MARIN
BIOLOGIC
LABORATORIES, INC.

Contract Research Organization

Specializing Pre-clinical & Clinical Studies

GLP GMP Compliant CRO

Our Commitment

INNOVATIVE CLIENT LABORATORY SERVICES
TO MEET YOUR NEEDS

378 Bel Marin Keys Blvd, Novato, CA 94949 (415) 883-8000
www.marinbio.com

LETTER FROM CEO:

Dear Client,

Marin Biologic Laboratories, Inc. is a leading contract laboratory that provides collaborative and custom research, testing and manufacturing services (GMP/GLP optional) for the biotechnology, pharmaceutical, cosmetic, diagnostic and agricultural industries. We are located in our spacious, custom-designed laboratory in beautiful Marin County, California, between the Golden Gate Bridge and bucolic Napa and Sonoma vineyards. Since 1995, we have served hundreds of clients ranging from the largest pharmaceutical companies, to midsize biotechs, to virtual companies with no laboratories for whom we are their scientists, to our US and our International clients.

Our mission is to provide unparalleled client research services in the forefront of scientific innovation

Sincerely,

TANIA L. WEISS, PH.D.
PRESIDENT AND C.E.O.

TABLE OF CONTENTS

MARIN BIOLOGIC LABORATORIES

CONTRACT RESEARCH ORGANIZATION (CRO)

What distinguishes Marin Biologic from other contract laboratories is our:

- Breadth and depth of scientific knowledge
- Customized client communications
- Flexibility in meeting project demands
- Consistently on-time and on-budget
- Positive attitude
- Dependability
- Scientific excellence

CONTACT 415-883-8000

Preclinical & Clinical Laboratory

- Bioanalytical Assay Development
- Assay Validation & Qualification
- Central Laboratory Testing Services
- Cell Based Assays
- Cellular Immunology
- Immunoassays
- Biochemistry Assays
- Stem Cell Assays
- Regulatory
- *In Vitro* Toxicity
- Off-the-Shelf Assays
- Manufacturing

WITH MARIN BIOLOGIC YOU GET:

Quality output: clients rave about our unique consultative process.

Cost control: we work within your budget requirements to help you meet your bottom line.

Closed loop communications: unlike other CROs we keep you informed throughout the entire project.

Project timeliness: you have important deadlines and we meet them.

Scientific excellence: our Ph.D. scientist to research associate ratio exceeds industry standards

OUR SCIENTIFIC EXPERTISE:

We blend the fields of cell biology, immunology, molecular biology and biochemistry to tackle complex projects in an innovative and timely manner. Simultaneously, our in-depth expertise in each individual field allows for a more competent approach to complement your team of scientists.

Our Commitment

Our commitment is to deliver exceptional custom service to our commercial and academic clients at the very best rates.

Our team of scientists is known for solving challenging scientific issues by adapting scientific principles, experienced based knowledge and for our collaborative partnership with our client's scientific staff.

Many of our scientists and staff have years of experience leading many projects and their backgrounds range in multiple scientific fields of expertise., including cell biology, immunology, biochemistry, microbiology, molecular biology, and neurobiology

- Created a culture that strives for the prompt and timely communication with our clients to reach across multiple disciplines

- Perfected scientific systems and best practices that are both efficient and effective to achieve your desired goals

- Invested in a custom-designed laboratory that allows us to better control and execute on client projects

CRO Services

EFFICIENT: Often this research service is conducted as a "research" project with the understanding that it may lead into a GLP or GMP project. Thus, vendors and suppliers are always selected with the quality and sustainability required for the more rigorous laboratory or manufacturing practice.

CONSISTENT: Reagent lots are selected so that critical reagents are in sufficient supply so that there will be no change in the lot when the project progresses to development.

KNOWLEDGEABLE: If a client needs to study pharmacodynamics, such as receptor binding, intracellular metabolism, activation of secondary signals, our scientists will be able to aid in these *in vitro* studies.

CAPABLE: With a full cell culture facility and years of cell biology experience, mechanistic studies can be fully integrated into your program. We employ scientists who bridge the various fields of classical biochemistry, cell biology, immunology and molecular biology.

COLLABORATION: Our scientists can consult with you to further your research project whether it is a small segment of your program or a full-blown project.

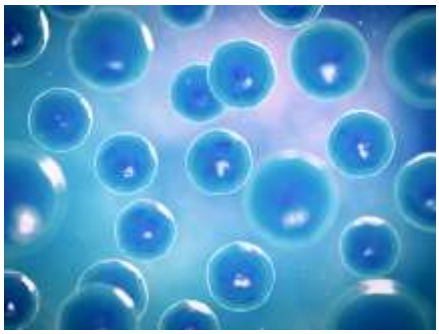
- Cell Biology & Bioassay Development
- Immunology & ELISA Development
- Biochemistry
- Molecular Biology

Projects can often require expertise in several fields to bring it to completion. For example, we may need to ensure that a large molecule drug (protein) is soluble in culture media, yet not adhere to other proteins (e.g. albumin) thus decrease it's effective concentration in a cell-based assay (*biochemistry & cell biology*).

Additionally, our scientists will determine whether the solvent used to ensure complete solubilization of a small molecule is not deleterious to the cell culture (*chemistry and cell biology*). There are projects we perform that require development of assays to detect an immune response. This requires exposing white cells to the immunogen or drug followed by measurement of the immune response (*cellular immunology, immunoassays & cell biology*).

