

Strategies to Advance mAb Production

New Approaches to Process Challenges Help Push the Industry Forward

K. John Morrow Jr., Ph.D.

While approval of new therapeutic antibodies has not progressed as rapidly as was forecast 10 years ago, new products are moving through the pipeline. As always, bioprocessing, critical to antibody manufacture, is a key factor in the cost and efficiency of production.

Interviews with company officials and researchers engaged in bioprocessing showed how novel approaches to these challenges are moving the industry forward. All of the experts GEN spoke to will discuss new scientific developments and recent technological advances at BIT's "International Congress of Antibodies" meeting in Beijing later this month.

"We have more than 60 programs in progress with our partners; the majority of these programs are building on IgG-type antibodies," states Bodo Brocks, Ph.D., director and group leader of analytics and head of quality control at MorphoSys (www.morphosys.com). "This is our preferred direction and our customers' favored format. Moreover, our high-throughput systems are designed to move in this direction, producing large quantities of antibody."

HuCAL, Morphosys' antibody-development platform, HuCAL, is a phage display technology consisting of a library of 40 billion possible human antibody sequences. Unlike earlier antibody-development platforms, it does not rely on immunization of mice or other animals.

In a typical run, a panel of a few thousand possible candidates can be selected and further analyzed. "We examine biological potency, specificity, and affinity of the antibody, while on the other side we look at the physical chemical properties like thermal stability or aggregation to make the antibodies fit for our pipeline," explains Dr. Brocks.

The antibodies from the library can be reconfigured, removing and replacing pieces so as to change their binding affinity or biological function without changing their overall human structure. "The strength of our technology is that we can do affinity maturation, bringing antibodies from nanomolar to picomolar affinity. By grafting alternative complementarity determining regions into promising candidates, we can develop highly potent antibodies."

Alternative scaffolds, based on protein families such as the ankyrins, have been the subject of considerable attention in recent years but have not yet resulted in FDA-approved products. "These are interesting from the standpoint of ease of production in bacterial systems," Dr. Brocks adds, "but in recent years mammalian upstream systems have improved significantly for antibody production, so that's not an area that we are pursuing at this time."

Single-Use Rapid Scaleup

"We are moving from the era of blockbuster drugs to that of niche busters," says Paul Chapman, Ph.D., vp at EMD Millipore (www.millipore.com). "There's probably not



MorphoSys recently introduced arYla™, which combines HuCAL technology with an additional solid-phase technology for high-throughput gene synthesis to accelerate and speed up the antibody-optimization process. The solid-phase method is based on a DNA-engineering platform that enables the controlled synthesis of DNA-fragments that represent all possible permutations.

a single antibody production company that doesn't carry over capacity based on business plans developed in the last decade."

The implications of this transformation within the bioprocessing industry, especially with respect to antibody production, are portentous. A decade ago many pharma and biotech built large-scale antibody-production facilities with elaborate and costly hardware for the purpose of generating kilogram quantities of a single recombinant protein.

Now much of this capacity is idle, as de-

mand has shifted due to the pursuit of therapies guided by the demands of personalized medicine, in which the amount of material required to meet the needs of a restricted market may be orders of magnitude less. EMD Millipore is one of a number of companies developing single-use processing systems and technologies to meet this exigency.

Single-use modules are ideal for therapeutics whose demand will be measured in milligrams to kilograms rather than tons. "In moving from the lab bench to the bedside, we are deploying a range of single-use technologies for antibody manufacture," Dr. Chapman continues. "This allows us to remove labor-intensive steps and obtain the same quality with a much higher level of flexibility and overall plant productivity."

According to Dr. Chapman, the Mobius CellReady 3L Bioreactor is the first single-use benchtop bioreactor designed to mimic the characteristics and performance of traditional glass stirred-tank bioreactors. The Mobius CellReady bioreactor reduces turn-around time from days to hours, improving operational efficiency and scheduling flexibility for process-development labs.

Currently, cost savings are a significant consideration for antibody-production companies. "Earlier on, I don't think companies were that hard-pressed to optimize every step as the industry is today," Dr. Chapman suggests. "But now we can shrink the template and remove labor-intensive steps, while still retaining the same quality and manufacturing capacity. This means that we can drive down costs with a faster turn-around time. Moreover, we can run two to three different products at the same time, which would not

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News BIOPROCESSING HIGHLIGHTS

ScinoPharm to Manufacture Clinical Data's API against Depression

Taiwanese firm ScinoPharm (www.scinopharm.com) will commercially manufacture vilazodone hydrochloride, the API in Clinical Data's (www.clda.com) Viibryd™, which was granted FDA approval on January 24 for the treatment of major depressive disorder in adults.

