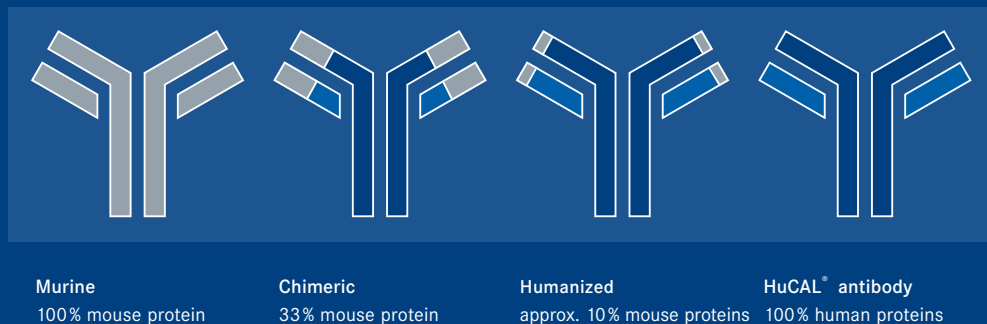


# HuCAL<sup>®</sup>—the Most Advanced Human Antibody Technology

Antibodies are produced by the human immune system as a reaction to foreign substances in the body, and are able to recognize and bind to almost any substance, from small molecules to whole microorganisms. It is this property which makes them ideal for use in medicine and research.

## Development of Antibody Technologies



In recent decades, antibody-generation technologies have been subject to constant development. Originally, monoclonal antibodies were obtained by immunizing mice. However, antibodies derived from mice are of limited use as therapeutic agents since the human immune system recognizes such antibodies as foreign molecules and can trigger a defense reaction. In this case the human organism combats the antibody, which reduces the benefits of the therapeutic substance. It is possible to reduce such defense reactions by chimerizing or humanizing the mouse antibodies, thus decreasing their immunogenicity.

MorphoSys has developed the most advanced technology for generating fully human antibodies. This technology allows the reproduction of the entire human antibody repertoire in a test tube. MorphoSys' method makes it possible to isolate all sorts of antibody types within a very short period of time. The Human Combinatorial Antibody Library (HuCAL<sup>®</sup>) comprises more than 12 billion human antibodies, the sequences of which are derived from an analysis of naturally occurring human gene sequences. Using the HuCAL<sup>®</sup> technology, fully human antibodies can be identified extremely quickly.



**Dr. Marlies Sproll**  
Vice President  
Research & Development and  
International Project Management

### **MorphoSys Technologies**

MorphoSys has developed a variety of technologies for use in the research, development and optimization of human antibodies. These technologies focus on the generation and screening of large high-quality collections, or libraries, of fully human antibodies, with the ability to engineer selected antibodies according to very specific requirements, as a means of developing new and useful drugs for the pharmaceutical industry. Although MorphoSys' technologies are potentially of wide-ranging application, MorphoSys has primarily focused its efforts on developing antibodies for applications in the pharmaceutical industry to date, as it considers this to be the most profitable opportunity.

The MorphoSys HuCAL<sup>®</sup> antibody library is based on an established technology called phage display. This technology exploits the biological characteristic of bacteriophages. Phages are viruses that infect bacteria, and are completely harmless for humans. The bacteriophages contain the genetic information for antibody fragments and display antibody fragments on their surface. The antibodies displayed in this way maintain their natural binding characteristics and structure, and can bind to a corresponding antigen. During the selection process, only phages with fitting antibodies bind to the target molecules. Under this method, antibodies recognizing target molecules can be identified. As well as the antibody protein, the bacteriophages also contain the genetic information for the antibody and allow for the subsequent production of the selected antibodies.

MorphoSys' principal proprietary technologies are summarized below:

#### HuCAL<sup>®</sup> and HuCAL<sup>®</sup> GOLD

The Human Combinatorial Antibody Libraries ("HuCAL<sup>®</sup>") including the latest and most powerful antibody library developed by MorphoSys, HuCAL<sup>®</sup> GOLD, are fully human antibody libraries based on human gene sequences. The HuCAL<sup>®</sup> GOLD library contains more than 12 billion different antibodies and contains a greater level of diversity than was present in earlier versions.