Other projects require the cloning of genes and expression of protein in bacteria or stable expression in mammalian cells with accurate refolding of the protein (*molecular biology, cell biology & biochemistry*).

Here is a partial list of our expertise:



GLP, GMP Assay Development

- Cell Based Assays
- Cytokine, Growth Factor, Antagonist
- ELISA Assay
- Antibody, other Immunoassays
- Enzyme Assay
- Compatibility Assays
- Protein Chemistry
- Chromatography
- Cell Based Immunoassays
- Efficacy Assays
    - Drugs that are Antibodies
    - Antibody-Dependent Cellular Cytoxicity (ADCC)

- Safety Screening-Inflammatory Response
    - Inflammatory cytokines
    - Monocyte-Neutrophils Assays
- Pharmacodynamics (PD), Biomarkers
- Mechanism of Action (MOA)
- Immunomodulation
- Enhancement of Immune Response
- Host Immune Response
- Neutralizing Antibodies
- Anti-Drug Antibodies (ADA)
- Cell Based– Immunoassays

    ELISA Assay

    High Throughput Screening Assays (HTS)

    Isolation and Characterization of B&T Cells, Neutrophils, and Monocytes

    Cytokine and Receptor Analysis

    Natural Killer (NK) Activity

    RIA (Radioimmunoassay)

    Western & Dot Blot

GLP, GMP Assay Validation

- GLP, GMP
- USP, FDA, ICH Guidelines
- SOPs
- Protocols
- Tech Transfer
- Assay Development
- Assay Validation
- Sample Analysis
- Potency Assay
- Drug Release Assay
- Stability Assay
- Regulatory Support, IND, NDA
- Study Reports for Submission

PROJECT MANAGEMENT EXPERTS

What to expect from

Marin Biologic Laboratories:

FDA Application

Is yours a research-level study or is the goal to be included in an FDA submission?

Typically these projects require the development of an assay to show potency (e.g. drug release assay) or to demonstrate efficacy in an IND submission. Often a client company will need or want to demonstrate the "lack of" immunogenicity of their drug.

Our scientists will lead you through the type of assay you'll need. During these communications our scientists will discuss the pros and cons of the various approaches so that you will be able to make an informed decision.

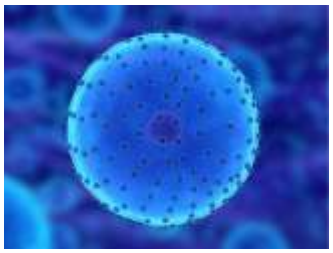
In essence we can act as your scientific consultants, though we do recommend that you obtain a regulatory consultant who will be apprised of and can coordinate

Proposal Process

We partner with you to design a fair-value proposal that meets your scientific and drug development needs.

- Jointly tease out sufficient contract detail for a successful project.
- Estimate the cost and time-line of your project.
- We can also make suggestions on how to reduce costs, such as bundling your assays by testing multiple samples at one time, thus requiring fewer assays.
- We may discuss how to enhance the precision and accuracy of the assay.
- The format and level of detail needed in your report will be set to meet your project needs.
- Marin Biologic will have staff assigned and a timeline set when you are ready to start the project.
- Your signed contract and retainer to cover upfront expenses (supplies and some labor) will initiate your project!

Project Management



KICKOFF:

After the project is initiated, the typical course of events will start with samples being shipped to Marin Biologic. From there...

- You inform us when to expect the sample.
- For GLP & GMP projects, a chain of custody form will be submitted with Certificates of Analysis and a list of all the samples.
- The samples will be logged in to provide traceability and stored at the required temperature.
- A project manager/scientist will be assigned to your project and will frequently communicate the progress of the project.

COMMUNICATION:

As decisions are made during the course of a project you will be kept informed of progress. You dial in how informed you want to be on each project. For example, on very complicated experiments we can transmit the data after every experiment. Or, if you want to be less involved, we will make sound scientific judgments as the project progresses and just keep you informed. If we are waiting to expand cells or waiting for reagents we will of course provide you with an update.

FINAL REPORT:

At the conclusion of the project a final report will be submitted for your review, as per the original proposal. Should additional reporting be required, we can always accommodate such requests. Your report will be submitted electronically, except for GLP/GMP projects where they are submitted in writing.

Our scientists at MBL are here to facilitate your comprehension of the data and report. It is difficult to know all the innuendos when you are not designing plate maps and dilution schemes yourself. If your level of involvement is at this level we will be happy to accommodate this degree of interaction. On the other hand, if you wish to be apprised of the results only, we will gladly send data and summarize the results for you too.

At the conclusion of the project if you need further assistance, we will be happy to provide it. In those cases where we are called up to represent our client in data discussions with the FDA, know that we observe strict confidentiality and formality in those situations.

Complex Projects

Because of our high Ph.D. to research assistant ratio, 1:2, Marin Biologic is able to successfully complete complex projects. We have Ph.D. expertise that spans the area of cell biology, biochemistry, molecular biology, and immunology. This enables our experienced scientist to work with complex biomolecules, to be cognizant of solubility and stability including -thaw and other methods to ensure no change in reactivity during transit from clinical cites to a central testing lab such as Marin Biologic.

