



Antibodies by Design

A Division of MorphoSys

Creating a new Paradigm in Custom Antibody Generation

Antibodies by Design uses proven MorphoSys recombinant antibody technology to provide high quality monoclonal antibodies to its customers in record time.

The HuCAL GOLD® library contains over 10 billion unique human antibody genes in Fab format. This wealth and diversity of sequences is coupled with proprietary automated screening techniques and advanced data management systems to quickly identify the best antibody for your antigen. Monoclonal antibody generation takes place completely *in vitro* and involves no animals.

Custom monoclonal antibodies in just 10 weeks!	Page 3
Design the antibody that is right for YOU	Page 4
Recombinant Monoclonal Antibodies for	
Life Science Research	Page 5
Proteomics and Protein Arrays.	Page 5
Drug Discovery	Page 6
<i>In vitro</i> Diagnostics	Page 7
Technology Overview	Page 8

MorphoSys means good company!

MorphoSys is a well-established biotechnology company focused on synthetic human antibodies. Its proprietary Human Combinatorial Antibody Library (HuCAL®) technology is used under license by many of the leading pharmaceutical and biotechnology companies.



Antibodies by Design is proud to use this proven technology to accelerate the pace of research and create a new paradigm in monoclonal antibody generation services.



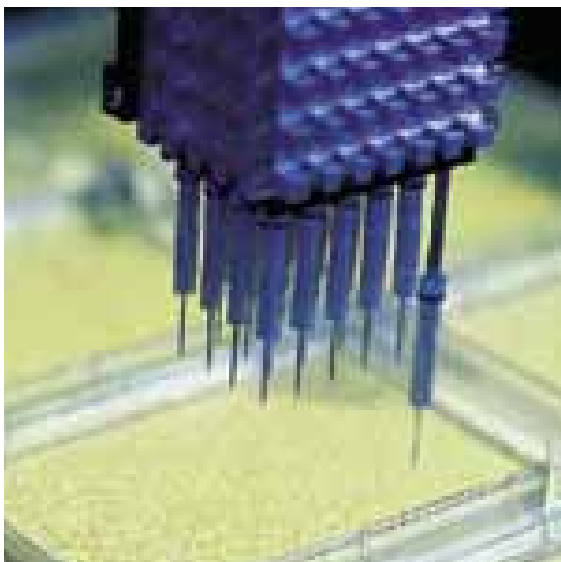
Custom monoclonal antibodies in just 10 weeks!

Now you can move your projects forward faster than ever before — with high quality recombinant antibodies from Antibodies by Design.

- **More than 10 billion individual antibody specificities available for screening**
The HuCAL GOLD® library mimics natural antibody diversity and selection — the immune system in a test-tube!
- **Monoclonal antibodies produced in just 10 weeks**
Our proprietary automated processes, AutoPan® and AutoScreen® rapidly detect the antibody sequences reacting with your antigen.
- **As little as 0.5 mg of protein is needed as antigen**
The antibody generation procedure involves no animals and no immunizations, so purifying large amounts of antigen is no longer necessary.
- **Optimized antigen expression from DNA**
When protein antigen is unavailable, proprietary HuCAL® EST technology is used to generate optimal protein fragments directly from DNA for screening against the library.
- **High-affinity antibody formats show low background**
Our antibodies are produced as monovalent Fab fragments or bivalent mini-antibodies. The lack of an Fc region significantly reduces non-specific binding and increases specificity.
- **Antibodies are supplied ready-tagged for further analysis**
Select the ideal tag for your needs. We offer 6xHis, Strep®, Myc, and Flag® protein tags.

Confidentiality

We take your privacy very seriously and place a high priority on confidential communication. You can be assured that our secure servers will protect your data throughout the antibody generation process.



Design the antibody that is right for YOU

Forget everything you thought you knew about antibody generation — the uniquely powerful MorphoSys technology sets new standards for speed, quality, and service.