HuCAL<sup>®</sup> technology has four characteristics which MorphoSys believes distinguish it from competing technologies:

- **Modularity:** The human genes used as the basis for the HuCAL<sup>®</sup> technology are designed on the DNA level in a way that allows a rapid, directed "plug and play" approach to engineering the antibodies. For example, HuCAL<sup>®</sup>'s modular construction allows a rapid and easy optimization of specific antibodies via variation of those regions of the antibody which contact the target molecule without compromising the human composition of the antibody.
- ***In vitro* approach:** Extensive experimentation has shown that HuCAL<sup>®</sup> provides a range of antibodies against a given target molecule even when it is difficult to obtain such antibodies with *in vivo* methods of antibody generation. This characteristic of HuCAL<sup>®</sup> results from the high diversity of the underlying library.
- **Production aspects:** Antibodies sourced from a HuCAL<sup>®</sup> library can be manufactured more easily and in higher yields compared to antibodies isolated from other antibody libraries due to particular features built into the genes encoding the antibodies.
- **Immunogenicity:** HuCAL<sup>®</sup>-derived antibodies are expected to show little or even no immunogenic response, since they contain, at most, only few mutations as compared to human germline-encoded antibodies. Antibody genes obtained by other methods which rely on antibody maturation frequently contain more such mutations, making them more distant from the human germline, which might contribute to unwanted immune reactions in patients.

#### TRIM

Trinucleotide-directed mutagenesis (TRIM) is a powerful technology for introducing variability into genes in a controlled fashion and thereby ensuring that the resulting gene libraries are of the highest possible quality. The use of this technology allows the introduction of any desired amino acid at will at each single position of the variable regions of the antibodies. All HuCAL<sup>®</sup> libraries have been generated using TRIM technology which has led to very high-quality HuCAL<sup>®</sup> libraries by avoiding unproductive variations in the antibody genes.

### CysDisplay™

Cysteine-mediated phage display (CysDisplay™) is a novel, proprietary and efficient technology for selecting high-affinity antibodies from libraries, and is designed to provide a more efficient process of antibody identification. CysDisplay™ combines the advantages of the phage display technology such as phenotype-genotype linkage with the additional feature of a cleavable disulfide bond allowing efficient elution of interacting partners during the panning procedure. The technology is an advancement of the original phage display and is fully compatible with MorphoSys' other technologies.

### HuCAL® EST

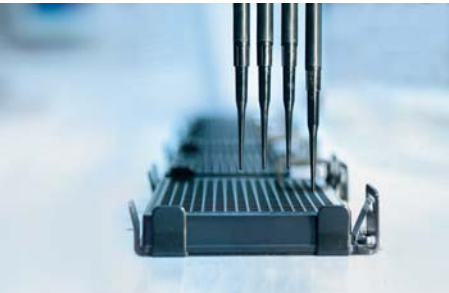
HuCAL® EST is a proprietary technology that enables high-throughput generation of antibodies against protein fragments encoded by expressed sequence (EST). ESTs are fragments of DNA which contain parts of genes or complete genes. ESTs are sometimes used as tools for the analysis of unknown genes. Antibodies against such protein fragments are required to determine when, where and how much of the EST-encoded protein is expressed in various tissues, and to elucidate their function.

### AutoCAL™

AutoCAL™ is a system of laboratory robots and software components developed by MorphoSys that enables the high-throughput screening of HuCAL® antibody libraries, resulting in the rapid selection of a highly diverse pool of specifically binding fragments of antibodies. AutoCAL™ is a modular and expandable system, allowing maximum flexibility.

### *In Situ* Protein Expression Profiling

Staining of tissues with specific antibodies or immunohistochemistry (IHC) is a powerful method in target identification and validation. Antibodies selected from HuCAL® libraries have been shown to be ideal tools for high-throughput IHC. MorphoSys' proprietary dimeric (two-armed) mini-antibodies are best suited for this application, because they can easily be produced in bacteria. In combination with the HuCAL® EST technology, novel targets, such as those derived from genomics approaches, can be validated by immunohistochemical studies within weeks. Through MorphoSys' cooperation with Oridis Biomed GmbH, it has gained access to one of Europe's largest tissue collections combined with Oridis Biomed GmbH's broad expertise in the field of molecular pathology.



The antibody selection process can be automated for high-throughput screening of the library

## MorphoSys' Patent Portfolio



**Dr. Bernhard Virnekäs**  
Senior Director  
Intellectual Property

Over the last few years, MorphoSys has built a strong intellectual property portfolio around its proprietary technology, HuCAL<sup>®</sup> (Human Combinatorial Antibody Library). To date, MorphoSys has 8 patents granted and more than 40 applications pending worldwide. The patents and pending applications cover a variety of different technologies, including antibody libraries, screening methods, certain antibody fragment formats and specific antibodies.