Assay development performed at Marin Biologic includes a wide variety of assays, whether cell-based receptor binding or other modalities of activity (e.g. cell signaling), interaction with biomolecules, effective concentration and potency determination.

We routinely perform inhibition of enhancement generate cGMP cell banks for future use. Some assays have included receptor binding in membranes of cells, equilibrium dialysis, phosphorylation or receptor, adsorption onto substratum or serum proteins, or activation of immune cells.

We have phlebotomists on call to help us obtain white blood cells. We have cloned difficult DNA sequences that are large and optimized expression and restabilized (refolded) those found in inclusion bodies. We have purified protein to homogeneity.

Since our scientists are experienced PhD's, working with experienced research associates, we can efficiently and successfully take your project to completion.

Assay Development and Validation

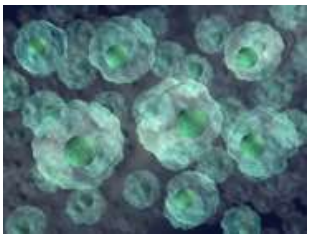
In our assay projects we typically analyze a positive and negative controls and some assays require a dose-response curve or are a cut point assay. We develop assays with the knowledge that it will be validated. Only reputable reagent vendors are used, and if needed a backup vendor for critical reagents are identified.

As the assay development nears completion, Quality Control (QC) Standards will be discussed with you and enough produced to last through validation and sample analysis. During this stage it will be decided whether single use aliquots will be manufactured and stability of critical reagents need to be studied.

Critical reagents such as serum for cell based assays or animal / human serum for the QC matrix will be determined with you and sufficient amount purchased to last the study lifetime.

Our scientists act as your consults, making recommendations and allowing you the final decision. On the other hand, if you wish to be much less involved our scientist can carry out the entire project with your outlined goal in mind. Once the development is completed prevalidation will allow our scientist to determine whether the assay's final format is ready to pass validation.

Once the assay is ready for validation, a protocol will be written and submitted to you for approval. Frequently there will be a small section citing the history of the project which our scientist — will help you to undertake while you are reviewing the protocol. During this time the SOPs and batch records will be written.



Once the laboratory work commences plan on about two weeks for the ELISA, to about 1-2 months for a cell based assay. For immunoassays the time line around 2-3 week period, since primary cells are utilized.

Marin Biologic has a registry of blood donors it successfully uses for its immunoassay. After validation data and a report will be delivered to you after a QC review. Any changes you wish to make happen at this juncture and final regulatory QA review is undertaken prior to issuing the final report. The validation report can be customized to your format.

Central Laboratory

Marin Biologic has experts as a central laboratory performing assays on our client's pharmacokinetic samples and human clinical samples. We interface with individual clinical sites or your clinical studies director to receive samples.

We will arrange with your clinical studies director to have a chain of custody form ready. We need a hard copy and an excel copy of the samples ID numbers/letters as the number is frequently in the multi hundreds or low thousands. We will discuss with you how the samples will be analyzed.

Some clients want all samples from the same project including the pre-dose sample to be analyzed together at one time. Marin Biologic is a custom laboratory and will accommodate your requests and needs with uncompromised scientific quality.

For drug release assays, if available, one lot of drug will become the gold study against which all future lots will be measured for assay development and validation. If no gold standard is available then 2 lots will be used.

Marin Biologic Laboratories Vast Experience

Let our experienced Scientists help you get *FDA Approval* by performing analysis with analytical instruments and methods for your Early Drug Development, Phase I, II and III Clinical Trials.

- Assay Development
- GLP, GMP Assay Validation
- Potency & Drug Release Assay

Feel free to request the CVs of our experienced Scientific and Regulatory Team

Please call us for a free quote and consultation with our Scientists. No obligation.

Get references and testimonials of our work from our clients.

Call for our Accreditation Documents.

Make an appointment to visit our facility and site.

MEET OUR SCIENTISTS

Tania L.Weiss, Ph.D.

Marin Biologic Laboratories, Founder & CEO

From her Research Experiences, including:

Built & staffed own academic research laboratory at UCSF and company laboratory at Marin Biologic, trained post doctoral fellows/students, managed multi-laboratory collaboration, organized seminars/courses, lectured, wrote grants/publications. Developed two compartment endothelial cell models for drug delivery mimicking arteries. Purified and characterized novel angiotensin protease. Oligonucleotide Therapeutics (Cancer, HLA, Proliferation): Designed oligos, developed cellular models, developed methods for enhanced cellular deliver, oligo stability and studied mechanism of action which culminated in patents. Studied cellular recognition in cerebral histogenesis.Developed hybridomas, ELISA, HPLC and bioassays. Developed hollow fiber bioreactor cell culture for production of proteins. Developed immunology laboratory, immunology support services for a consulting company. Created and implemented immunology business program and customer support services.

To her Industry Experiences: 1995-present

Marin Biologic Laboratories, Inc.

President and C.E.O., Founder Marin Biologic Laboratories, Inc., Contract Research & Manufacturing.

Funded laboratory equipment acquisition. Located, designed, built-out, and set up facilities including laboratories, tissue culture laboratory and offices. Developed initial client base, identified laboratory service niches culminating in a catalog of services. Instituted procedures for client bidding and project management. Performed and managed scientific projects including NIH grant funded research.