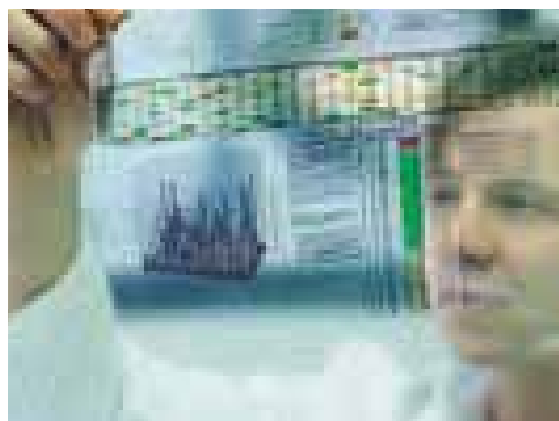
- **Choose the monoclonal antibody format you need**
 - Monovalent Fab fragments
 - Bivalent mini-antibodies (equivalent to F(ab')₂ fragments)
 - Genetic fusion to a variety of common protein tags
- **Choose the starting material you want to use**
 - Purified protein
 - DNA fragment, clone, or PCR product
 - Non-protein antigens
 - Non-immunogenic antigens (*in vitro* procedures require no animals)
- **Choose the extra services you need**
 - Additional antibody candidates binding to various epitopes and with varying affinities
 - Rapid screening of antibody pairs for 'sandwich assays'
- **MorphoSys offers collaborations for many other services**
 - Access to one of the largest collections of human tissue with 1.4 million paraffin-embedded samples and 18,000 frozen samples
 - Protein expression profiling
 - Functional validation
 - Antibody optimization (affinity maturation)
 - Generation of various IgG formats

Your satisfaction is guaranteed!

We are confident that you will be more than satisfied with the speed and quality of our custom antibody production services. Our staff will keep you informed about the status of your project at all times, and consult with you whenever necessary to ensure an optimum result. If you are dissatisfied with our services in any way, simply let us know and we will do whatever is necessary to make it right!

Antibodies for non-research applications

Our recombinant monoclonal antibodies are provided with a license for laboratory use only. If you are interested in using our antibodies for applications beyond research, or for incorporation into products for resale, please let us know. Our license policy is flexible and we will do our best to meet your needs. We also offer the possibility of gram-scale production of recombinant antibodies.



Let us know what you need: Simply complete the non-binding Inquiry Form in the Contact section of our website at www.AntibodyServices.com. We will respond with an offer within the next few days.

Recombinant Monoclonal Antibodies in Life Science Research

- **Use only a small amount of your precious antigen**

We need just 0.5 mg of each antigen for screening against the HuCAL GOLD® library, and our fully automated procedures allow generation of antibodies to multiple antigens in a single run.

- **Start with DNA and get an antigen *and* an antibody**

Our proprietary HuCAL® EST technology efficiently generates optimized protein antigens from DNA. We can provide you with your recombinant antibody and your antigen at the same time, so you can focus on your research.

- **Choose the tag or label you need**

Tagged antibodies are typically ready in just 10 weeks.

- **Generate antibodies against poorly immunogenic antigens**

We use no animals and work *in vitro* with a combinatorial library. This fully synthetic library is very likely to contain antibody sequences against highly conserved antigens that are often poorly immunogenic in animals.



References

There are numerous publications concerning the HuCAL® technology. Please see the enclosed reference list for more details.

Recombinant Monoclonal Antibodies in Proteomics and Protein Arrays

- **Enjoy high signal-to-noise ratios**

Recombinant antibodies are supplied as monovalent Fab fragments or as bivalent mini-antibodies. Their small size and minimal cross-reactivity makes them ideal for dense arraying where high signal-to-noise ratios are required.

- **Choose from a range of antibodies for each antigen**

Unique screening and production systems allow multiple antibodies to be selected for each antigen, so that a wide range of target concentrations can be detected in a single sample.

- **Generate capture molecules in just 10 weeks**

High-throughput processes allow dozens of antigens to be screened against the HuCAL GOLD® library in a single production run.

