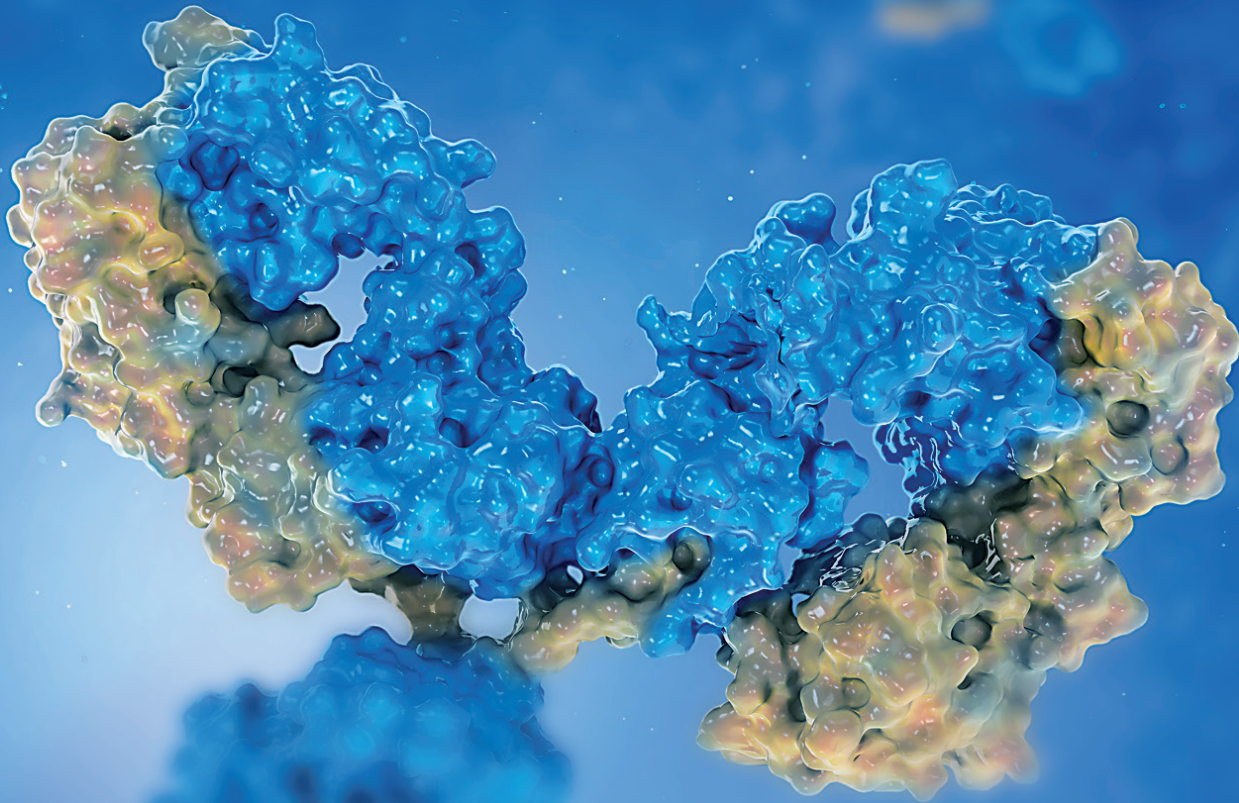




LakePharma
The Biologics Company



Antibody Discovery & Engineering Services



Overview of Antibody Discovery and Development at LakePharma

The LakePharma Antibody Center offers comprehensive antibody discovery and engineering services, including identification, optimization, and characterization of new leads.



- Hybridoma platform for *in vivo* discovery
- *In vitro* phage and yeast display platforms
- Antibody functional characterization
- Epitope binning and mapping

- Humanization
- Affinity maturation & measurement
- Sequence liability identification
- Therapeutic developability assessment

- Downstream antibody transient and stable production, process development, and GMP manufacturing services are offered by other LakePharma sites. Please visit the website for more details.

The Antibody Center's goal is to help researchers discover potent and functional antibodies.