Peter Ralph, PhD

Marin Biologic Laboratories, Vice President of Scientifc Affairs

Distinguished academic career at the Salk Institute for Biological Studies and Memorial Sloan Kettering Cancer Center in immunology, hematopoiesis and cancer biology. Over 120 scientifically reviewed papers and 24 issued patents. Developed and patented method to detect Herceptin, and was the developer of the biometric GLP potency assay for Rituximab. Managed over 100 projects for clients at Marin Biologic Laboratories.

Education

BA, Yale University, Physics

MS, University of California, Berkley CA, Physics

Ph.D., Massachusetts Institute of Technology, Biology

Experience

Marin Biologic Laboratories, Novato, CA 2001- Present

Vice President, Scientific Affairs March 2010

Head, QA

GENENTECH Inc., South San Francisco, CA

Senior Scientist, Depart of BioAnalytical Sciences

Director, Department of Immunology

CETUS Corporation, Emeryville, CA

Senior Director, Research Division; Head, Immune Suppression Project Manager, M-CSF Project; Senior Scientist, Director, Department of Cell Biology

Sloan-Kettering Institute for Cancer Research, Rye. NY

Associate Member; Associate,

Department of Hematopoiesis

Cornell Medical School, New York, NY

Associate Professor; Assistant Professor

CRO Preclinical and Clinical Assay

BIOANALYTICAL ASSAY DEVELOPMENT

Marin Biologic provides a wide variety of bioanalytical assay development for small and large molecules that includes potency for drug release, in vitro toxicology, methods requiring antibody recognition, pharmacokinetics (PK) drug binding studies, and patient immune responses to drugs

Assay development requires sensitive, accurate and reproducible assays.

New fully-equipped laboratory facility to handle your most urgent project

Quick turnaround time for your bioanalytical assay development

Expertise in multiple areas, such as biochemistry (for large molecule drugs or excipients) and cell biology (for potency assays)

Experienced Scientists and Staff Proven success to help you meet your goals.

Our scientists have also improved on previously developed assays, such as sensitivity, selectivity, enhance signal to noise, and extractions. Depending upon your requirements, different levels of bioanalytical assay development will be performed:

- Initial assay
- More optimized assay
- GLP/GMP validated assay, suitable for submission to the FDA for an IND or NDA filing.
- MSD, Meso Scale Discovery platform for increased sensitivity, expanded range and decreased matrix effects.

ASSAY VALIDATION, DEVELOPMENT AND QUALIFICATION

Marin Biologic offers assay validation and assay qualification services to meet your unique needs.

Our validation services support your IND and NDA applications to the FDA. The assay validation services include validation of small and large molecules used as Active Pharmaceutical Ingredient (API), formulations, and finished pharmaceutical and biopharmaceutical products. Marin Biologic has validated assays used for:

- Preclinical and clinical trials,
- Pharmacokinetic (PK) studies,
- Anti-drug antibody (ADA) assays and biomarker studies, and
- Potency studies and quantitative detection of manufactured product.

The quality assurance support of our validation services ensures accurate and precise data collection and reporting. Because our services are customized to your needs, the format of your data can be easily incorporated into your statistical data sheet for your analysis.

Assay qualification services are available for those projects not yet ready for full validation.

HOW CAN I INITIATE AN ASSAY? VALIDATION?

Prior to the beginning of the project, our scientist/ project manager will communicate with you about the format of the data collection (e.g. EC50, 4 parameter curve fit, cut point assay, parallel line analysis, Quality Control Standards), the time lines of your project and any additional issues that need addressing.

During the validation project, a protocol will be submitted to you for approval prior to the start of the laboratory work. Once the data are collected and discussed, a validation report will be written and submitted for approval.

Variables that are included in the validation are:

Accuracy
Precision (e.g. within plate, between plates, between days-intermediate precision)
Specificity (Selectivity)/ Interference
Linearity
Range
LLOQ (Lower Limit of Quantification),
LLOD (Lower Limit of Detection)
ULOQ (Upper Limit of Quantification)
Quality Control (QC) Standards
Stability
Ruggedness

CELL BASED ASSAYS

More than 20 years experience in cell biology and cell culture enables our staff at Marin Biologic to employ both the scientific approach and the "art" of cell culture to your projects.

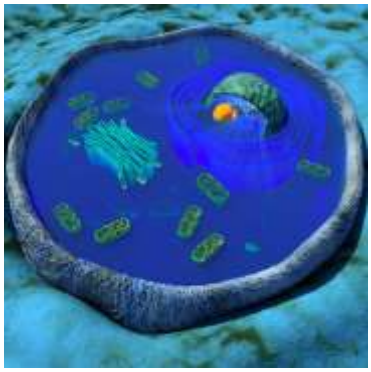
We can recommend strategies and provide contract services for cell-based assays, tissue culture, cell culture optimization, bioassays including stem cells and protein expression systems for large-scale tis-

CELL-BASED ASSAY, BIOASSAY DEVELOP-

Cell-based assay or bioassay development can range from cytotoxic assays including apoptosis to cell proliferation and metabolic assays.

Cell-based assay development can also include high throughput screening assays and other custom bioassays used to characterize drug stability for GLP GMP lot release, drug potency and for drug purification and production support.

