



ANTIBODY PRODUCTION

AT MORPHOSYS





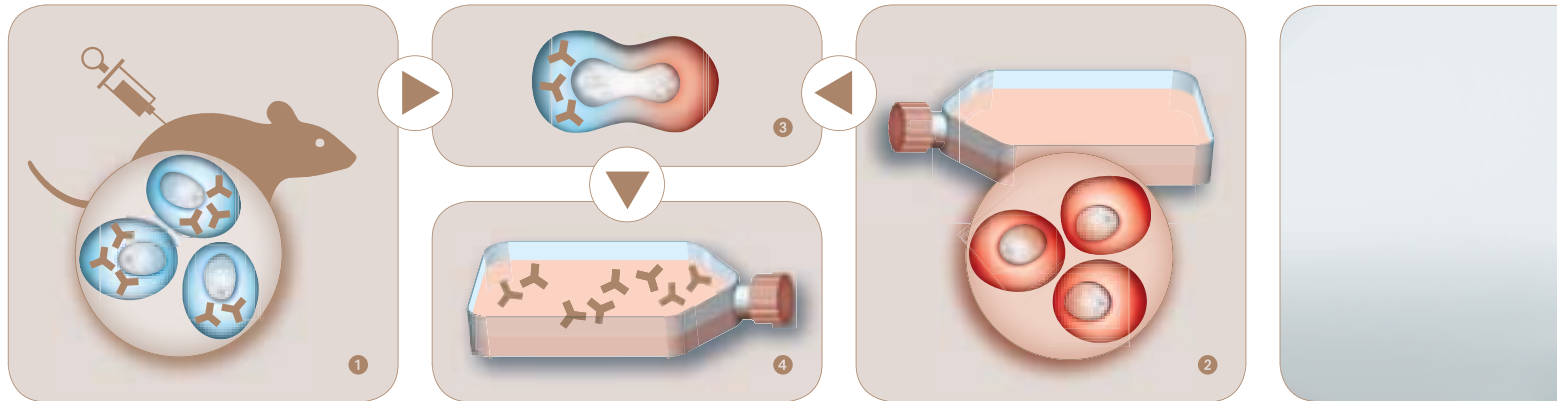
MorphoSys’s antibody library offers the opportunity to identify suitable antibodies for a variety of applications in research, diagnostics or therapeutics. The Company has a variety of methods that can be used to produce large quantities of antibodies for its own purposes, as well as for its partners and customers. The production of therapeutic antibodies in particular is a process of considerable technical complexity with associated high costs. For this reason, among others, MorphoSys is always aiming to improve on its current technology and monitors all innovations in this sector.

From the first scientific use of antibodies until today, there have been significant developments in methods for the production and application of antibodies. Antibodies produced in animals were suitable only for a limited number of research and medical applications, and only small quantities could be prepared. The research of Nobel laureates Georges J. F. Koehler and César Milstein in 1975 paved the way for fundamental specific applications and led to a massive increase in the use of antibodies in science and medicine. Their technology, called hybridoma technology, in which an immortal blood cancer cell is fused with an antibody-producing B cell derived predominantly from mice or rats, enabled the production of specific antibodies in large amounts.

Additionally, their discovery enabled for the first time the continuous production of a defined monoclonal antibody that recognized a characteristic target molecule, whereas earlier methods produced a mixture of different antibodies.

Production methods were improved further by the introduction of synthetic methods based on gene technology, in which the genetic blueprint required for the generation of a protein is inserted into a host organism. At the end of the 1970s, these methods enabled the production of human insulin in bacteria, and the introduction of such insulin for the treatment of diabetes in 1982 was regarded as a major milestone. Today, antibodies are also often produced using

MOUSE-HYBRIDOMA TECHNOLOGY ACCORDING TO KOEHLER AND MILSTEIN



1 The production of monoclonal antibodies according to Koehler and Milstein uses antibody-producing B-cells from the spleen or lymph nodes of an animal that has been challenged several times with the antigen of interest. 2 These B-cells are then fused with B-cell cancer cells that can grow indefinitely in culture but have lost the ability to produce antibodies. 3 Being cancer cells the fused hybrid cells, called hybridomas, will multiply rapidly and indefinitely. 4 Large amounts of antibodies can therefore be produced.

recombinant methods. The most appropriate production method is now selected largely according to the downstream application and the amount of antibody required. Over the past years, MorphoSys has established highly efficient production platforms and currently uses all the production methods described below.

