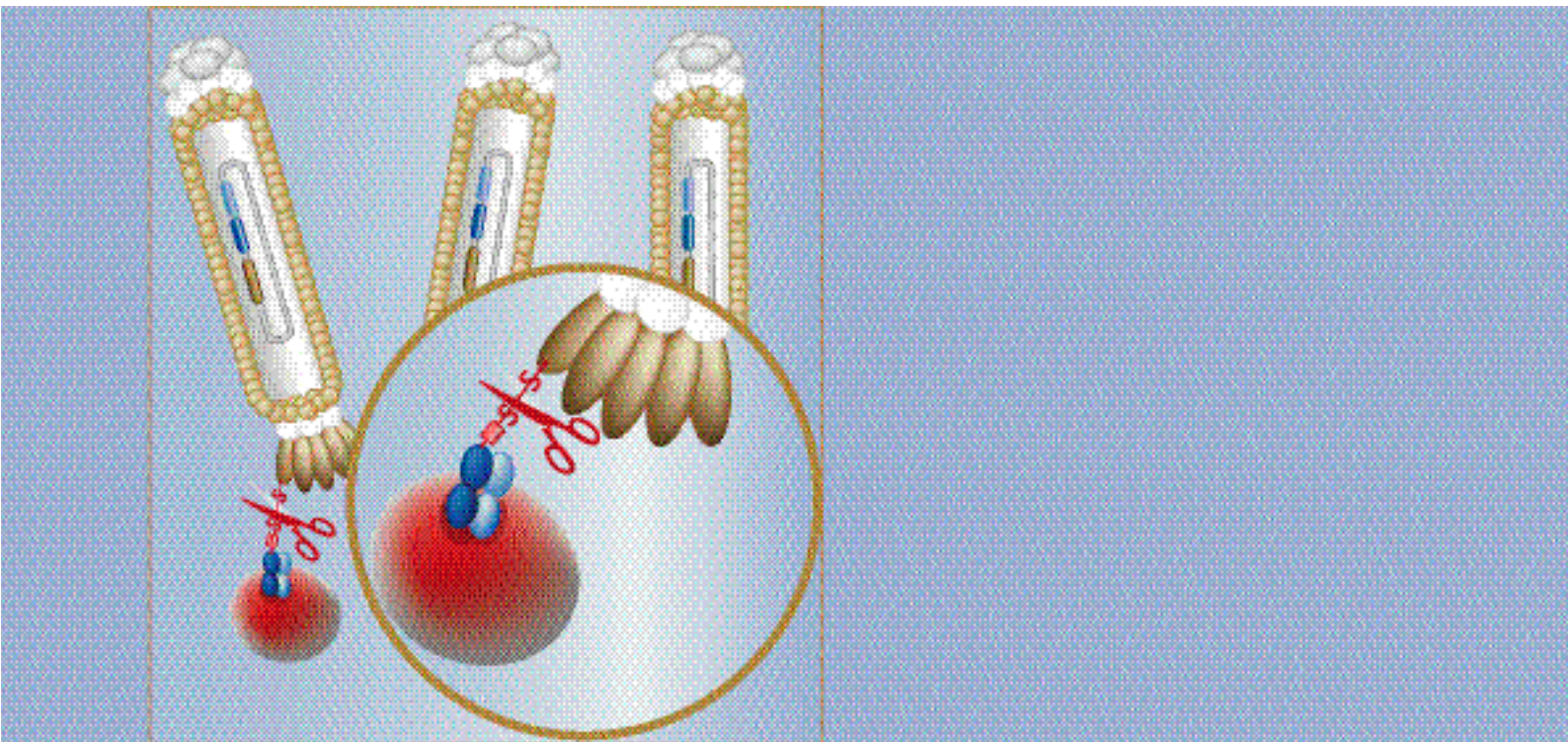


HuCAL[®]

Custom Monoclonal Antibodies



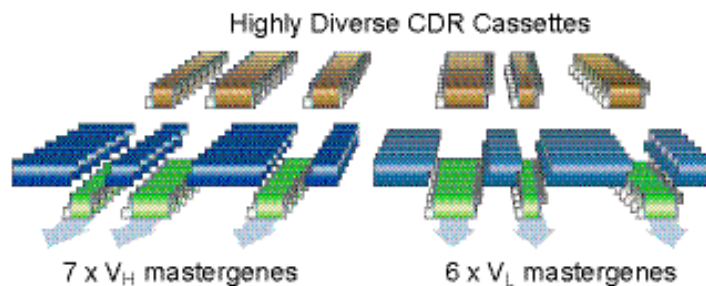
HuCAL[®] technology facilitates the generation of novel high-affinity antibodies significantly faster than the current market standard

What is HuCAL[®]?

HuCAL[®] stands for Human Combinatorial Antibody Library, a unique collection of billions of recombinant human Fab antibodies which encompass the entire human antibody repertoire. It is an integral part of a sophisticated system that has been proven to deliver exquisitely specific antibodies for all classes of antigens, without the use of animals. HuCAL[®] technology was developed by MorphoSys and is one of the most powerful methods available for generating fully human antibodies for research, diagnostic, and therapeutic applications.