Mechanisms of action, such as receptor binding, receptor activation, cell signaling, drug internalization and subcellular localization can be delineated in cell-based assays following treatment with your pharmaceuticals.



CUSTOM CELL CULTURE

Custom cell culture can be performed for your cells, whether it is primary explants, cloning and optimizing expression of a cell line or developing the optimum medium, to include serum-free medium. Large scale cell cultures using bioreactors can be implemented for production of your specific protein. Additionally purification of your protein can be performed from either the cells

PROTEIN EXPRESSION

Using mammalian or insect cell cultures, our scientists can manufacture proteins on a 100 gram level. Our staff can provide cell pellets, conditioned media or membrane preparations. With our experience in classical protein purification and we can optimize your protein expression and production. Our scientists are very experienced in transfection and stable cell line generation.

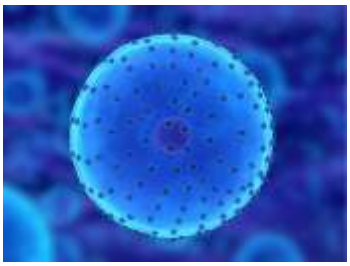
CELLULAR IMMUNOLOGY

CELL-BASED IMMUNOASSAY ▪ DRUG EFFICACY ▪ SAFETY SCREENEING ▪ INFLAMMATORY RESPONSE ▪ INFLAMMATION HOST IMMUNE RESPONSE ▪ BIOMARKERS ▪ POTENCY- EFFICACY

(CELL-BASED IMMUNOASSAYS)

Many of our clients develop pharmaceuticals that require cell-based immunoassays to measure an immune response. We can test sera not only for IgG or other antibody isotype responses, but can also determine whether cell activation is involved by using cell-based immunoassays such as the mixed lymphocyte reaction (MLR) or natural killer cell activation.

We can determine for toxicity studies whether cytotoxic T lymphocytes have been sensitized to your drug or whether the immune system cells have been activated by the detection of released cytokines or the presence of a specific cellular receptor



OUR EXPERTISE IN CELL BIOLOGY

Our expertise in cell biology enables us to develop, validate and perform cell-based assays from primary tissue, such as bone marrow, spleen, blood, as well as with culture cell lines.

These assays can be performed as “research level” assays or can be developed and validated as GMP or GLP assays. Once the assay is developed and validated, then your preclinical or clinical samples can be analyzed).

- Efficacy, Potency, GMP Lot Release
- Safety – Inflammatory response, Inflammation
- Pharmacodynamics (PD), Biomarkers
- Mechanism of Action (MOA), Immunomodulation
- Host immune response, Neutralizing antibodies, Antidrug Antibodies (ADA)

There is a menu of assays that can be used to select the appropriate assay for your specific use. Examples of uses would include:

- Targeting specific cells using antibodies or other moieties (as in cancer drug development)
- Determine whether drugs cause inflammation when administered to animals in PK studies or in people in their preclinical or clinical studies
- Cell-based assays used for drugs that are designed to modulate the immune system, or to detect host antibodies against a drug that neutralize its activity.

CELL BASED ASSAY DEVELOPMENT

Cell-Based Assay Development

- High Throughput Screening Assays (HTS)
- MSD, Meso Scale Discovery platform
- Stem Cell Differentiation
- Cell Proliferation
- Cell Death (Necrosis vs. Apoptosis)
- Cell Metabolism and Protein Turnover
- Molecular Labeling (Radioactive, Fluorescent, Colorimetric)
- Other Cell Biological Assays
- Analysis of Subcellular Fractions for Activity
- Flow Cytometry
- Phase and Fluorescence Microscopy
- Cell Receptor Binding, Activation and Turnover
- Cell Signaling and Downstream Events
- Immunocytochemistry
- Reporter Gene Assays

Drug Action On Cells

- Functional Assay including:
  Receptor Mediated Transport
  Enzyme Inhibition and Activation
  Translation, Transcription, Metabolism
- Cell Proliferation, Cytostatic or Cytotoxic Effects
- Stem Cell Expression
- Receptor Binding and Activation

Tissue Culture

- Cell lines
  Wild Type and Transfected
- Primary Cell Isolation and Culture
- Stem Cell Culture
- Adherent & Suspension Cell Cultures
- High Cell Density Tissue Culture Media Optimization, Serum-Free Adaptation
- Cell Culture Systems:
  Static, Roller Bottle, Membrane, Porous Bead, Hollow Fiber Bioreactor, Glass, Plastic
- Cell Cloning and Selection
- DNATransfection
- Protein Production in Scale-Up Bioreactors

Drug, DNA, RNA Delivery
Drug Metabolism

- Receptor and Protein Mediated Transport
- Transient and Stable Transfection
- Electroporation
- Subcellular Localization
- Mechanisms of Internalization

HOST IMMUNE RESPONSE, NEUTRALIZING ANTIBODIES, ANTI-DRUG ANTIBODIES (ADA)

It is important to determine if your drug is eliciting host antibodies, as measured by ELISA, and particularly if any antibodies neutralize the action of the drug. In recent years, the FDA has been very vigilant about monitoring animal and clinical trials for these possibilities.