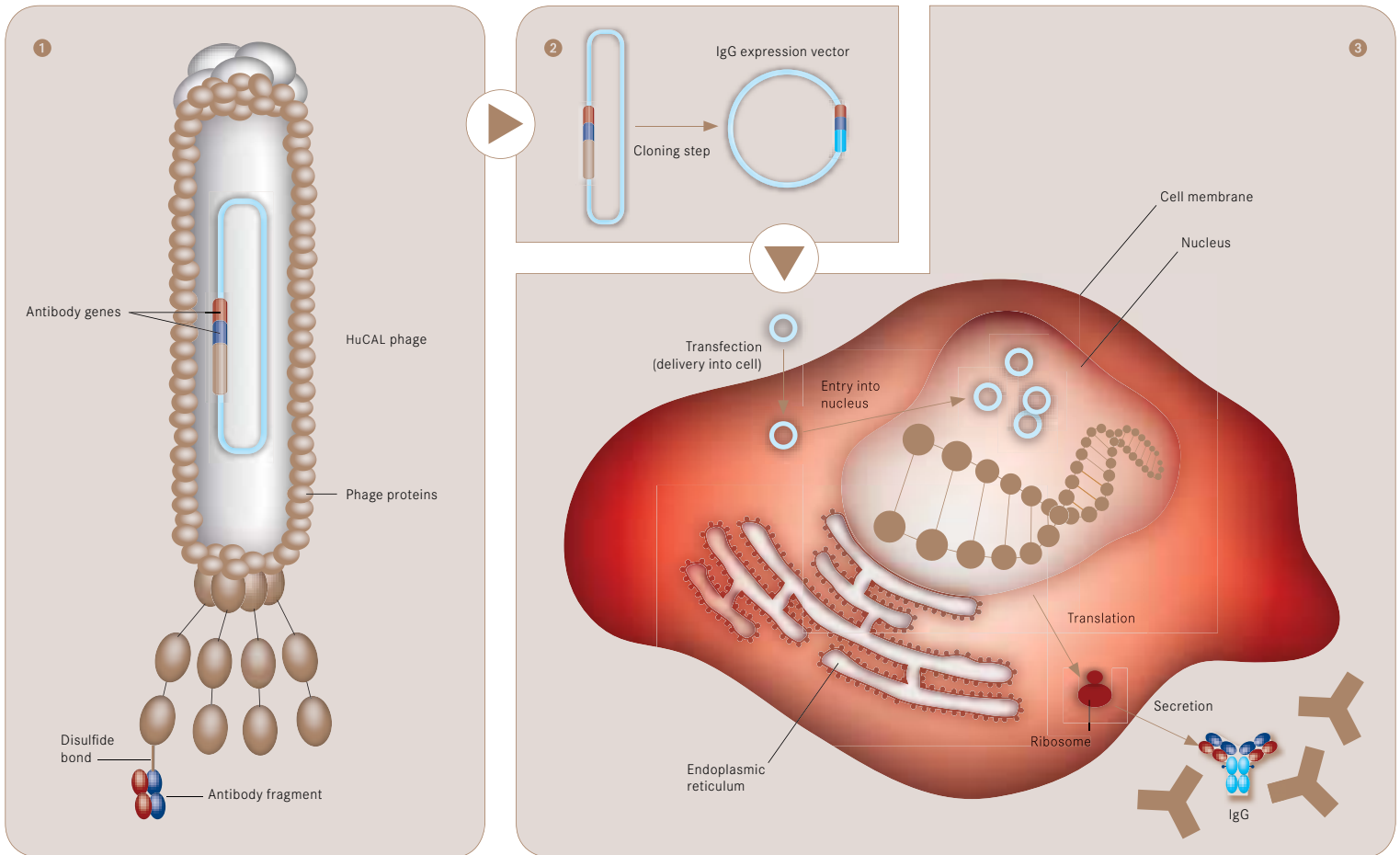
PRODUCTION IN BACTERIA

The advantages of producing antibodies in bacteria such as *Escherichia coli* (known simply as *E. coli*) are mainly the relatively safe and straightforward handling of bacterial cells and the rapid replication cycles of microorganisms. Overall, bacteria are significantly less demanding than other cell types used for antibody production. However, bacteria are used to produce only smaller fragments of antibodies as they lack the cellular mechanisms needed to modify and create the complex structure of a complete antibody molecule. In the bacterial cell, the genetic information encoding the antibody fragment is read and translated into a protein. Thanks to a specific signal sequence, the resulting antibody

fragments accumulate in a specialized compartment inside the cell, the periplasmic space. To harvest purified antibody, the antibody must be released by breaking up the bacterial cells. Finally, all bacterial components and media residues must be completely separated, as they may have toxic effects in pharmaceutical applications of the antibody. A subsequent quality assurance step checks that resulting antibodies perform according to specifications.