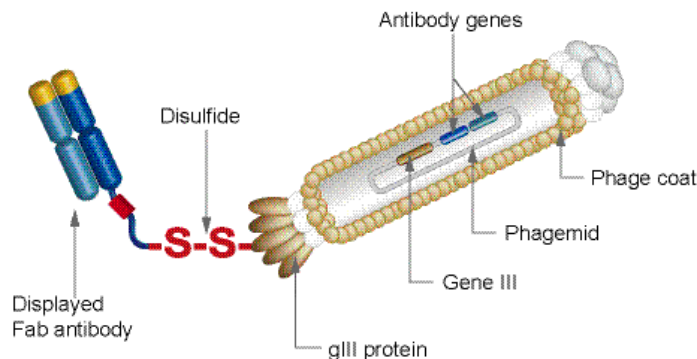
Cutting Edge Technology

AbD Serotec scientists use advanced phage display technology, intelligent screening protocols, and high throughput processes to identify Fab antibodies specific for all types of antigens. Since the process is highly automated, it is fast and very flexible, allowing for a wide range of selection conditions and tailoring of antibody formats to your specifications. The cornerstones of this technology are the HuCAL PLATINUM[®] library and CysDisplay[®] technology.



The HuCAL PLATINUM[®] Library

With 45 billion members, HuCAL PLATINUM[®] is one of the largest high-quality antibody libraries in the world. It is based on a set of framework master genes with highly diversified complementarity determining regions (CDRs) and has been optimized for expression in *E.coli*.



CysDisplay[®] Technology

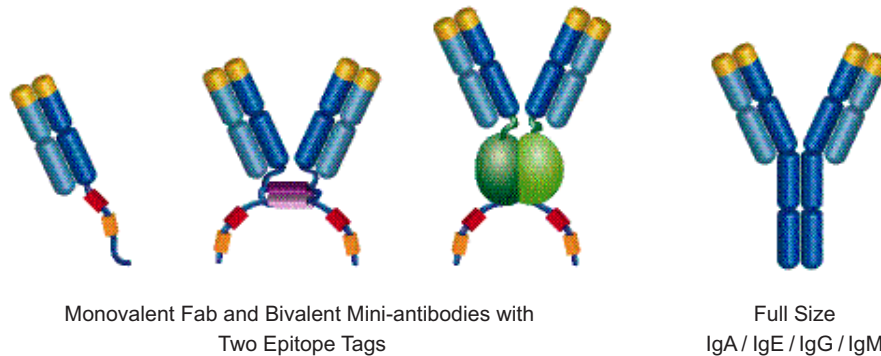
CysDisplay[®] technology is a novel and efficient phage display method featuring a cleavable disulfide bond which supports the efficient elution of high affinity antibodies.

HuCAL[®] Antibodies Accelerate Your Research

Three Reasons for You to Choose HuCAL[®]

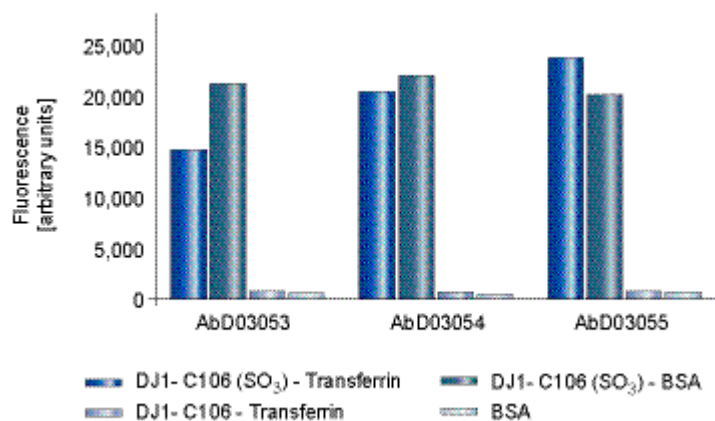
Fast: Just 8 weeks until the delivery of high-affinity purified Fab antibodies

Flexible: The modular design of the HuCAL[®] genes allows for a wide choice of Fab antibody formats, with opportunities to vary epitope tags and fusion partners. Once candidates are identified, it is easy to switch Fab formats or convert them to different immunoglobulin (Ig) isotypes.



Powerful: *In vitro* selection and screening offer complete control of antibody generation, with very few restrictions on the antigen used and selection procedures designed to identify highly specific antibodies. Antigens can include toxins, peptides, or immunosuppressive agents, while selection conditions can mimic the final application.

HuCAL[®] Antibodies Specific for the Oxidized Form of DJ1 Peptide¹



DJ1 - C106 (SO₃) peptide is oxidized at cysteine residue C106.

DJ1 - C106 is the non-oxidized control peptide of identical sequence.

HCA024 (AbD03055) was shown to perform with high reactivity in Western blotting.

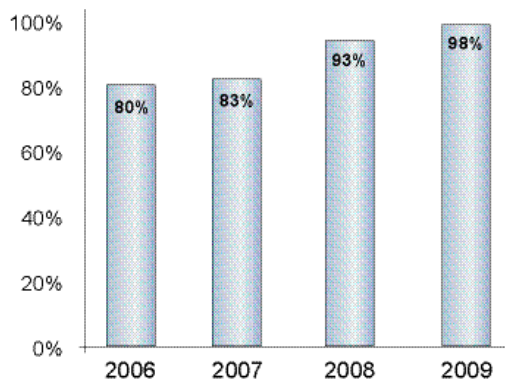
¹ Ooe, H., *et al.* (2006) *Neurosci Lett.* **404**:166-169

Our Guarantees

No Antibody – No Charge

We are absolutely confident that at least one of the more than 45 billion antibodies in our library is the perfect match for your antigen. Should we not deliver at least one ELISA-positive antibody, there will be no charge for the HuCAL® Library Screening.

