Director R&D

**Dr. Ralf Ostendorp**  
Senior Director R&D



### **Innovative Bacterial Production Systems**

One of the measures taken in 2005 to advance the Company's proprietary technology was a feasibility study with Wacker Biotech on the production of antibody fragments, which was completed at the beginning of November. The patented Wacker technology is a secretion system based on the bacterium *Escherichia coli*. It functions differently to all previously used bacterial systems in which the antibodies are enriched within the bacteria producing them. The bacteria have to be destroyed before the product can be obtained. However, using the Wacker system, the protein of interest is passed into the surrounding culture medium by the bacteria during the production process, or fermentation. Until now, Wacker has used the system to produce proteins with simple structures. The study commissioned by MorphoSys proved for the first time that it is also possible to produce antibody fragments using this system. This is remarkable as their structure is considerably more complex, consisting for example of two different subunits. The Wacker system will enable MorphoSys to produce antibody fragments in larger quantities and much more easily in the future, which will be more cost-effective. These fragments can be used for diagnostic and therapeutic purposes, both for MorphoSys's own projects as well as for therapeutic projects conducted with partners. MorphoSys has also acquired the relevant research licenses from Wacker. For the development of research antibodies such improvements in production methods promise a decrease in production costs, as well as increased profit margins.

### **Production in Human Cell Lines**

In addition to production in bacteria, production in human cell lines is an important method for MorphoSys. As well as producing a very high yield of the complete antibody molecule, a human cell line ensures the antibodies are glycosylated in a human pattern—glycosylation is a natural process in which a protein is modified with sugar molecules. In this way, HuCAL antibodies, which already have fully human amino acid sequences, will resemble even more closely their

natural counterparts. In 2004, MorphoSys acquired rights to work with the human cell lines HKB11 from Bayer AG and Per.C6 from Crucell N.V. Both cell lines are now being intensively studied in various areas of application for the production of antibodies. This provides MorphoSys, as well as the Company's present and future partners with an extensive range of production methods.

### New Lead Compound MOR103



**Dr. Robert Friesen**  
Director, Head of  
Pre-clinical Development

As a result of the strategic review process initiated in 2005, MorphoSys decided to focus the majority of its efforts on its anti-inflammatory compound MOR103 as new lead compound in the indication of rheumatoid arthritis. MOR103 targets inflammatory diseases such as psoriasis, multiple sclerosis, inflammatory bowel disease, asthma, and especially rheumatoid arthritis, where MorphoSys sees a huge potential for additional innovative therapies. Pre-clinical development of the compound started in March 2006. After completion of pre-clinical testing, MorphoSys will provide all necessary information to regulatory authorities and ethics committees within the second half of 2007 to start human trials. The Company intends to evaluate the clinical efficacy of the compound.

The fully human HuCAL antibody MOR103 is directed against an undisclosed target. Rheumatoid arthritis is a chronic disease, mainly characterized by the inflammation of the lining of the joints. It can lead to long-term joint damage, resulting in chronic pain, loss of function and disability. The disease affects approximately 4–6 million people worldwide. The current standard of care amongst biologicals are the anti-TNF therapies, namely Enbrel®, Humira® and Remicade®. While these compounds have been successful, there is a clear need for alternatives. In addition to concerns about potential long-term toxicity associated with anti-TNF approaches, the fact is that 50% of patients no longer respond to their anti-TNF therapy after two years of treatment. Doctors are therefore constantly looking for new modalities, and MorphoSys believes MOR103 offers this potential.

With regard to its other existing therapeutic antibody programs, MorphoSys decided to discontinue further development of its anti-ICAM program, which consists of the MOR101/MOR102 therapeutic antibody projects. With regard to MorphoSys's cancer-related antibody program MOR202, the Company intends to generate additional pre-clinical data around this project, which will determine further steps.

### New Areas of Application for HuCAL Antibodies

With the Antibodies by Design initiative launched in 2003 and the acquisition of the Biogenesis Group in 2005, MorphoSys gained a foothold in the market for research antibodies. Research antibodies are used for a very wide range of applications. It is possible that antibodies originally used in research projects by customers of Antibodies by Design and Biogenesis will be com-

mercially developed after successful trials for diagnostic or even therapeutic use. The relevant rights would then need to be secured by a developer by taking a commercial license from MorphoSys. In January 2006, MorphoSys has acquired the Serotec Group of companies, which will be integrated in the MorphoSys Research Antibody segment during 2006.

#### **HuCAL Antibodies in Biochips**

Together with the Natural and Medical Sciences Institute at the University of Tübingen and ProQinase GmbH, MorphoSys's Antibodies by Design division implemented a joint research project in the summer of 2005. The goal of the collaboration is the analysis of all human protein kinases. Protein kinases are highly promising targets for the treatment of various diseases such as cancer, inflammation, and cardiovascular diseases, and research on these molecules has consequently received intense investment. Although more than 500 protein kinases have currently been identified, there is a shortage of antibodies to examine the majority of them. Antibodies by Design aims to generate around 250 new antibodies against these proteins. The collaboration between the three partners aims to produce a biochip—a miniaturized analysis system—which will enable the function of all protein kinases to be determined individually. The project will be supported by the German Federal Ministry of Education and Research with a grant of approximately € 2 million over the next three years.

#### **HuCAL Antibodies in Tumor Research**

Antibodies by Design and Armbruster Biotechnology GmbH launched a joint research project in April 2005 to explore new therapy opportunities against bone cancer metastasis, a life-threatening disease associated with various advanced cancers. This project is also supported by the German Federal Ministry of Education and Research with a grant of approximately € 1 million. Bone metastases develop from tumor cells that spread through the body and then settle in the bone marrow. The resulting bone tumors are among those tumors with the smallest chance of healing. The project will explore the effectiveness of a specific antibody in preventing the formation of bone metastases and the destruction of existing tumors. The antibodies from MorphoSys's HuCAL GOLD antibody library should identify tumor cells via the tumor-specific Bone-Sialo-Protein (BSP) and thus make them treatable.

#### **HuCAL Antibodies in HIV Research**

Results published in November 2005 showed that antibodies of an Antibodies by Design customer have achieved very promising results in a project exploring HIV infections. Researchers at the U.S.-based National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) analyzed eight antibodies from MorphoSys's HuCAL GOLD library for their ability to prevent HIV-1 virus particles from infecting their target cells. In a special test procedure, two antibodies displayed promising results and blocked the process in which the virus merges with healthy cells.