ScinoPharm has research and manufacturing facilities in both Taiwan and China. The firm will be the sole API supplier of vilazodone hydrochloride for Clinical Data during the drug's launch.

DSM Biologics Inks Deal with NKT Therapeutics

DSM Biologics (www.dsmbiologics.com) signed a contract with biotech firm NKT Therapeutics (www.nktr.com) for the

process development and cGMP manufacture of the latter's lead product, iNKT mAb.

DSM's new client is focused on developing a pipeline of antibody therapeutics that can either activate or inactivate natural killer T (NKT) cell function for the potential treatment of cancer, infectious diseases, autoimmune diseases, asthma, and dermatitis.

Kalobios Chooses BioWa and Lonza's Potelligent CHOK1SV Cell Line

Kalobios Pharmaceuticals (www.kalobios.com) inked a research and commercial agreement for the use of BioWa (www.biowa.com) and Lonza's (www.lonza.com) Potelligent® CHOK1SV cell line for the development and production of its Humaneered® antibody products. The Potelligent CHOK1SV cell

line for manufacturing recombinant antibodies combines BioWa's Potelligent engineered glycosylation technology for generating fucose-free antibodies with Lonza's GS Gene Expression System™.

Native Antigen Established to Provide Purification Services for IVD Industry

A new firm specialized in the purification and supply of native viral and bacterial antigens for the in vitro diagnostic (IVD) industry has been established as a spin-out from U.K.-based psiOxus (www.psioxus.com; formerly Hybrid BioSystems). The Native Antigen Company (NAC; www.thenativeantigen.com) claims to have the scope and capacity to produce almost any native antigen, from low volumes to bulk.

NAC will specialize in manufacturing of

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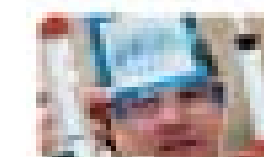
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mAb Production

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have been possible without the flexibility of these single-use processing technologies."

Shaken Disposable Bioreactors

Disposable bioreactors for cell culture have recently taken over the intermediate volume component of the industry, given their convenience and ease of regulatory compliance. For high-throughput screening and other tasks requiring low volumes and many samples, microtiter plates are the receptacles of choice.

"Working with UNIL-EPFL, we have evaluated shaker technology for cell cultivation going all the way from microtiter plates to 2,500 L bioreactors," states Tibor Anderlei, Ph.D., head of science and business development at Adolf Kühner (www.kuhner.com).

Although Wave Disposable Bioreactor Bags (GE Healthcare) have dominated cell

culture disposable technology for a number of years, there are alternatives that tender important advantages. According to Dr. Anderlei, orbitally shaken cylindrical bioreactors offer superior mixing and gas transfer, thus avoiding concentration gradients that can be harmful for mammalian cells. Scaleup calls for disposable 50 mL Erlenmeyer flasks, then to 1 L, 10 L, 100 L, and 250 L.

"However, we can go much higher, and we have pilot disposables that hold 100 L and even 2,000 L," adds Dr. Anderlei. The EPFL team has published evaluations of the technology, demonstrating that the mixing time decreases as the agitation rate increases until a minimal value is reached. As the shaking diameter was reduced, a higher agitation rate was needed to reach the minimal mixing time. These studies have established that the

Adolf Kühner's SB200-X is a disposable shaking bioreactor system for cell cultivation. It was developed and tested in cooperation with ExcellGene and UNIL-EPFL.



mixing in orbitally shaken cylindrical bioreactors ensures homogeneity for mammalian cell cultures at scales up to 1,500 L.

"We strongly endorse the shaken bioreactor as an alternative to disposable bag systems," Dr. Anderlei explains. "The easy scaleup, low shear stress, and straightforward handling are known advantages of shaken bioreactors. In addition, they provide performance, flexibility, and cost-effectiveness when compared with more conventional technologies. Further scaleup is already being considered, and initial successful experiments have been carried out with a 2,000 L shaken bioreactor prototype."