HuCAL® Project Success Rate



We have achieved a success rate of 98% in 2009 for all HuCAL® projects by continuously improving the high throughput processes and the HuCAL® library.



“We are all very impressed with the quality and the efficiency of the work and our only regret is that we did not start the project much earlier.”

- Dr Scott Fry, Alere®
(Inverness Medical Australia Pty Ltd)

A Secure and Unlimited Supply

Our backup system is triply redundant with the antibody clone, separate storage of the plasmid DNA, and a full DNA sequence insuring that every HuCAL® antibody can be regrown, reproduced, or even resynthesized *de novo* from the stored DNA sequence.

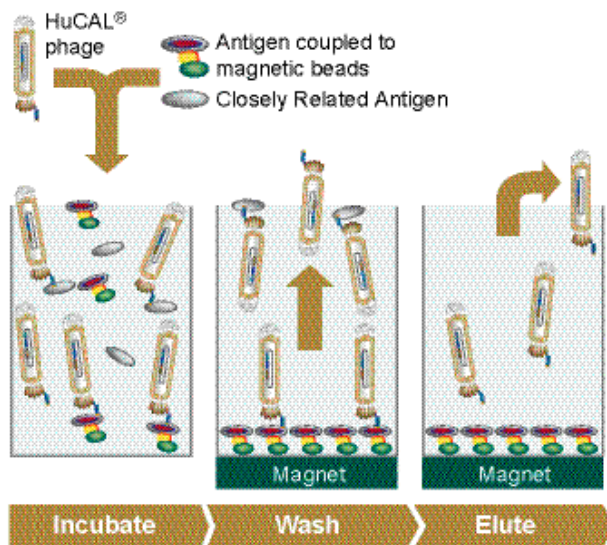
No Animals Required

HuCAL® technology sets the standard for the generation of antibodies without the use of animals. When regulations demand it, AbD Serotec also offers the large scale production of Fab antibodies without the use of animal-derived media components.

Guided Selection Insures the Desired Specificity

Performing HuCAL® antibody selection *in vitro* enables AbD Serotec scientists to control and drive the antibody specificity towards the desired outcome, a feature no animal-based technology can offer. By applying guided selection strategies, HuCAL® has successfully delivered thousands of antibodies, including the following:

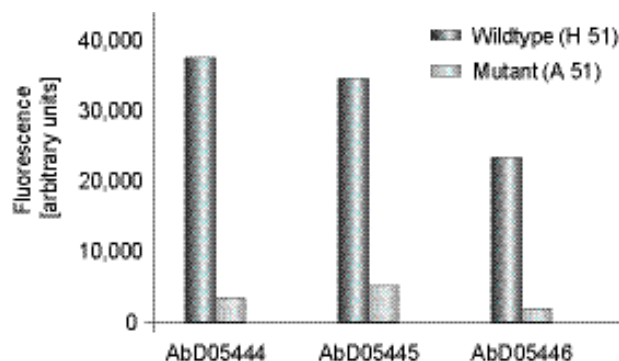
- Phosphospecific or other modification specific antibodies ¹
- Antibodies that bind and block the active site of an enzyme ²
- Antibodies specific for single amino acid mutations ²
- Anti-idiotypic antibodies specific for the binding site of another antibody ³
- Matched antibody sandwich pairs (page 10)
- Antibodies with desired pan-reactivities that target homologous regions ⁴



Guided selection with blocking is used to enrich for antibodies that do not recognize a closely related antigen (CRA).

Pre-incubating the library in solution with an excess of the CRA removes antibodies that bind to the undesired target.

Antibodies Targeted Against the Active Site of West Nile Virus Proteinase²



Inhibitory antibodies were generated that target the active site of the wild type protein by using the mutant virus enzyme, with a single amino acid substitution at position 51, for counter-selection.

The antibodies inhibit substrate turnover of the enzyme with K_i values between 35 and 289 nM.

¹ Ooe, H., *et al.* (2006) *Neurosci Lett.* **404**:166-169

³ Torretta, M. *et al.* (2007) *J Immunol Methods* **328**:34-444

² Shiryayev, S. A. *et al.* (2010) *Biochem J.* **427**:369-76

⁴ Example: human Fc-specific antibodies bind equally well to all four IgG subclasses, e.g. HCA081 (AbD06860)

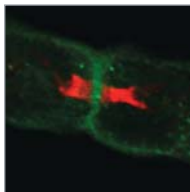
Using HuCAL[®] Antibodies

HuCAL[®] antibodies work as well as conventional antibodies in all standard applications. They also offer assay-specific advantages, for example, there is no need to remove Fc-regions in order to avoid Fc-receptor binding or to minimize human anti-mouse antibody (HAMA) reactions. Tag-specific detection antibodies further improve the specificity in many applications.