To achieve this goal, the Antibody Center offers a variety of high-performance hybridoma- and display-based technologies. The specific discovery approach depends on project-intrinsic parameters, which include goals, timelines, and scientific considerations.

In vivo Hybridoma Approach to Identify Novel Therapeutic-Grade Antibodies

The LakePharma hybridoma platform offers multiple immunization approaches to achieve maximum plasma titers. LakePharma has developed a robust hybridoma-based workflow for the discovery of diverse high-quality monoclonal antibodies with desired functional and specificity attributes.

Chain of Discovery™ Service Package includes:

- Strategy design
- Multiple immunization approaches
- 384-well plate-based hybridoma screening
 - Target binding via ELISA or FACS
 - Cyno and/or mouse cross-reactivity
 - Counterscreens for specificity
- Kinetics and epitope binning using Octet or Carterra LSA
- Ligand blocking
- Cell assays
- Hybridoma subcloning and variable region sequencing
- Purified mAbs from hybridoma for EC₅₀, KD analysis, etc.

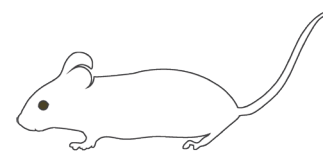
The package is fully customizable.

LakePharma's Due Diligence

To increase the probability of campaign success, LakePharma conducts rigorous target analysis utilizing bioinformatics, literature, and patent data to identify target-specific considerations that could impact discovery effort. Throughout the campaign, clients will receive data updates, enabling Chain of Discovery tracking from immunizations to mAb sequences.

Hybridoma.com

A website dedicated to the education of hybridoma-based antibody discovery. Visit the website to learn more about the technology and LakePharma's capabilities.



Hybridoma Campaigns by the Number

95+

completed discovery campaigns

97%

hit identification success rate

45+

clients served

Campaign Customization Options

Rodents

Wildtype and fully human antibody-producing transgenic mouse strains are available.

Binding and Functional Assays

LakePharma can customize epitope binning, blocking, internalization, cell assays, and more.

Immunogen Options

LakePharma can custom design and prepare antigens based on client needs.

Immunizations

A variety of immunizations are available to suit each client's project goals and timelines.

- Tolerance-breaking approaches can achieve titer against mouse targets and increase epitope diversity.
- Proprietary DNA immunogen and UberCell™ approaches can lead to high titers against challenging transmembrane targets such as GPCRs.
- Rapid protein-based approaches such as RIMMS7™ and HT-HOCK™ can achieve high titer within a short time frame.



LakePharma's PentaMice™ Platform

A Proprietary Set of Wildtype Mice Designed to Achieve Maximum Plasma Titers in Hybridoma Campaigns

Conventional immunization approaches utilized in hybridoma-based antibody discovery campaigns typically use one or two common wildtype (WT) mouse strains (e.g. Balb/c or C57Bl/6). This approach likely limits the identification of high-quality antibodies to just those target antigens that are efficiently processed and presented by a restricted major histocompatibility complex (MHC) repertoire.

LakePharma's PentaMice™ Platform is a royalty-free set of mice comprising 5 WT strains that cover 9 distinct MHC haplotypes. A total of 10 mice (2 mice of each strain) are included in each set to achieve maximum plasma titers, thus boosting the opportunity to generate high-quality antibodies *in vivo*.

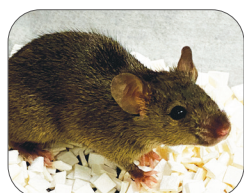
The Five Wildtype Strains in the PentaMice Platform