Settlement of the long-standing patent dispute with Cambridge Antibody Technology enabled MorphoSys to further strengthen its patent position. In another pending patent dispute brought against MorphoSys by Applied Molecular Evolution (AME), MorphoSys received a positive recommendation in January 2003 (Report and Recommendation). The Magistrate Judge recommended that the District Judge of the district court in Boston uphold MorphoSys' petition for non-infringement of the patents and reject AME's petition for patent infringement by MorphoSys. The Magistrate Judge's recommendation has now been submitted to the District Judge for a final decision. If the District Judge accepts the Magistrate Judge's recommendation, i.e. that MorphoSys has not infringed the patents in suit, all counts of AME's charge will be decided in favor of MorphoSys.

### MorphoSys' Proprietary Intellectual Property

MorphoSys' proprietary intellectual property consists of the following:

#### HuCAL<sup>®</sup>

HuCAL<sup>®</sup> patents have been granted in Australia, at the European Patent Office and in the United States, each patent having a life until 2016. The European patent was granted in June 2002 and has become effective across all E.U. countries, whereas the patent applications are still pending in Canada and Japan. Further divisional patent applications are pending in Australia, the United States and before the European Patent Office, with certain divisional applications already having been allowed for grant in the United States. Effective December 31, 2002, these patents as well as the pending patent applications have been assigned to MorphoSys IP GmbH.

#### HuCAL<sup>®</sup> EST

A patent application under the PCT was filed in 1999, designating Canada, Japan, the United States and the European Patent Office. The national/regional phases were entered into in 2001. In November 2003, the first HuCAL<sup>®</sup> EST patent was granted in the U.S.A.

#### CysDisplay<sup>™</sup>

A patent application under the PCT was filed in 1999, designating Australia, Canada, Israel, Japan, Norway, the United States and the European Patent Office. The national/regional phases were entered into in 2001.

### HuCAL<sup>®</sup> GOLD

In July 2003, the Company filed a PCT application identifying Australia, Canada and the United States as countries in which it wished to subsequently secure patent protection through national granting procedures. The application covers a new vector concept, which is used in the HuCAL<sup>®</sup> GOLD library, and is based on a preliminary application filed in July 2002. Effective December 31, 2002, this patent application and every continuation of it was assigned to MorphoSys IP GmbH.

### Third-Party Rights

Depending on the library format and screening system being used, the application of MorphoSys' proprietary technologies requires access to various third-party licenses to guarantee the unrestricted utilization of its own technologies. Alternatively or in addition to entering into licensing agreements for proprietary third-party rights, MorphoSys may attempt to invalidate or restrict the rights so owned by third parties. As of the date of this report, MorphoSys had inlicensed the following proprietary third party-rights:

#### TRIM (trinucleotide-directed mutagenesis)

MorphoSys has obtained an exclusive license to the trinucleotide-directed mutagenesis (TRIM) technology patented by the Johns Hopkins University, U.S.A., and thus is able to use the technology in-house, or assign the rights to use this technology to licensees of its proprietary HuCAL<sup>®</sup> technology. The TRIM technology has been patented in the United States and at the European Patent Office. In December 2001, the European patent was opposed by two parties, Maxygen, Inc. and Novozymes A/S.

#### SCA Ventures, Inc., U.S.A.

MorphoSys has obtained a non-exclusive license to the scFv estate patented by SCA Ventures, Inc., a subsidiary of Enzon, Inc., and thus is able to use the technology in-house, or assign the rights to use this technology to licensees of its proprietary HuCAL<sup>®</sup> technology.

#### Genentech, Inc., U.S.A.

MorphoSys has a license to monovalent phage display from Genentech, Inc., with the rights to sublicense this technology to licensees of its HuCAL<sup>®</sup> technology.

#### Dyax Corporation, U.S.A.

MorphoSys possesses a worldwide, non-exclusive license to the patents of Dyax Corp. This license allows MorphoSys to practice conventional phage display in the areas covered by the Dyax claims. An important part of the agreement between Dyax and MorphoSys is that commercial partners of MorphoSys may obtain licenses to Dyax's phage display patents for use in conjunction with a MorphoSys technology such as HuCAL<sup>®</sup>.