- A full description of HuCAL[®] technology, application procedures, and examples can be found in the HuCAL[®] Antibodies Technical Manual
- Find HuCAL[®] negative and positive controls at www.abdserotec.com/HuCAL

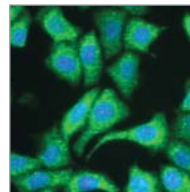
Examples of the Use of HuCAL[®] Antibodies

Immunofluorescence and Immunohistochemistry



Anti-rat Caspr antibody HCA091 (AbD06152).

Staining of Caspr protein in paranodes in mouse cerebellum (red). Ankyrin G protein delineates the nodes of Ranvier (green)⁵.

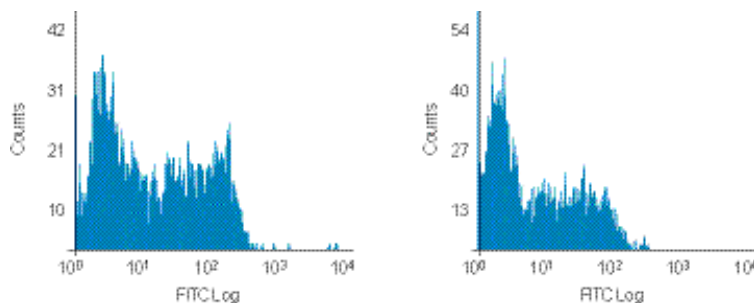


Anti-human CD127 antibody HCA145 (AbD11592).

Staining of MCF-7 cells with human anti human CD127 (green), counterstained with Hoechst (blue).

Flow Cytometry

The data below clearly show comparable performance to currently available mouse monoclonal antibody standards.



Anti-human CD127 antibody HCA145 (AbD11592).

Staining of human lymphocytes with HCA145 (left). Mouse monoclonal antibody standard from another vendor (right).

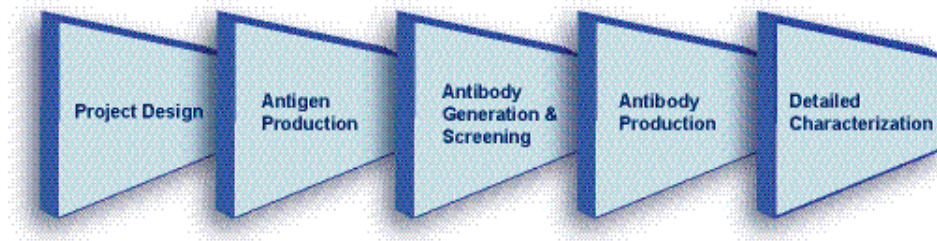
⁵ Courtesy of Prof. B. Ranscht, The Sanford Burnham Medical Research Institute, La Jolla, CA, USA

A Universe of HuCAL® Project Solutions

Tailored Services Start with Project Design



When you trust your antibody projects to AbD Serotec, we will work with you to develop a project plan that ensures the maximum potential for success. Dedicated account managers and experienced scientists offer expert guidance throughout the process, from developing the best antigen production strategies to deciding on optimal selection conditions based on the antigen type and intended use. Project design also includes assistance choosing optimal Fab antibody formats and tags, as well as a discussion of options for production and further characterization of antibody candidates.



Antigen Production

We are committed to working with you to identify the best antigen generation option to meet the project goals. Antigens can be provided by you or produced in house as part of the project. AbD Serotec offers a full range of optional antigen services, including:

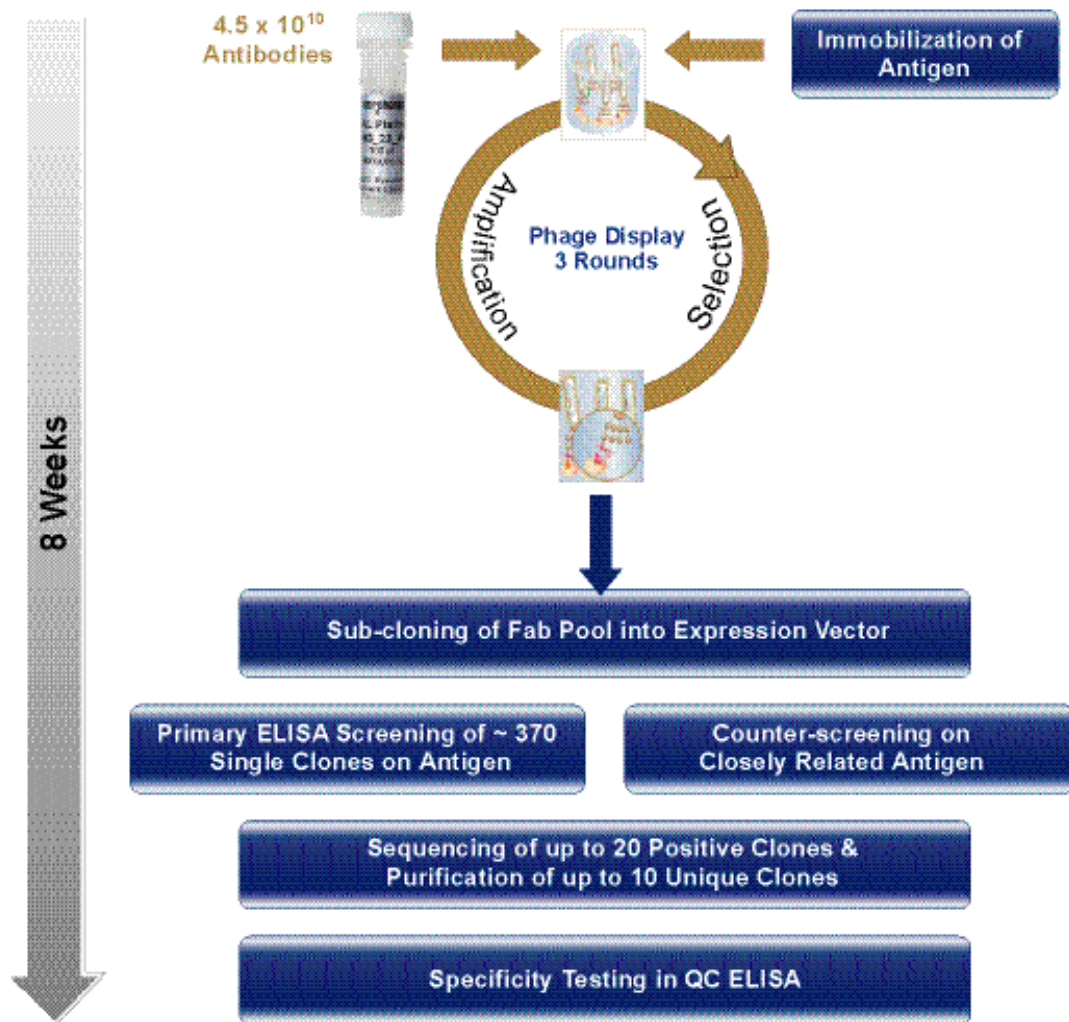
- Gene synthesis of antigen DNA
- Peptide synthesis services, including design and conjugation
- Bacterial expression of recombinant protein fragments using our AgX® system
- Mammalian expression of epitope-tagged or Fc-fusion proteins