Human or humanized products are likely to be immunogenic in animal studies, and the FDA expects findings of this. Total antibodies can affect the pharmacokinetics (PK) or toxicokinetics (TK) of the drug in animals, thus impacting toxicology studies. Neutralizing antibodies can limit toxic effects and also activity in efficacy trials. In addition, the chance of anaphylaxis is if particular FDA concern, and is measured by the IgE class of antibodies.

This partial list indicates the techniques we perform.

Cell-Based Immunoassay

- ELISA Assay
- High Throughput Screening Assays (HTS)
- Isolation and Characterization of B & T Cells, Neutrophils, Monocytes
- Mixed Lymphocyte Reaction (MLR)
- Cytokine and Receptor Analysis
- Natural Killer (NK) Activity
- RIA (Radioimmunoassay)
- Western & Dot Blot

EFFICACY STUDIES

Drugs that are Antibodies If your drug is an antibody and you want the antibody to kill a mammalian target cells, then the Antibody Dependent Cellular Cytotoxicity (ADCC) Assay is appropriate. If your antibody drug kills target cells using complement, then the Complement-Mediated Cytotoxicity (CMC) Assay is appropriate.

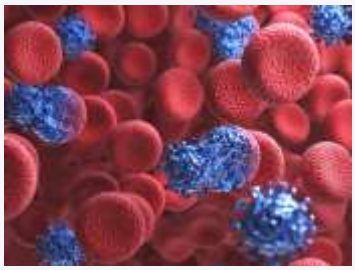
Antibody-Dependent Cellular Cytoxicity (ADCC) This assay determines the ability of an antibody to kill target cells, for example, a class of tumor cells, in the presence certain lymphocytes (NK or K cells) or other effector cells.

Complement-Mediated Cytotoxicity (CMC) This assay determines the ability of an antibody to kill target cells, such as a class of tumor cells, in the presence of a group of protein enzymes in the blood known as complement.

SAFETY SCREENING–INFLAMMATORY RESPONSE-INFLAMMATION If you are concerned about the safety of your drug, or a trace, contaminating microbial product, and want to determine whether it causes inflammation, the production of inflammatory cytokines or monocyte-granulocyte inflammatory mediators are applicable.

Monocyte-Neutrophil Assays In addition to assays with lymphocytes, we perform studies on nitric oxide (NO), reactive oxygen intermediates (ROI), prostaglandin related molecules, cytokine release, and other activation states of monocytes, macrophages and neutrophils.

IMMUNOASSAYS



ELISA ASSAY DEVELOPMENT ▪ MONOCLONAL ANTIBODY DEVELOPMENT

ELISA (ENZYME LINKED IMMUNO-SORBANT ASSAY)

ELISA technology can be used for preclinical or clinical PK studies and for detection of host anti-drug antibodies (ADA), Some purposes and methodologies include:

- GMP lot release assay,
- affinity (Kd) measurements,
- quantitation of cytokines or other proteins produced by cells or in the body,
- triggering of signal transduction as detected by phosphorylated receptors, and other purposes.

At Marin Biologic, we have:

- Employed optical, fluorescent, luminescent, time-resolved and radioimmune (RIA) detection methods using either monoclonal or polyclonal antibodies.
- Proprietary methods:
- For reducing the background in complex matrix such as serum, plasma, or tissue extracts, and for
- Removing interferences such as analyte binding to proteins and receptors or interfering host antibodies of various types.
- Developed over 60 ELISAs, starting with producing our own monoclonal antibodies and polyclonal antibodies or screening commercial sources, and
- Validated over 30 methods for GLP or GMP use.

This partial list indicates the techniques we perform :

Polyclonial Antibody Purification and Characterization

- Affinity Chromatography
- Ion Exchange Chromatography, HPLC (see Biochemistry)
- Electrophoresis
- Ig Class Identification and Affinity
- Epitope Mapping

Monoclonal Antibodies

- Hybridoma Production and Cloning
- Monoclonal Antibody Production
- Monoclonal Antibody Assay Development
- Monoclonal Antibody Manufacture
  Hollow Fiber Reactor
  Suspension Culture
  (mg to 100 g level)
- Monoclonal Purification (see Biochemistry)

Antigen Conjugation / Antibody Derivatives

- Peptides and Haptens
- Biotin, Fluorochrome
- Enzyme
- Radiolabel Conjugates
- Fab, $F(ab')_2$ Derivatives

BIOCHEMISTRY

ELISA TEST ▪ ENZYME ASSAY ▪ PROTEIN PRODUCTION, PURIFICATION, ANALYSIS

BIOCHEMISTRY OVERVIEW

Marin Biologic's scientists are classically trained biochemists with extensive experience in protein purification, characterization and analysis. We have purified native proteins to homogeneity isolated from cell culture and tissue as well as recombinant proteins from bacteria and mammalian cells and from baculovirus infected insect cells.

ELISA TEST

Frequently, we are asked to develop an ELISA test to quantify specific proteins or small molecules (metabolites) for a cell-based assay. We will work with you to develop or to in-source a commercially available ELISA test or other immunoassaysthat will quantitatively detect your molecule. Our scientists will consult with you and discuss the most efficient strategies that can be employed. Should you need specific monoclonal antibodies to use in your ELISA test, we can generate the hybridomas and pro-

ENZYME ASSAY

Enzyme assays have been used to monitor protein purification and production. If your pharmaceutical is an enzyme inhibitor, we have used enzyme assays to characterize drug potency and measure drug concentration. Some of the enzyme assays we have developed are used for drug

PROTEIN PRODUCTION, PURIFICATION, ANALYSIS

Our scientists will consult with you on optimizing protein production, protein purification and analytical analysis. If your protein is generated via recombinant methods, we will employ the appropriate affinity methods of purification.