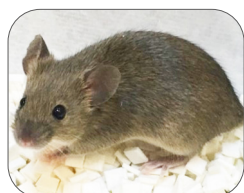
b x s



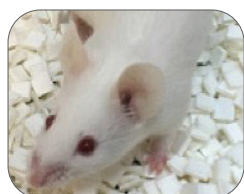
d x u



k x g7



q x v

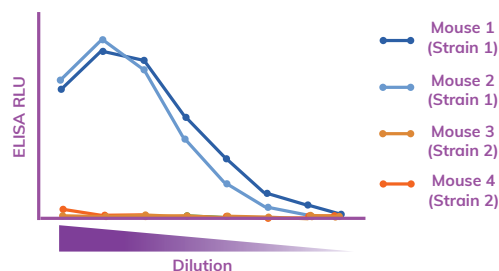


Mixed

The Concept Behind the PentaMice Platform

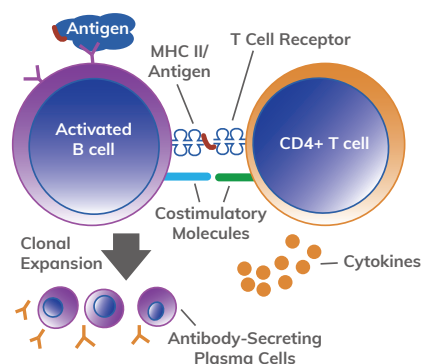
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Plasma titers are highly predictive of antibody discovery success. Based on LakePharma's experience, there is often a strong strain-dependent difference in plasma titers for most targets.



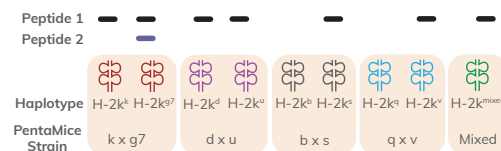
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High plasma titers require T cell help, and one of the requirements for effective T cell activation is recognition of cognate antigens presented by the MHC. Only certain peptides are effectively presented by certain MHC.



3

MHCs are highly polymorphic. LakePharma's scientists hypothesize that this polymorphism drives strain-dependent differences in plasma titers. Hence, the PentaMice Platform is designed to cover a wide range of MHC haplotypes to enable effective T cell help.



Two different peptide binding profiles are shown as examples. Peptide 1 is efficiently presented by most MHC II. Peptide 2 is only efficiently presented by H-2k^{q7}.

In vitro Display Approach for Antibody Discovery and Development



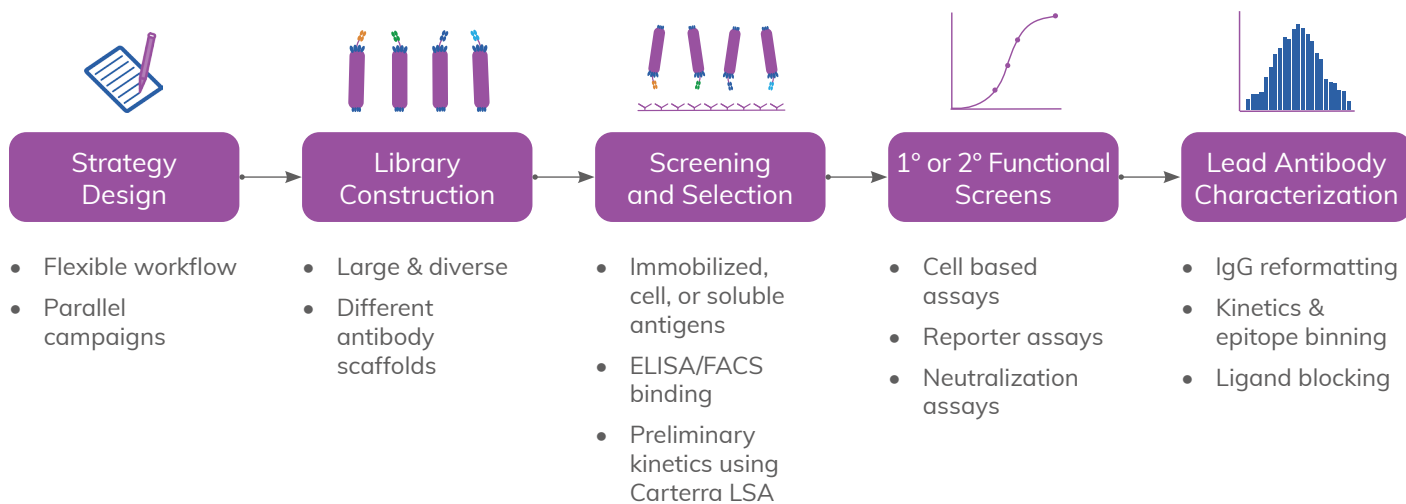
LakePharma offers various display platforms for de novo antibody discovery and engineering.