- **Select a format that matches your needs**

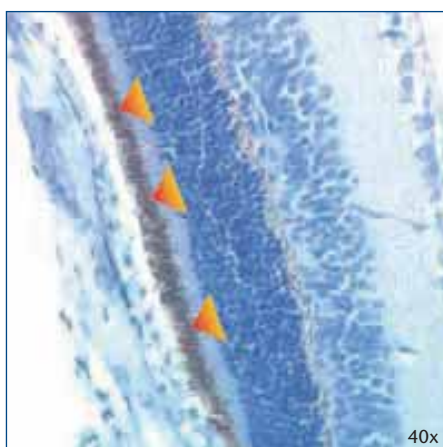
Antibodies can be supplied with your choice of tag for immobilization. We offer 6xHis, Strep®, Myc, and Flag® protein tags.

Recombinant Monoclonal Antibodies in Drug Discovery

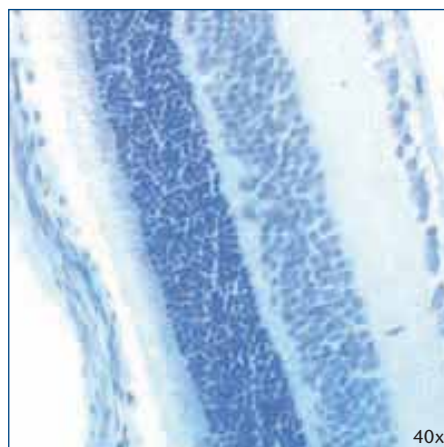
- Quickly identify key leads from multiple targets**
 Proprietary automated technologies rapidly and efficiently screen up to 96 antigens against the entire HuCAL GOLD® library in a single production run, so you can generate dozens of antibodies at one time.
- Reduce your time to market**
 The AutoPan® and AutoScreen® technologies rapidly select the best antibody sequences from the library for your antigens. Basic antibodies are typically ready for delivery within 10 weeks.
- Work with a panel of antibodies for a single target**
 Our screening process often yields several different antibody candidates. These alternate candidates can be delivered with the main antibody if desired.
- Increase the affinity of your antibody**
 Recombinant antibodies can be rapidly optimized via affinity maturation*.
- Move rapidly into functional testing**
 Our recombinant antibodies are *de facto* human antibodies and can be seamlessly transitioned from target validation to drug discovery*.
- Rely on our experienced Technical Service**
 MorphoSys has long-standing partnerships with many leading pharmaceutical companies and understands the needs of drug discovery researchers. Simply call us whenever you have a problem or question.
- Enjoy freedom from 'reach-through-royalties'**
 All of our antibodies are supplied with full freedom of use for research purposes, with no charges attached to the results of the research project.
- Outsource further target research to MorphoSys**
 MorphoSys has been collaborating with pharmaceutical companies in the development of therapeutic antibodies for more than 6 years, and offers a wide variety of services in the areas of antibody optimization.

* These services are offered under collaboration with MorphoSys.

Fig. 1
Immunohistochemistry
 Protein expression analysis in murine eyes (formalin-fixed, paraffin embedded) using a mini-antibody generated against a 256 aa protein fragment expressed from an EST. Data provided courtesy of BIOGEN.



Mini-antibody against expressed protein fragment



Negative control mini-antibody

Recombinant Monoclonal Antibodies in In vitro Diagnostics

- **Rapidly screen for optimized antibody pairs**
High-throughput AutoPan® and AutoScreen® technologies rapidly generate antibody pairs for 'sandwich assays'.
- **Say goodbye to interference elimination**
The HuCAL GOLD® library contains human antibody sequences, so there is no need to incorporate HAMA blockers into the diagnostic assay.
- **Generate primary antibodies already labeled**
Recombinant antibodies can be attached to enzymes such as alkaline phosphatase by genetic fusion directly after the screening process.
- **Upscale easily to gram-level production**
E.coli production can be simply transferred from shaking flasks to fermenters.
- **Eliminate post-production antibody modifications**
Recombinant antibodies are produced directly in the Fab format (mono- or bivalent), so there is no need for Fc fragment removal before use.
- **Optimize the affinity of your antibody**
Access to the antibody sequence allows affinity maturation of identified antibodies to increase their performance. This service is offered in collaboration with MorphoSys.