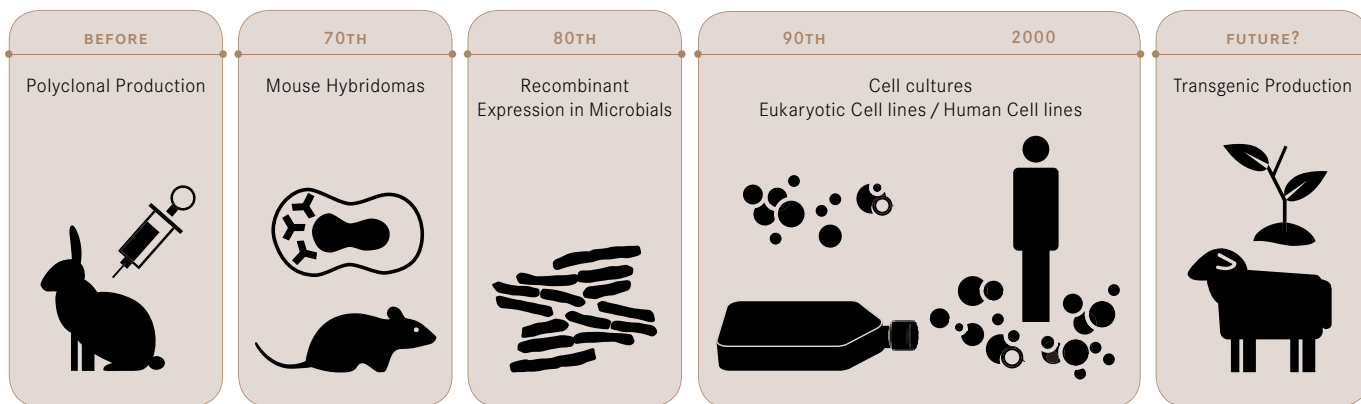
In 2005, MorphoSys, together with the company Wacker, carried out a feasibility study of a new, *E. coli*-based secretion system. It differs from the bacterial production methods used until now, in that the bacteria release the protein into the surrounding culture medium during the production process. Wacker used this system for the production of simple proteins for use in technical applications. The studies carried out on behalf of MorphoSys showed that this system can also be used to produce antibody fragments for use in therapeutic and research applications.

EUKARYOTIC CELLS AS PRODUCTION MACHINES



1 The genetic information for constructing antibody molecules is extracted from the HuCAL antibody library of MorphoSys and 2 introduced into eukaryotic cells in the form of a gene vector. 3 This step is known as transfection. The cells are able to read the gene sequences and translate them into proteins. Depending on the origin of the host cell the resulting antibody molecule is further modified and receives a respective glycosylation pattern. Finally, the resulting IgG antibody is secreted by the cells into the surrounding culture media.