For standard HuCAL® projects, it is only necessary to provide 0.25 to 0.5 mg of protein antigen at 80% purity.

HuCAL® Antibody Generation and Screening

The 8 week antibody generation process starts with 3 rounds of selection against the immobilized antigen. Next, the enriched Fab pools are sub-cloned into the chosen expression vector which determines the desired Fab format and epitope tags.

370 single monoclonal antibody clones are propagated for primary ELISA screening on the antigen and a closely related antigen, if applicable. Up to 20 clones with the desired reactivity pattern are then sequenced to ensure that only unique candidates are delivered. This saves time and effort when testing the monoclonals in your application.



Each standard project includes the delivery of up to 10 monoclonal Fab antibodies (250 µg each) specific for the antigen and final quality control (QC) ELISA data.

HuCAL[®] Antibody Production and Characterization

Production and Downstream Services

Once the initial set of antibodies has been tested at your facilities, the antibody candidates of choice are purified on larger scale (from µg up to gram quantities).

Following production, we offer antibody labeling using horseradish peroxidase, biotin, fluorescent dyes, or gold, depending on application requirements.

Since HuCAL[®] antibodies are recombinant, significant engineering options are also available, including switching of Fab formats, conversion to a full length Ig, and affinity maturation to further increase the binding affinity of your antibody.

Characterization Services

Beyond our standard ELISA quality control, AbD Serotec offers various optional antibody characterization services using state of the art instrumentation at high throughput in conjunction with any HuCAL[®] antibody generation project.

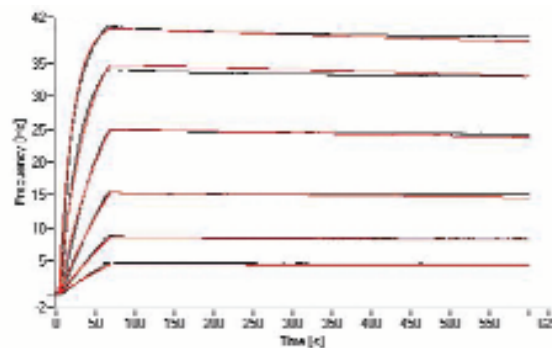
We support ELISA or bead-based platforms such as MSD[®], Luminex[®], or FMAT[®], as well as Attana A200[®] instrumentation for affinity measurements. We also offer high throughput Western blotting of up to 80 antibodies per week and flow cytometry analysis with the Beckman Coulter CyAn[®] ADP7 Color Analyzer.

Homogeneous Bead-based Assays



Anti-human GFP antibody HCA102 (AbD08969). Fluorescence linked immunosorbent assay (FLISA) using antigen coated to magnetic beads.

Affinity Measurements of Candidates



Example of affinity characterization data generated with the Attana A200[®] instrument.

The affinities of HuCAL[®] antibodies directly isolated from the library are comparable to typical animal-derived monoclonal antibodies. The best monovalent affinity usually ranges from low nanomolar to picomolar for standard protein targets.

HuCAL® Antibody Sandwich Pairs

Sandwich Pair Identification – Find the Perfect Match

Antibody sandwich pairs are the basis of many research and diagnostic assays.

HuCAL® technology offers several different ways to identify the best match.