	HuCAL® antibody	$K_{on}[s^{-1}]$	$K_d[nM]$	Improvement
Selected for Biological Function	MOR 8 Fab	29.0×10^{-3}	290.0	Parental
1 st Round	MOR 8.6 Fab	5.5×10^{-3}	55.0	5-fold
2 nd Round	MOR 8.6.2 Fab	0.9×10^{-3}	7.5	39-fold
	MOR 8.6.13 Fab	0.55×10^{-3}	2.9	100-fold
Conversion	MOR 8.6.13 IgG4	0.033×10^{-3}	0.5	580-fold

Fig. 2
HuCAL® antibodies binding to a specific antigen are identified in a first round of screening. Exchange of the CDRs and further screening rounds identifies antibodies with improved binding characteristics.



Technology Overview

The Antibody Generation Process

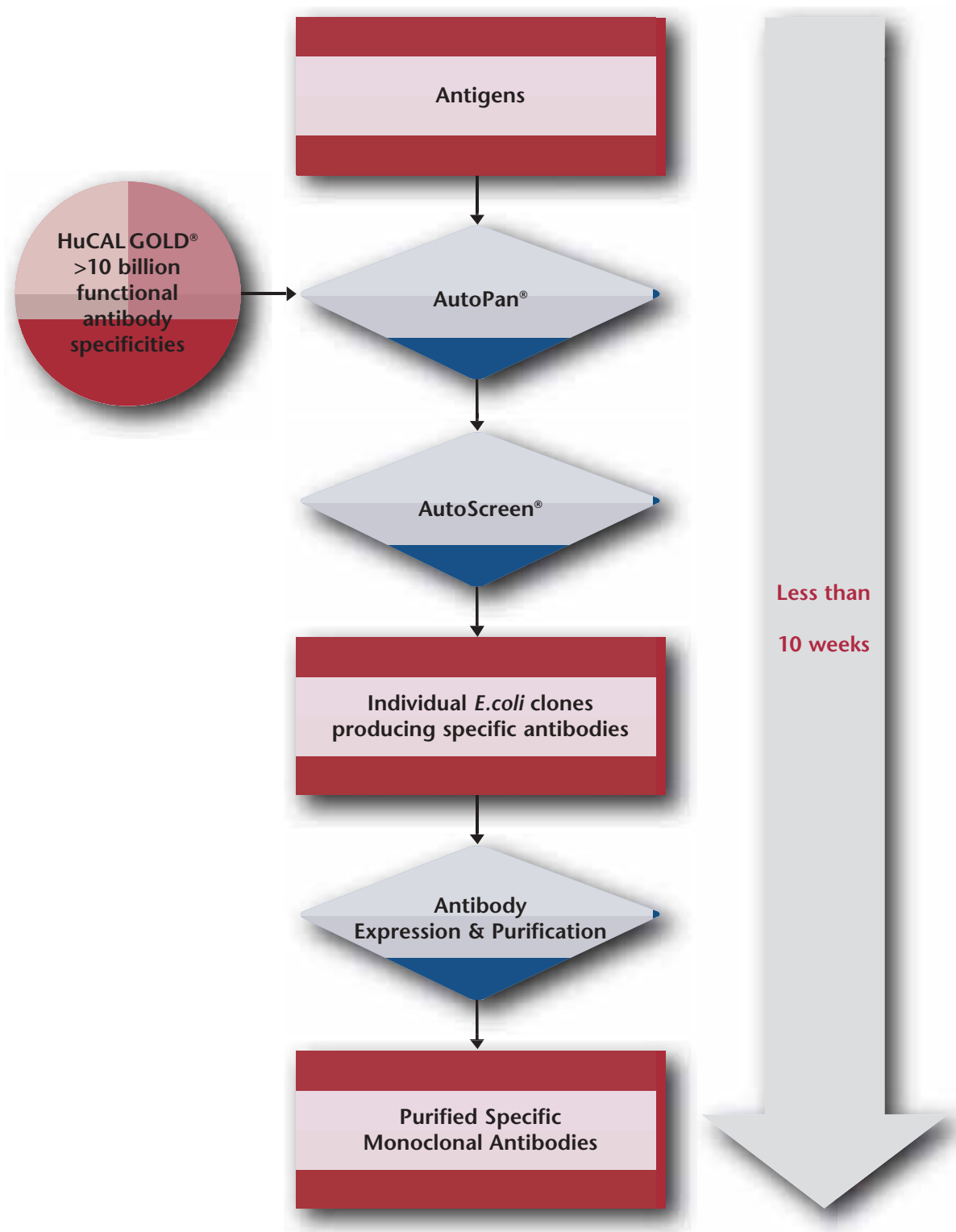


Fig. 3
Antibody Generation
Process

Technology Overview

Antigens

Antigens are screened against the HuCAL GOLD® library in 384-well microplates, so very little antigen is required for antibody generation. A 0.5 mg antigen sample is usually enough for comprehensive screening. Antigens can also be efficiently generated from DNA using our proprietary HuCAL® EST technology described on page 10.

HuCAL®

In the HuCAL® libraries, the structural diversity of the human antibody repertoire is represented by seven heavy chain and seven light chain variable region genes, giving rise to 49 frameworks in the master library. Highly variable genetic cassettes (CDRs – Complementarity Determining Regions) are then superimposed on these frameworks to mimic the entire human antibody repertoire (Fig. 4). More than 10 billion functional human antibody specificities in Fab format are already prefabricated and available in phage libraries.

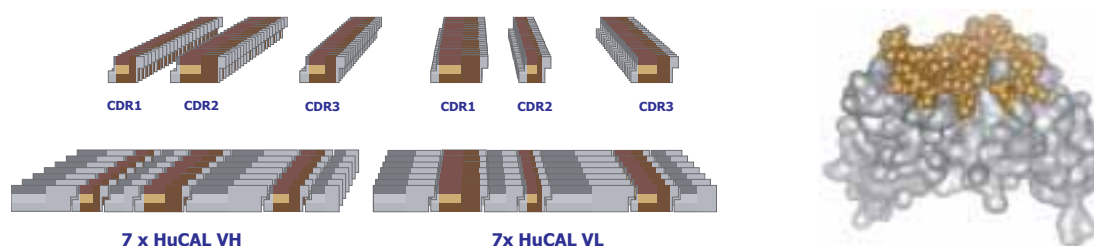


Fig. 4
Highly variable CDRs are combined with 7 heavy chain and 7 light chain variable region genes to create more than 10 billion antibody specificities.