EMERGING TECHNOLOGIES FOR ANTIBODY PRODUCTION



The development of antibody production methods over the course of the past decades has resulted in a broad spectrum of systems and hosts used for production purposes. Today, all of these are still in use but each system was continuously improved and upgraded over time. For the future, new approaches such as the production in transgenic organisms like plants and animals are in discussion. Potential advantages of these methods include the possibility to produce large amounts of antibody material in a costly manner.

PRODUCTION IN MAMMALIAN CELLS

Production of antibodies in bacterial cells is cost-effective, but has its limitations. First, it yields only antibody fragments, whereas intact antibodies in a format known as IgG are still most frequently used for therapeutic applications. Furthermore, proteins produced in bacteria lack some of the typical modifications found in mammalian cells.

For this reason mammalian cell lines have been used for production in parallel with bacterial cells. An example is the frequently used CHO cell line, which is derived from Chinese hamsters.

These cells can be used to produce larger amounts of protein. However, a disadvantage of these cells is that antibody production takes longer than in bacteria, because animal cells divide only once every 24 hours, whereas bacteria divide every 20 minutes. Furthermore, although CHO cells are relatively robust, some mammalian cell cultures are extremely sensitive and require stringently controlled conditions for optimal growth. A further drawback associated with using CHO cells is the resulting animal glycosylation patterns – the natural modification of the antibody's surface with sugar molecules – which differ from human patterns.

PRODUCTION IN FULLY HUMAN CELL LINES

MorphoSys's HuCAL antibodies are of fully human origin in both their amino acid sequence and in their structural configuration. Furthermore, production in completely human cell lines results in antibodies with a human glycosylation pattern. This makes the resulting antibodies even more similar to their natural counterparts and minimizes the risk of side effects from their use as drugs. This advantage is the main driving factor for MorphoSys for producing therapeutic antibodies in fully human cell lines.

In 2004, MorphoSys acquired rights to use human cell lines from the companies Bayer and Crucell. Both cell lines were tested in detail for the production of antibodies for different application areas. In August 2005, Crucell's PER.C6® cell line was also selected for production of clinical antibody material in the Company's MOR103 program. The production of the HuCAL antibody is being performed in the audited production facilities of DSM Biologics in Groningen, the Netherlands.



COST CONSIDERATIONS

Antibody production, whether to provide for clinical grade material or for production of the antibody product on an industrial scale, makes a very significant contribution to the cost of drug development for a number of reasons. The development of biologically active agents in living systems requires multiple stages, in which the individual steps must be optimally integrated. Starting from the establishment of a cell culture capable of production, through the actual production step, to fermentation, purification and transfer into a suitable application format, every step requires a very narrow range of conditions. A critical consideration is that every step in the production must conform to standards required by international pharmaceutical authorities in order to maximize the quality of the resulting drug and provide the highest degree of security for patients treated with it. However, setup and operation of suitable facilities is expensive, and companies that offer antibody production as a service have to set their prices accordingly.

RESEARCH VS. THERAPEUTIC USE – EFFECTS ON ANTIBODY PRODUCTION METHODS

While main drivers for improvements of production methods in the therapeutic antibody sector are complex, considerations in the research antibody space are relatively simple and aim

predominantly on an increase of high-throughput capabilities and cost reduction. As an *in vitro*-based technology, MorphoSys's HuCAL platform offers significant advantages in both aspects. It is highly automatable and scalable, and thus allows MorphoSys not only to cope with a huge amount of projects to run in parallel, but also shows economies of scale effects. An increase in the number of research antibodies produced causes a decrease in the average fixed cost of each unit.

FUTURE OUTLOOK

Antibody production remains a very active field with major innovations. MorphoSys is directly involved at many levels. Optimization of production methods increases the attractiveness of MorphoSys to pharmaceutical customers interested in therapeutic antibodies. In the research antibody segment, it promises reduction of production costs and an associated increase in profit margins.

Improvements are primarily aimed at a gradual improvement of existing systems, but radical changes are being discussed in the scientific world. Ideas such as antibodies produced in plants, e. g. tobacco, or in various animals, have existed for some years. Although these methods have not yet resulted in a breakthrough, their potential, particularly for cost savings, is of great interest to antibody companies.