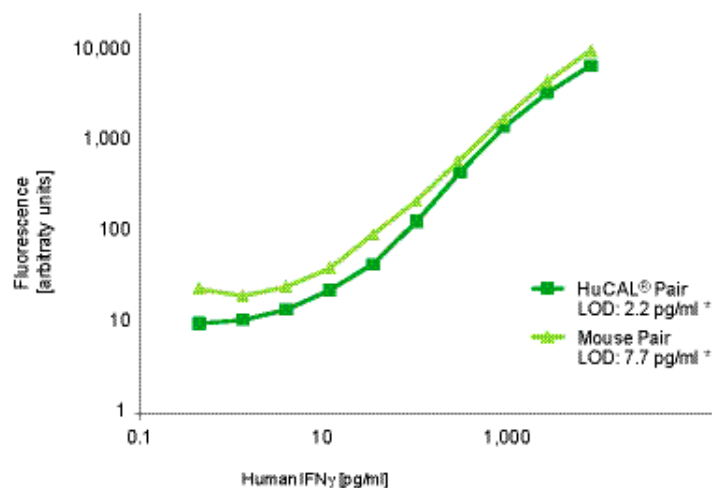
Matched Pair *de novo*

- Selection on antigen
- Sandwich ELISA screening of purified antibodies to isolate the sandwich pair *de novo* by cross testing of pairs
- Quantitative assays to determine best pair

Matching Partner

- Direct selection on the antibody-antigen complex
- Sandwich ELISA screening of antibody-antigen complex to isolate matching partners
- Quantitative assays to determine best pair

Luminex® Bead Assay Comparing a HuCAL® Pair to a Market Standard



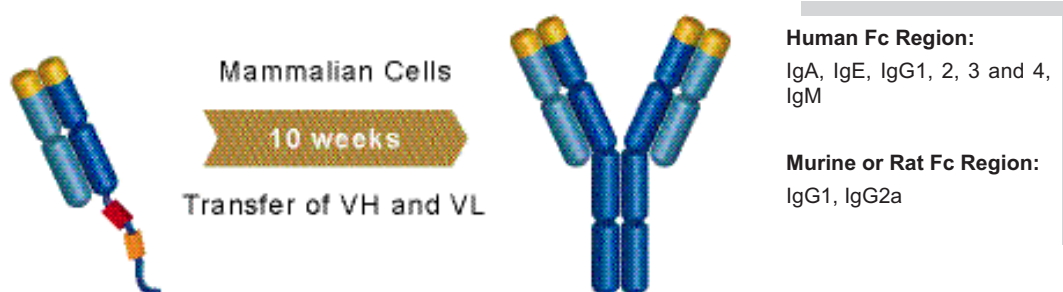
The HuCAL® pair, HCA043 (AbD00676) and HCA044 (AbD02503), is directly comparable to the antibody pair used in a commercial kit with respect to overall sensitivity and is superior at detecting the lowest ranges of the analyte human IFN γ (PHP050).

* LOD: Limit of detection

HuCAL[®] Immunoglobulins

Convert Your HuCAL[®] Fab to an IgA, IgE, IgG, or IgM

When the Fc-region is required, we convert Fab candidates into full-length human or chimeric human-mouse and human-rat Ig molecules, delivering purified Igs within 10 weeks. After cloning of VH and VL genes into vectors with desired constant regions, the light and heavy chain vectors are co-transfected into mammalian cells for transient expression.

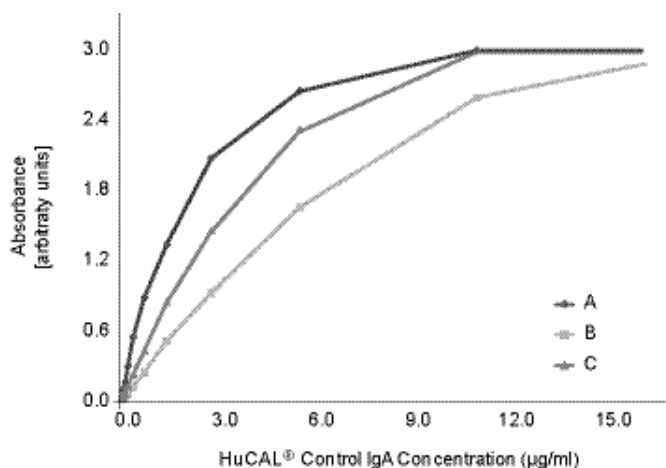


Controls and Calibrators

HuCAL[®] Ig antibodies have been successfully used as defined, fully human control and calibrator reagents in quantitative autoimmune⁶ and infectious disease assays.

Replacement of patient-derived antibodies minimizes quality control analysis of sera batches and provides a secure, fully-characterized, long term source of control human antibodies.

HuCAL[®] Control IgA in Anti-Phospholipid Syndrome ELISAs



The HuCAL[®] IgA anti-cardiolipin control antibody demonstrates a dose-responsive performance in three commercial ELISA assays for anticardiolipin (A, B, and C).

The HuCAL[®] IgA binding profile is linear and is comparable to human sera standards.

(Figure modified from "Development of recombinant human IgA for anticardiolipin antibodies assay standardization"⁶).