Screening your antigen against the HuCAL® library

Your antigen enters the automated panning process (AutoPan®), where it is immobilized for screening against antibody-displaying phage. CysDisplay™ technology provides simple elution of high-affinity binders (Fig. 5), and reduces the number of potential antibody candidates to several hundreds or thousands of sequences. These candidates are then screened in a robust 384-well ELISA (AutoScreen®). Positive clones are automatically forwarded for further validation, sequenced, and entered into the central database.

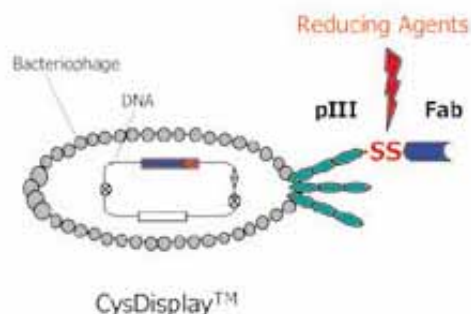


Fig. 5
CysDisplay™ allows specific elution of antibody displaying phage binding to immobilized antigens through the disruption of a disulfide bridge between phage and antibody. This ensures that all specific binders are eluted, independent of their binding affinity to the antigen.

Generating your monoclonal antibody

Antibody candidates from the screening process are expressed in bacteria and affinity purified. The basic antibody format is a monovalent Fab fragment, which can be easily converted into a bivalent mini-antibody format. Mini-antibodies are two identical Fab fragments linked by a helix-turn-helix region. They are functionally equivalent to a F(ab')₂ fragment. Fab fragments and mini-antibodies are ideal for use in most applications and offer significant advantages over full antibodies due to their smaller size and lower cross-reactivity.

Technology Overview

Generating antigens from DNA samples

HuCAL[®] EST is a proprietary technology for high-level expression of protein fragments for screening against the HuCAL GOLD[®] library.