Purification Strategies

Larry J. Cummings is a consulting scientist involved in antibody purification at Bio-Rad Laboratories (www.bio-rad.com). "BioRad has collaborated with the pharma industry, going back to 1981, working with ascites fluid. As the technology has evolved over the years, the favored strategy for antibody purification is to do a capture step with protein A, followed by an ion-exchange step and the final purification on our turnkey product, CHT™ Ceramic Hydroxylapatite media."

According to Cummings, protein A has long been favored for antibody capture, given its abilities to bind immunoglobulins from cell culture harvests; reduce host-cell proteins, nucleic acids, endotoxins, and viruses; as well as its flexibility over a wide range of conditions. However, the elution conditions may promote aggregate formation, and a major shortcoming is its tendency to leach into the product.

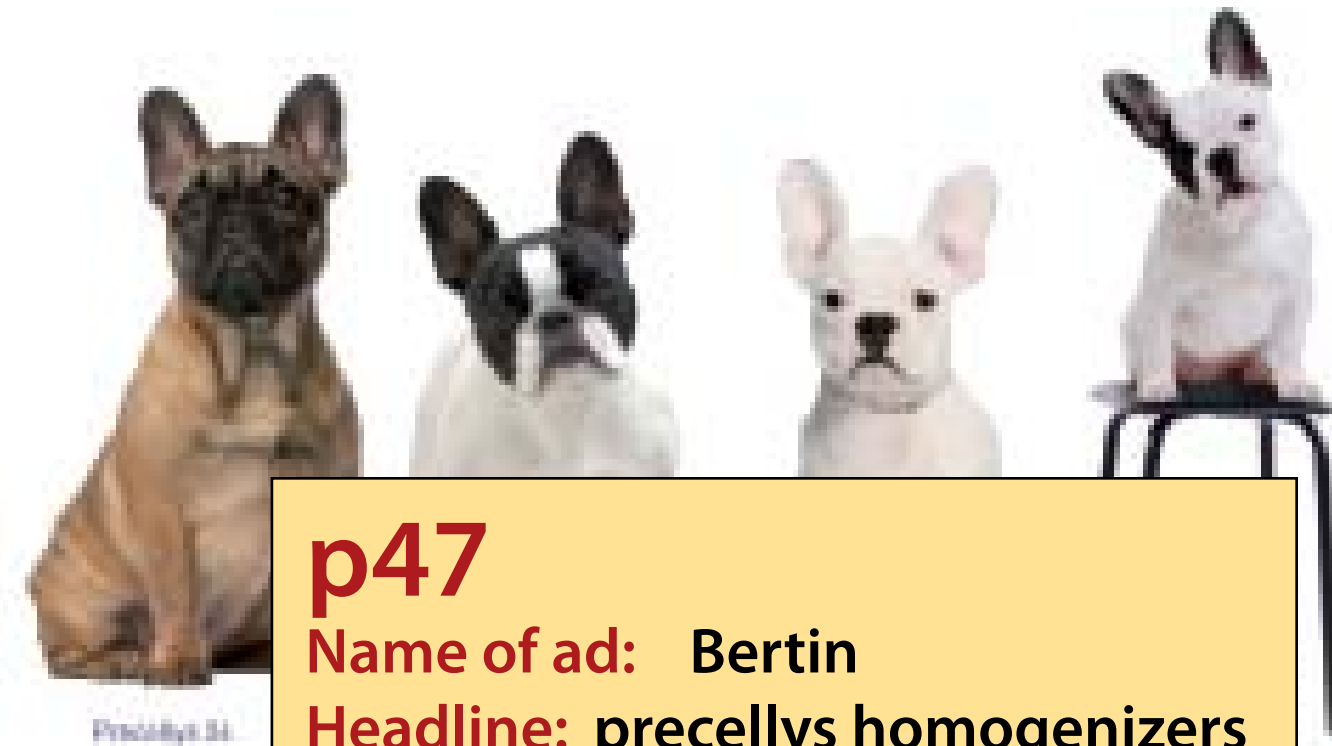
"Protein A developed a high visibility in the industry because it provided high affinity and selectivity, while capturing a moderate load of antibody," Cummings continues. "Very few materials had that capability."

However, the demands of higher antibody-expression levels coming from the pharma industry, combined with the shortcomings of

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