⁶Knappik, A. *et al.* (2009) *Ann NY Acad Sci.* 1173:190-198

HuCAL[®] Immunoglobulins

Chimeric Surrogate Antibodies

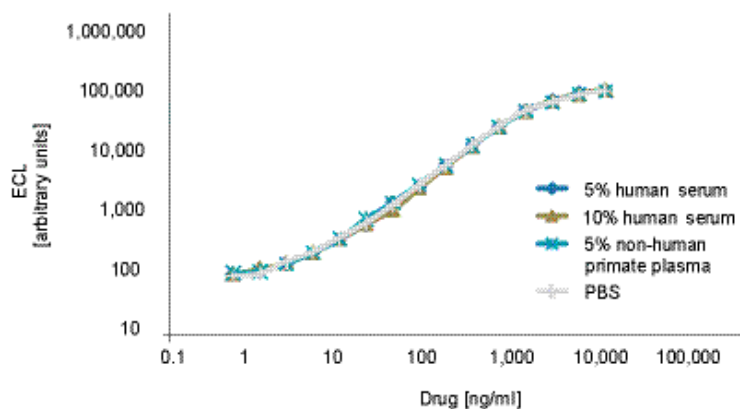
The development of human therapeutic antibodies demands *in vivo* validation of the target-antibody interaction in various animal models. To address situations where the drug antibody candidate under development does not cross-react with the target in the relevant species of the animal model, full-length HuCAL[®] chimeric surrogate antibodies can be created.

First, the Fab antibodies with the desired functionality are isolated, and then they are combined, for example, with a mouse or a rat constant region to facilitate the validation of therapeutic targets in corresponding animal models.

PK Tools

HuCAL[®] technology now allows pharmaceutical companies to develop one single high-affinity antibody which can be used first as a Fab reagent in pharmacokinetic (PK) studies and later as an Ig positive control in immunogenicity testing, as shown on page 13. This eliminates the need for sera derived from animals or patients, and greatly reduces assay development time and effort.

Sensitive PK Assay with a Drug-detecting HuCAL[®] Antibody



In the presence of complex serum matrices, the HuCAL[®] antibody permits the detection of the corresponding drug candidate in concentrations ranging from 5ng/ml to 10µg/ml, without matrix interference. Both Fab and Ig formats are well suited for such assays.

HuCAL[®] Immunoglobulins

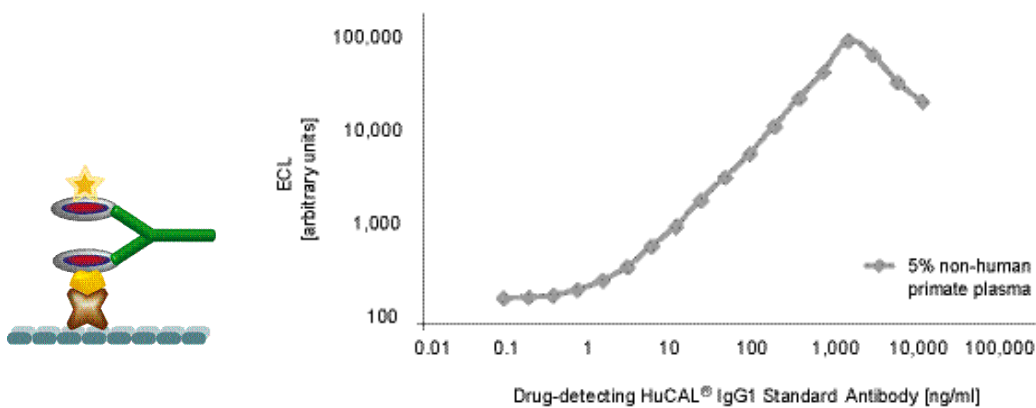
Fully Human Standards for Immunogenicity Testing

Converting one HuCAL[®] Fab candidate into various IgG isotypes quickly creates the ideal human standards for the evaluation of anti-drug antibody (ADA) responses in immunogenicity testing.

The option to convert the standard into additional formats, such as IgA and IgM, adds additional benefit when the potential immune response to the drug has to be monitored in greater detail.

HuCAL[®] Ig antibodies overcome the supply and revalidation issues associated with the limited antibody supply of human or primate sources in clinical studies.

HuCAL[®] IgG1 Reference Standard in a Homogenous Bridging Assay



As a positive control standard, the HuCAL[®] drug-detecting antibody was spiked into plasma containing drug molecules with two different labels, one for immobilization and one for detection. The standard curve obtained has a screening threshold of 1 ng/ml.

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Working With Us

To begin a detailed discussion of your antibody generation project with one of our specialists, please complete the Project Inquiry form found on our website:

www.abdserotec.com/Inquiry

Terms and Conditions of Use

Complete Terms and Conditions of Use can be found on our website at:

www.abdserotec.com/HuCAL-TnC

Confidentiality

AbD Serotec's Standard Terms and Conditions of Use guarantee that AbD Serotec adheres to strict policies of confidentiality from initial discussions through to completed projects, even if discussions do not result in an order.

Licensed Use

HuCAL[®] antibodies and derivatives thereof are initially developed, designed, licensed and labeled "For *In Vitro* Research Use Only". Any other use that is not *in vitro* research use is not allowed, unless under a specific license from AbD Serotec. Such additional license(s) can include *in vivo* research use, commercial use of HuCAL[®] antibodies in the sale or manufacture for sale of products or services in the field of *in vitro* research use, diagnostic use, or the use of the HuCAL[®] antibodies in clinical studies as a tool to demonstrate the safety and effectiveness of a drug.