Bioinformatics algorithms are used to select the optimal antigen sequences for expression and screening.

Antibody generation against these expressed protein fragments dramatically reduces screening efforts in comparison to peptide antigens. In addition the resulting antibodies are more likely to bind the parental protein than antibodies against peptide fragments.

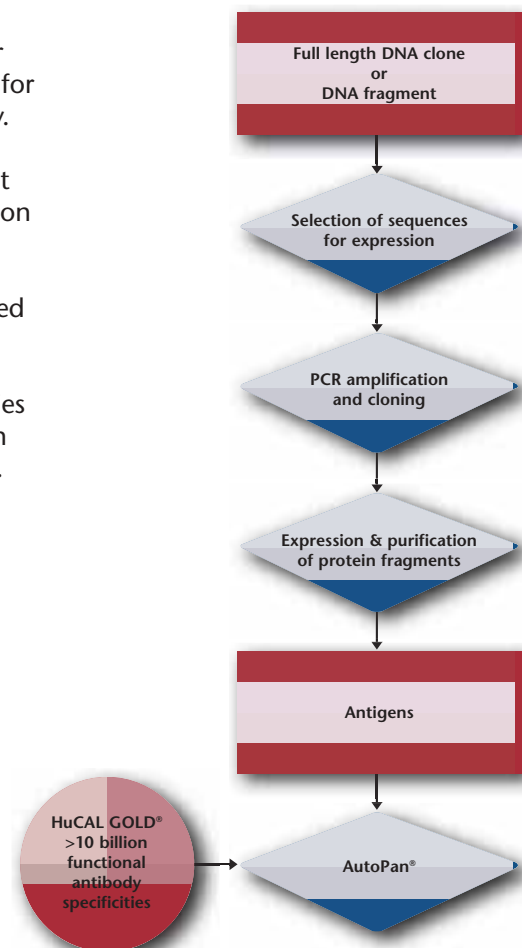


Fig. 6
Generating antigens from DNA samples

Improving performance via antibody optimization

Recombinant antibodies from the HuCAL[®] libraries can be easily optimized by affinity maturation at MorphoSys. The unique modular structure of these antibody genes allows the Complementarity Determining Regions (CDRs), which mostly contribute to target binding, to be easily exchanged with prefabricated CDR libraries (Fig. 7). Sequential exchange of CDRs can result in greater than 100-fold increase in affinity, leading to sub-nanomolar monovalent binders.

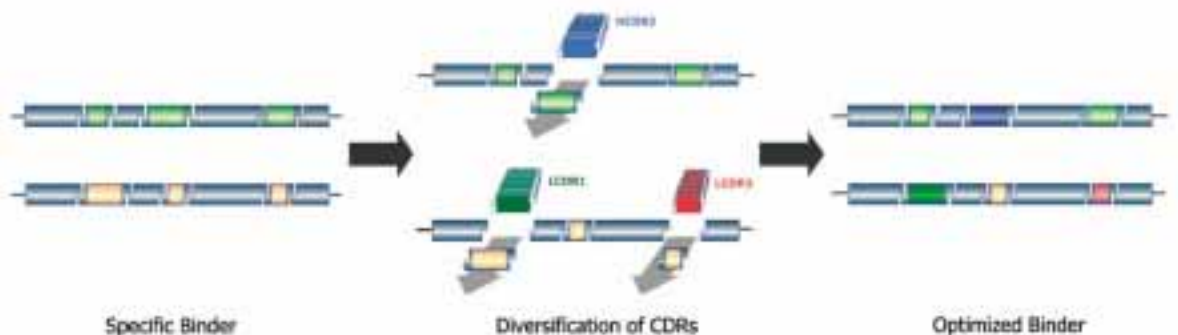


Fig. 7
The modular structure of the HuCAL[®] libraries allows CDRs to be easily exchanged and further screened to identify optimized binders.

Trademarks

HuCAL[®], HuCAL GOLD[®], AutoPan[®], and AutoScreen[®] are registered trademarks of MorphoSys AG, Flag[®] is a registered trademark of Sigma Aldrich and Immunex, Strep[®] is a registered trademark of IBA.



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