Should you wish a homogeneously purified protein, we will discuss the strategies with you prior to final purification. Of course, if you have a protein purification strategy, we will gladly employ your purification scheme. With many of the protein purification protocols, we will develop a purification scheme to monitor increase in yields and specific activity.

Should you not have a method to quantitate protein activity; our scientists will consult with you about assay development.

The following is a partial list of Biochemistry techniques:

Protein Production and Purification

- Protein Production

  Secreted or Intracellular
  Animal, Baculovirus, Bacterial
- Protein Purification
  Salt Fractionation
  Chromatography: HPLC and Liquid
  Gel Filtration, Affinity, Ion Exchange,
  Reverse Phase, Hydrophobic
- Stable Formulation Development

Protein Analysis

- Concentration
- Electrophoresis
  SDS-PAGE, Nondenaturing, Isoelectric Focusing
- Chromatography
  RP-HPLC, Size Exclusion
- Binding, Receptor Assays
- K_d, Scatchard Analysis
- Amino Acid Analysis and Sequence
- Carbohydrate Analysis
- Equilibrium Dialysis
- Solubility
- Bioassays (See Cell Biology)

Enzyme Assay and Immunochemistry

- Assay Development
  Colorimetric, Fluorescent, Radiometric
  Substrate Specificity
  Inhibitor Kinetics
- High Throughput Screening (HTS) Assays
- Enzyme Stability
- Immunoassays
  ELISA test, RIA, Western Blot
- Immunoprecipitation
- Immunohistochemistry

Other Biochemistry Methods

- Data Base Characterization
- Endotoxin
- Centrifugation, Ultra, Gradient, High Speed
- Detergent Solubility for Membrane Extraction

STEM CELL

STEM CELL OVERVIEW

Stem cell therapy development is an exciting area of research that promises the future treatment of many diseases. Since this area in drug development is in its infancy, there are many hurdles to overcome. T

The scientists at Marin Biologic are here to assist you in the many phases of your stem cell therapy development. We can culture adult or embryonic stem cells and monitor the differentiation markers for your therapy development. Please think of Marin Biologic as your stem cell research laboratory.

Many scientific considerations are involved with stem cell replacement therapy. We can aid you in the following scientific endeavors; microenvironment, transfecting markers into adult or embryonic stem cells, replacement of specific molecules, etc.

Microenvironment may contribute to stem cell "homing" events or differentiation. Our scientists can study microenvironments, whether generated in culture or from exogenous tissue, and their effects on stem cell differentiation using *in vitro* methods.

Transfecting adult or embryonic stem cells with a genetic marker to follow their "homing activities" can be performed prior to inoculation *in vivo*. Development of "homing" stem cells as a delivery vehicle for cancer therapy can be undertaken at Marin Biologic.

Replacement therapy for hormone, cytokines and metabolic intermediates can be implemented using stem cell therapy. Insulin production is a key target for diabetes therapy using stem cells because of their "normal" detection of glucose levels and "normal" synthesis and release of insulin. Our scientists can help you to develop stems cells that synthesize your therapeutic molecule by initiating differentiation and monitoring specific production.

To implement stem cell therapy, there must be many levels of investigation ranging from the cell culture of stem cells, triggering differentiation, expanding stem cell cultures to large scale cultures for replacement therapy, determining whether immunocompatibility of embryonic stem cells is retained for transplant, down regulating HLA molecules in adult stem cells, etc.

The scientists at Marin Biologic are very experienced and creative in cell biology and can bridge this field with molecular biology and biochemistry for potential cell therapy and assay development.

REGULATORY
GLP, GMP COMPLIANT

REGULATORY OVERVIEW

Marin Biologic Laboratories is a contract research organization - CRO - performing GLP and GMP laboratory services. We have extensive experience in assay development and validation for new drug substances and drug products for biologics. Assay development for GLP and GMP studies as well as GLP and GMP assay support is performed for lot release, sample analysis, IND, BLA and NDA submissions.

ASSAY DEVELOPMENT

If you need assay development or simply to transfer an assay to a contract research organization - CRO - to analyze samples for FDA submissions, we will work with you to meet your long term needs, whether or not it requires GLP, GMP compliance.

GLP, GMP ASSAY VALIDATION

Once the parameters and range are set during the assay development or transfer, we will discuss with you the number of experiments necessary to show linearity, accuracy, precision, specificity, robustness, ruggedness and system suitability.

POTENCY ASSAY, DRUG RELEASE ASSAY

If we have developed and validated your potency assay, whether it be a cell-based assay, enzyme assay, ELISA assay or some other assay, and you have accepted the final report, we can begin to analyze your samples under GLP or GMP compliance.