**Biosite Diagnostics, Inc., U.S.A.**

MorphoSys has obtained a license to phage display of multimeric antibody fragments, such as Fabs, and is now able to sublicense the rights to use this technology to licensees of its proprietary HuCAL<sup>®</sup> technology.

**XOMA Ireland Ltd., U.S.A.**

MorphoSys entered into a license agreement in 2002 with XOMA, under which MorphoSys and its partners received certain rights to use the XOMA antibody expression technology for developing antibody products (including Fab and scFv formats) using MorphoSys' phage display-based HuCAL<sup>®</sup> antibody library. MorphoSys also received a license for the production of antibodies (including Fab and scFv formats) under the XOMA patents.

**Cambridge Antibody Technology Ltd., Great Britain**

As part of the settlement agreement between MorphoSys and Cambridge Antibody Technology (CAT), signed in 2002, leaving MorphoSys free to develop and commercialize its HuCAL<sup>®</sup> GOLD activities without restriction. In addition, MorphoSys also received a license to the CAT patent estate in respect of previous HuCAL<sup>®</sup> libraries. Under the terms of the agreement, CAT received an equity stake of 588,160 ordinary shares in MorphoSys, as partial payment.

**MOR101 and MOR102**

Under the terms of the agreements with Boehringer Ingelheim, in February 2003, MorphoSys received an exclusive, worldwide license to patents owned or controlled by Boehringer Ingelheim to develop, make and sell therapeutic and diagnostic antibodies targeting the ICAM-1 molecule.

**Number of granted and pending patents of MorphoSys, including third-party rights, by technology at December 31, 2003**

Technology [third-party, from which patents were inlicensed]	Description	Granted patents and pending patent applications*
HuCAL <sup>®</sup> and HuCAL <sup>®</sup> GOLD	Fully modular and fully synthetic human combinatorial antibody library based on consensus sequences	Patents granted in Australia, U.S.A. and Europe; further patent applications pending
Trinucleotide-directed mutagenesis (TRIM) [Johns Hopkins University]	New technique for generating mixtures of oligonucleotides in a single automated synthesis using trinucleotide mixtures	Patents granted in U.S.A. and Europe
scFv antibody fragments [Enzon]	Antibody fragment format	Patents granted <i>inter alia</i> in U.S.A. and Europe
Mini-antibodies [Merck Patent GmbH]	Multimeric antibody fragments linked via association domains	Patents granted <i>inter alia</i> in U.S.A. and Europe

Technology [third-party, from which patents were inlicensed]	Description	Granted patents and pending patent applications*
Mini-antibodies II	Targeted hetero-association of recombinant proteins to multifunctional complexes	Patents granted in the U.S.A.; further patent applications pending
Mini-antibodies III	Multimeric antibody fragments	Patent applications pending
scFv display [Enzon]	Display of scFv antibody fragments on an organism	Patents granted in Europe
Phage display [Dyax]	Display of proteins on phage	Patents granted in the U.S.A.
Fab display [Biosite]	Display of Fab antibody fragments on phage	Patents granted <i>inter alia</i> in U.S.A., Japan and Europe
Monovalent phage display [Genentech]	Display of proteins on phage in monovalent form	Patents granted <i>inter alia</i> in U.S.A. and Europe
SIP screening technology [MorphoSys/Garching Innovations]	Selectively infective phage particles	Patent granted in the U.S.A.; further patent applications pending
Library versus library	Interactive screening of two libraries	Patent applications pending
Fab display	Display of Fab antibody fragments on polyphage particles	Patent applications pending
Generation of antibodies against ESTs	Generation of antibody fragments against EST-encoded polypeptides	Patent granted in the U.S.A.; further patent applications pending
Alternative phage display technology	Display of proteins on phage using disulfide bridges	Patent applications pending
Secretion in <i>E. coli</i> [XOMA]	Functional expression of antibody fragments in <i>E. coli</i> using secretion into periplasm	Patents granted <i>inter alia</i> in U.S.A., Japan and Europe
Anti-MHC II antibodies [GPC/MorphoSys]	Antibodies binding to human MHC class II molecules	Patent applications pending
Anti-TIMP-1 antibodies [Bayer/MorphoSys]	Antibodies binding to human TIMP-1	Patent applications pending
Anti-RTK antibodies [ProChon/MorphoSys]	Antibodies that block receptor tyrosine kinases	Patent applications pending
Anti-A $\beta$ antibodies [Roche/MorphoSys]	Antibodies binding to human A $\beta$ peptide	Patent applications pending

\* Includes proprietary and inlicensed patents