Such additional license requests for HuCAL[®] antibody candidates should be addressed to AbD Serotec at sales.muc@abd.serotec.com.



Customers with the intention of developing therapeutic antibodies are invited to contact MorphoSys AG business development at bd@morphosys.com.

Client Rights with a Standard Custom Project

The customer retains all rights and title to any material sent to AbD Serotec for the purpose of antibody generation. All intellectual property developed by the customer while using the HuCAL[®] antibodies remains the property of the customer.

Exclusivity

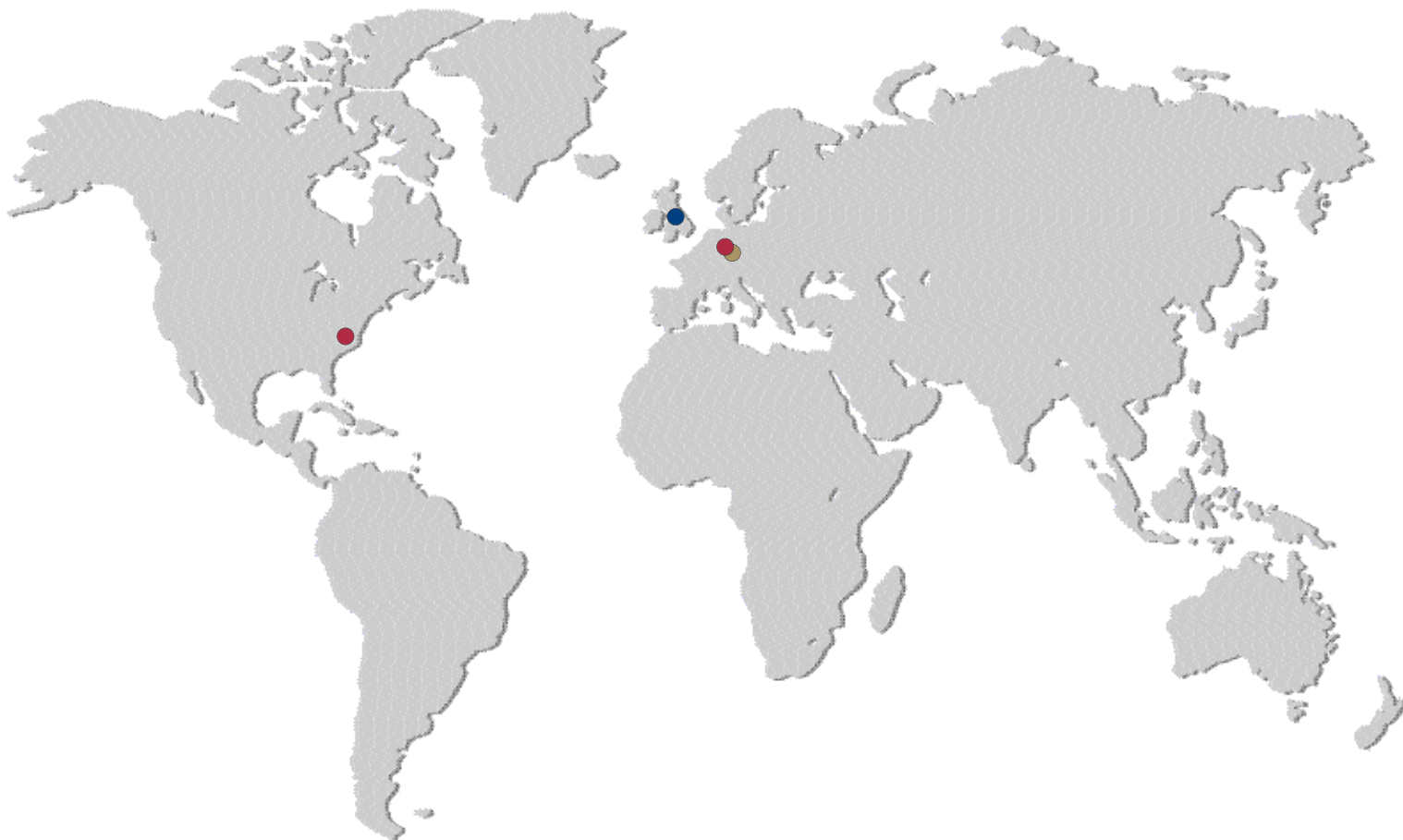
Custom-made antibodies and the associated bacterial or mammalian expression clones generated under a customer project are reserved for the customer exclusively, and are stored for a period of at least five years. Neither antibody material nor information from a custom order will be transmitted to any third party without the express permission of the customer.

Supply of HuCAL[®] Antibodies

AbD Serotec retains ownership of the bacterial expression clones generated during the course of a customer project and offers competitive production solutions.

AbD Serotec is the research and diagnostic antibody division of MorphoSys, one of the world's leading companies in the field of therapeutic antibody development.

We offer more than 25 years of experience manufacturing antibodies for research and diagnostic applications.



- HuCAL® custom monoclonal development is performed at the facility in Martinsried, near Munich, Germany.
- The AbD Serotec headquarters, with its ISO-certified catalog and bulk antibodies manufacturing facilities, are based in Kidlington, near Oxford, UK.
- Additional sales and support offices are located in Raleigh, North Carolina, USA, and Düsseldorf, Germany.

Custom HuCAL® Antibody Projects

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