This is a partial list representing our expertise:

GLP, GMP Assay Development

Cell Based Assays
Cytokine, Growth Factor, Antagonist
ELISA Assay
Antibody, other Immunoassays
Enzyme Assay
Compatibility Assays
Protein Chemistry
Chromatography

Molecular Biology

GLP, GMP Assay Validation
GLP, GMP Support

- GLP, GMP
- USP, FDA, ICH Guidelines
- SOPs
- Protocols
- Tech Transfer
- Assay Development
- Assay Validation
- Sample Analysis
- Potency Assay
- Drug Release Assay
- Stability Assay
- Regulatory Support, IND, NDA
- Study Reports for Submission

IN VITRO TOXICOLOGY

Apoptosis ▪ Cell Growth ▪ Cytotoxicity Assay

IN VITRO TOXICOLOGY OVERVIEW Marin Biologic performs a variety of in vitro toxicity tests and assays. We offer a number of assays performed under strict GLP and GMP compliance with FDA and EPA guidelines. and biochemical techniques.

APOPTOSIS You may want to know whether your drug candidates demonstrate cytotoxicity through apoptosis or necrosis.

We will measure different parameters for apoptosis compared to necrosis. We will discuss with you parameters such as drug concentration, time of exposure, measurement of DNA fragmentation in order to customize your in vitro cytotoxicity assay.

CELL GROWTH Another measure of cytotoxicity is the inhibition of cell growth or proliferation. No one mechanism may be responsible for this observation, however, proliferation rates can be measured as a response to drug concentration.

Some drugs may have a threshold level rather than a linear response for inhibition of cell growth. We will discuss parameters such as optimal target cell line, drug concentration, drug exposure time and drug delivery to customize your in vitro cytotoxicity assay.

A partial list of assays is listed below.

Cellular

- Mitogenesis, Proliferation Rates (
- Inhibition of Growth (FDA Guidelines)
- Adherence
- Morphology
- Apoptosis
- Protein Synthesis
- DNA, RNA Synthesis

Gene Mutation and Cell Transformation

- Bacterial Assays
- Mammalian Cell Assays

Toxicity

- Cr^{51} Release
- Protein Metabolism
- DNA Synthesis
- RNA Synthesis
- Dose Range-Finding Investigation
- Hemolysis

IN VITRO TOXICOLOGY

Viral Removal

- Plaque Titering Assay

in vitro Cytogenetics

- Cell Cycle Kinetics

Other Methods

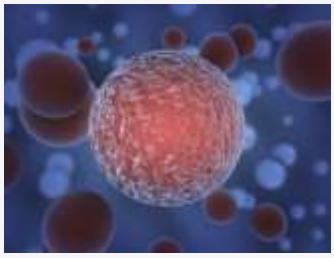
- Cytokine Release
- Bacterial Endotoxin (LAL)
- Determine Toxicity Mechanisms
- Elucidate Potential Cytotoxicities in Target Tissues
- Drug Screening to Prevent Cytotoxicity
- Cytochrome P450 Induction Studies

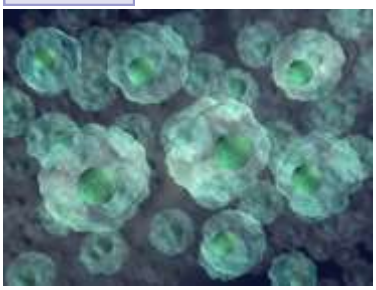
PATENT PROTECTION AND LITIGATION SUPPORT

We are Marin Biologic have helped other pharmaceutical and biotechnology companies to protect and defend their patents.

- Add value (product equity) to your drug by successfully defending against litigation
- Benefit from a cost-effective contract research team to work with your legal advisors to perform scientific research.
- Increase your odds of winning by working with an experienced and flexible litigation-support scientific research team.

Marin Biologic has been able to aid law firms involved in patent litigation to successfully prove their case. Written and electronic records and emails are kept to a minimum, if needed, and do not contain conclusions, suggestions or opinions if directed by our legal clients.





FREQUENTLY ASKED QUESTIONS

What markets does Marin Biologic Laboratories serve?
We provide services to the Pharmaceutical, Biotechnology,Legal, Agricultural, Environmental and Academic Research Communities. Our client base is broad , both in the US and in the International communities.

Have you ever been inspected by the FDA? Yes. Marin Biologic Laboratories is in full compliance with the FDA. Copies of these reports and compliance documents are available upon request.

What are your certifications and accreditations?
Please refer to the Accreditations page.

How can I obtain a quote or request a consultation with a Scientist Simply contact us at our website at www.marinbio.com and request a quote. You can also go to Contacts or call us directly at (415)883-8000. Please feel to contact us via email at marinbio378@marinbio.com.

What kind of turnaround time can I expect?
MBL makes a great effort to process your project request and engage with our clients to ensure deadlines are met. Our dedicated team of Scientists is available whenever any questions might arise with your project(s).

Is your company set up to work with human serum and cell samples? Yes. MBL has many years of experience working with both human serum and cell samples. Our trained employees follow cGMP laboratory procedures and have been trained to handle the complexity of your samples.

Where are you located? We are located at 378 Bel Marin Keys, Novato CA 94949, in Marin County USA. For more detailed directions to our facility, please go to our website www.marinbio.com.

What's New at Marin Biologic Laboratories? Please visit us at our new and updated website at www.marinbio.com. We are a growing and would like to stay in touch with you all. Follow us at Linked-In, request our newsletters, and call our Business Development Team if you have any comments or suggestions for us.

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