Comprehensive service includes:

- Strategy design
- Custom library construction and screening using naïve, semi-synthetic, or immune libraries of scFvs, Fabs or llama VHH
- Primary and secondary functional screens (multiple hits)
- Lead antibody characterizations:
 - Kinetics and epitope binning using Octet® or Carterra® LSA
 - Ligand blocking
 - ELISA
 - Cell assays

Engineering Projects by the Number

105+	completed projects
88%	lead identification success rate
25+	clients served



“ LakePharma was a great partner; very helpful, focused, and committed. Thank you for your antibody engineering and production services which made this project a success. ”

—ImmuNext

LakePharma Library Collections for Phage and Yeast Display

LakePharma Custom Immune Library

Antibody Formats

scFv/Fab/VHH via phage scFv
via yeast

Turnaround Time

5 months

Licensing Terms

None

LakePharma's custom immunization-based libraries are very versatile as they can be applicable to multiple species, antibody formats, and transgenic models. Utilizing patients' or animals' natural immune response coupled with the advantages of phage/yeast display platforms enables discovery of high affinity and specificity antibodies. In many cases, there is no additional need for affinity maturation.

Risk Mitigation

Early developability assessment of hits, *in silico* immunogenicity prediction, and humanization are recommended.

Applications

- Antibody discovery for therapeutics, diagnostics, and reagents purposes
- Suitable for diverse targets and antigen formats as well as CAR T generation

XOMA Human Fab and scFV Library

Antibody Formats

scFv/Fab via phage

Turnaround Time

3 months

Licensing Terms

Pre-negotiated, reduced terms

LakePharma has partnered with XOMA to provide XOMA040 scFv and XOMA031 Fab human naïve phage libraries. Both libraries have large diversity ($>10^{11}$), fully human and natural repertoire, and originate from 30 healthy donors. A wide range of high affinity antibodies can be generated without affinity maturation.

Multiple antibodies generated from XOMA libraries are in clinical trials.

Risk Mitigation

Early developability assessment of hits are recommended.

Applications

- Antibody discovery for therapeutics purposes
- Bispecifics, scFv library is suitable for CAR T generation
- Suitable for diverse targets including toxins and pathogens

Twist Biopharma Synthetic Libraries

Antibody Formats

scFv via phage

Turnaround Time

3 months

Licensing Terms

Pre-negotiated, flexible

LakePharma has partnered with Twist Biopharma to unlock the discovery of antibodies to a difficult and long-sought class of drug targets: GPCRs.

Rationally designed and empirically screened: $>100,000$ GPCR binding motifs included in synthetic scFv library, with diversity of 10^{10} . HCDR3 sequences are included, with an average length of 45 amino acids.

Risk Mitigation

Early developability assessment of hits are recommended.

Applications

- Antibody discovery for therapeutics, diagnostics, and reagent purposes
- scFv, IgG, bispecifics, CAR T
- Suitable for GPCRs

Antibody Engineering

LakePharma offers a wide portfolio of antibody engineering and optimization services.

Affinity Maturation

Increase target binding affinity via light chain shuffling or heavy and light chain CDR mutagenesis

Antibody Humanization

Modify lead antibodies to be more human-like

- Humanization analysis via LakePharma's validated platform—the T20 score analyzer

Bispecific Antibody Generation & Characterization

- Binding and functional assays
- Expression and development

Epitope Binning

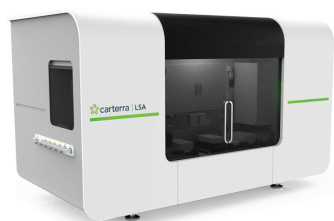
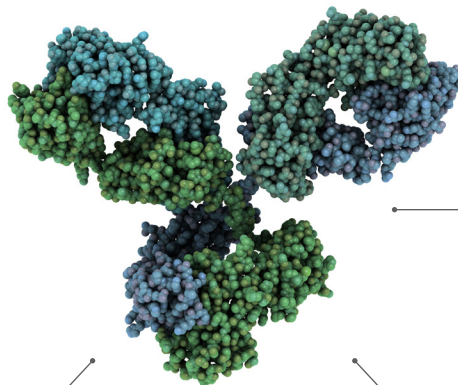
Group antibodies with similar profiles into bins specific to the same or overlapping epitopes using array SPR-based Carterra or BLI-based Octet HTX

Antibody Reformatting

Reformat different antibody scaffolds into IgGs of multiple isotypes or species

Sequence Liability Identification

Assess candidate quality by identifying sequences that can present potential liabilities to product quality



Carterra® LSA



Octet® HTX

HuMAT™ Approach

Save time and costs with LakePharma's proprietary one-step antibody humanization and affinity maturation approach.

Developability Assessment

Evaluating developability of antibodies early on can help circumvent potential development issues in downstream processes.



LakePharma offers a series of fast, small-scale tests and predictive tools to assess developability

***In silico* Developability Check**

- DNA codon preference
- Protein sequence liability analysis
- Immunogenicity analysis

Activity Check

- Affinity assays including SPR (Biacore, Carterra) or BLI (Octet)
- Epitope binning with Carterra LSA or Octet HTX
- Cell-based functional assays

PK Readiness Check

- Polyspecificity ELISA
- Surface hydrophobicity assay

Productivity Readiness Check

- Small-scale transient production in CHO system

Biophysical Profile Check

- Intact mass/peptide mapping by mass spectrometry
- Thermostability assessment by DSF or DSC
- Aggregation and purity analysis by SEC-UPLC and CE-SDS
- Biophysical profiling over various stress conditions



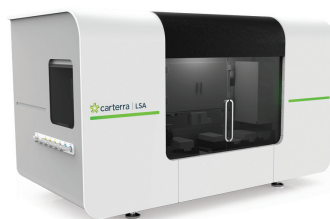
LabChip® GXII HT Touch™



NanoDSC



UNcle



Carterra LSA



Q-TOP Mass Spec

Three Developability Packages to Suit Your Needs

Rapid and Small-Scale Assessment of Drug Candidates

Developability Package 1

- *In silico* Sequence Liability analysis
- *In silico* Immunogenicity analysis
- Turnaround time: 1 week

Developability Package 2

- Polyspecificity Assessment
- Integrity and Stability Assessment
 - Aggregation
 - Purity
 - Charge Variant
 - Thermostability
 - Post-translational modifications
- Turnaround time: 2-3 weeks

Formulation and Stability Study

Developability Package 3

- Buffer Exchange
 - LakePharma standard panel formulations
 - Client may opt to choose their buffers
- Forced Degradation
 - Thermal stress
 - Freeze thaw
- Available optional stress services
 - Agitation
 - Oxidation
 - Photostability (Light)
 - pH acid/base



LakePharma's Integrated Solutions for Antibody Discovery through Development and Manufacturing

Antibody Discovery & Engineering

- Hybridoma platform for *in vivo* discovery
- Phage and yeast display for *in vitro* discovery
- Affinity maturation, humanization, and more



Antibody Sequencing

Cloning and sequencing services are available for:

- Hybridoma IgG regions from multiple species including mice, rats, rabbits, and hamsters
- Primate B cell IgG and IgM
- De novo sequencing of antibodies



Molecular Construction

Synthesis of antibody variable region, plasmid design and construction services:

- Multiple species and isotypes are available, with the option of synthesizing a custom constant region



Transient Production

CHO Transient Antibody Production

CHO cells are preferred since antibodies will maintain similar PTM profile to stable CHO cells. LakePharma's proprietary TunaCHO™ process offers:

- Productivity as high as 1.5 g/L

High-Throughput 96-Block Antibody Production

A fast and cost-effective way to produce large quantity of antibodies for fast antigen binding assays and productivity screening

- 96 antibodies can be constructed, produced, purified, and delivered in 5-7 weeks

Stable Production

Streamlined service includes stable cell line development using LakePharma's proprietary CHO-GSN™ platform for research/master cell bank generation.



Process Development

- Upstream, downstream, and analytical process development
- Assay development



GMP Production

GMP process design & development:

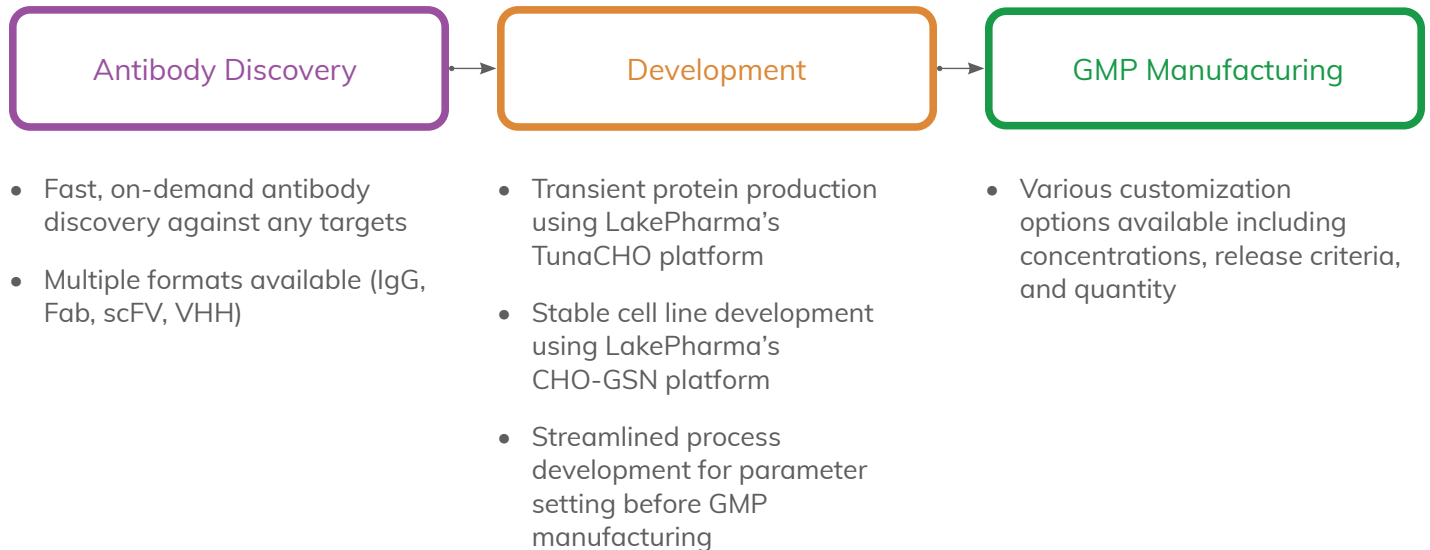
- Proof of concept
- Small-scale models
- Seamless tech transfer
- Reliable scale-up processes
- Engineering and GMP runs for DS and DP
- Release testing of DS and DP
- Stability studies for DS and DP
- Biorepository for GMP materials



LakePharma's Integrated Solutions for Discovery through Development and Manufacturing of Analyte-Specific Reagents

Analyte-specific reagents (ASRs) such as monoclonal antibodies against idiotypes, proteins, or haptens are used for identification and quantification of substances in biological specimens. LakePharma offers integrated solutions for ASR discovery, development, and GMP manufacturing, with all services performed in the Bay Area.

LakePharma Integrated Solutions



Working with LakePharma

- Complete technology platform
- Technical consultation with experts specialized in antibody discovery and development
- LakePharma's online client portal—the Data & Process Management System—allows 24/7 access to project information (timelines, data, team communications)
- Strong project management with regular project updates



LakePharma Antibody Center

LakePharma Provides Integrated Solutions for Biologics Development



Corporate Headquarters
201 Industrial Road
San Carlos, CA 94070

Tel. 650-288-4891
Tel. 888-406-5658 (Toll-free)
Fax 888-635-3618

Email inquiries@lakepharma.com
Web www.lakepharma.com

Contact Us