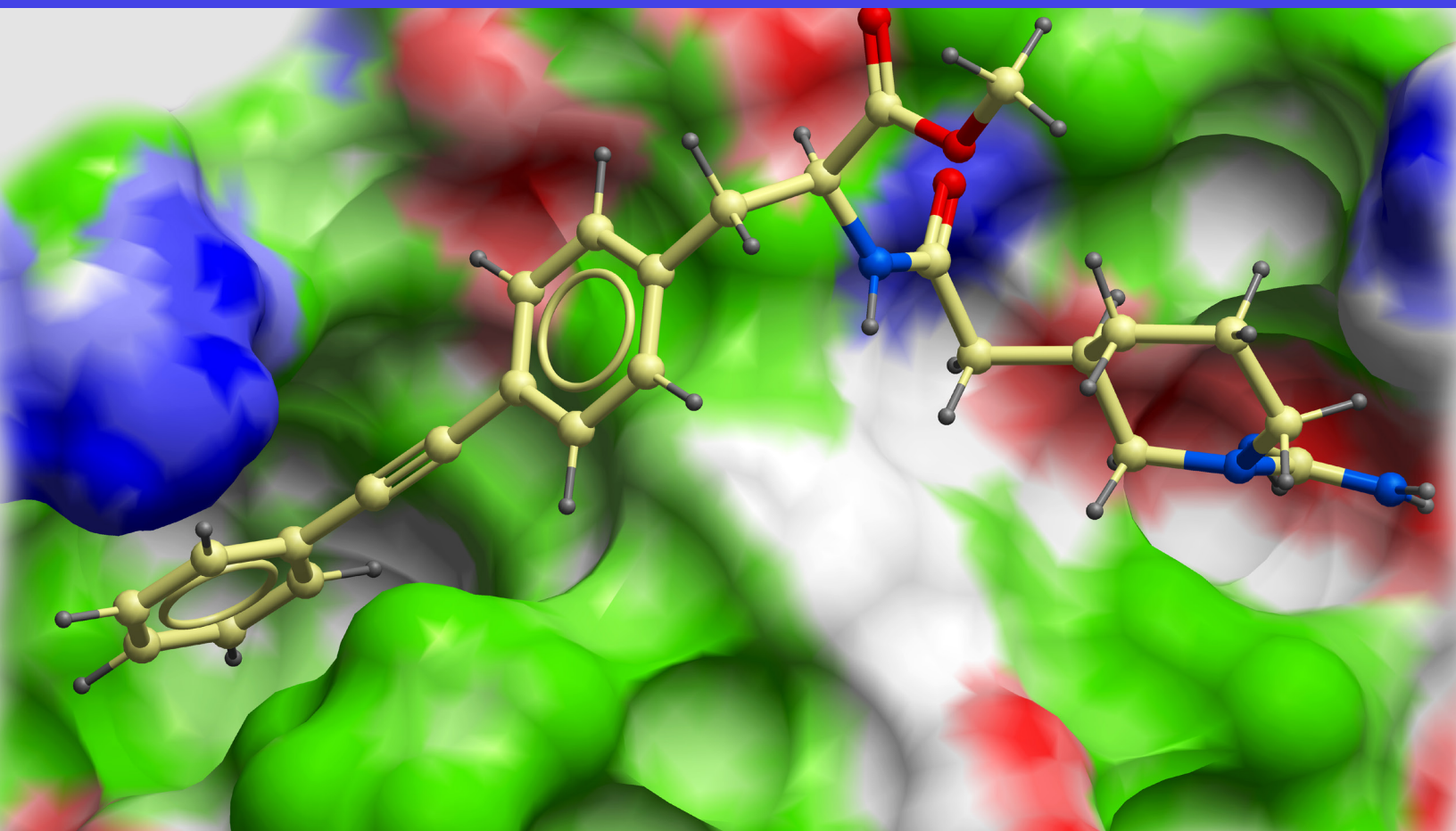
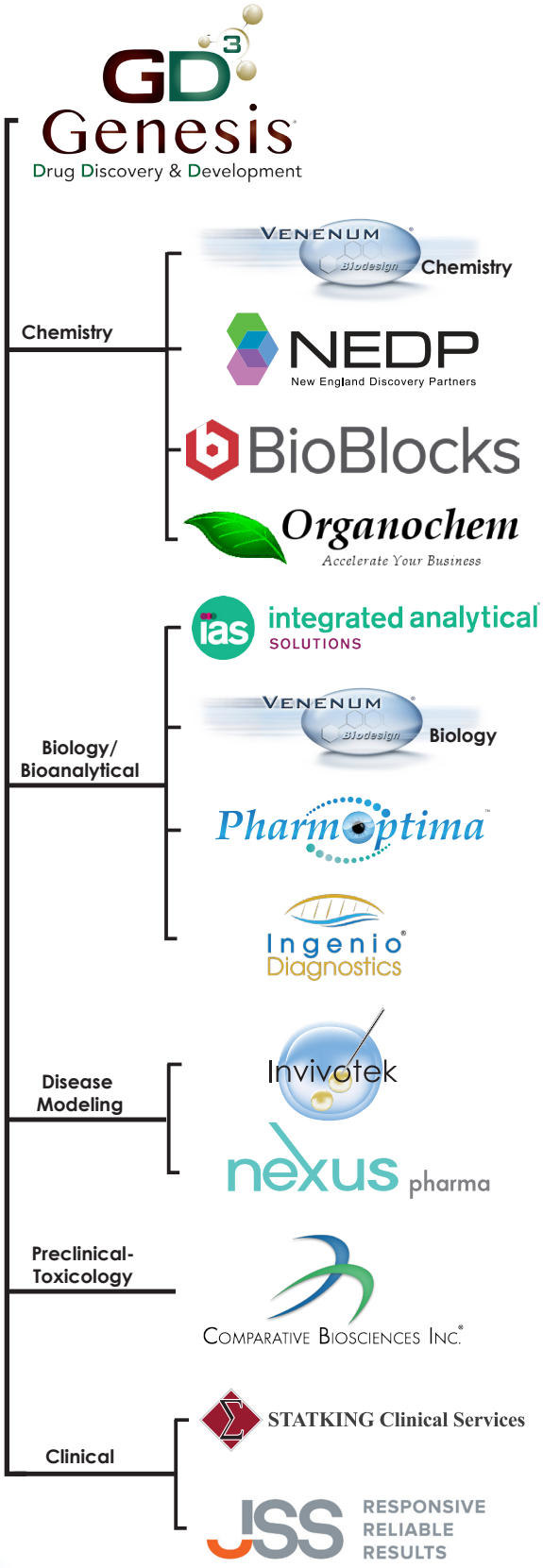
VENENUM®

Biodesign

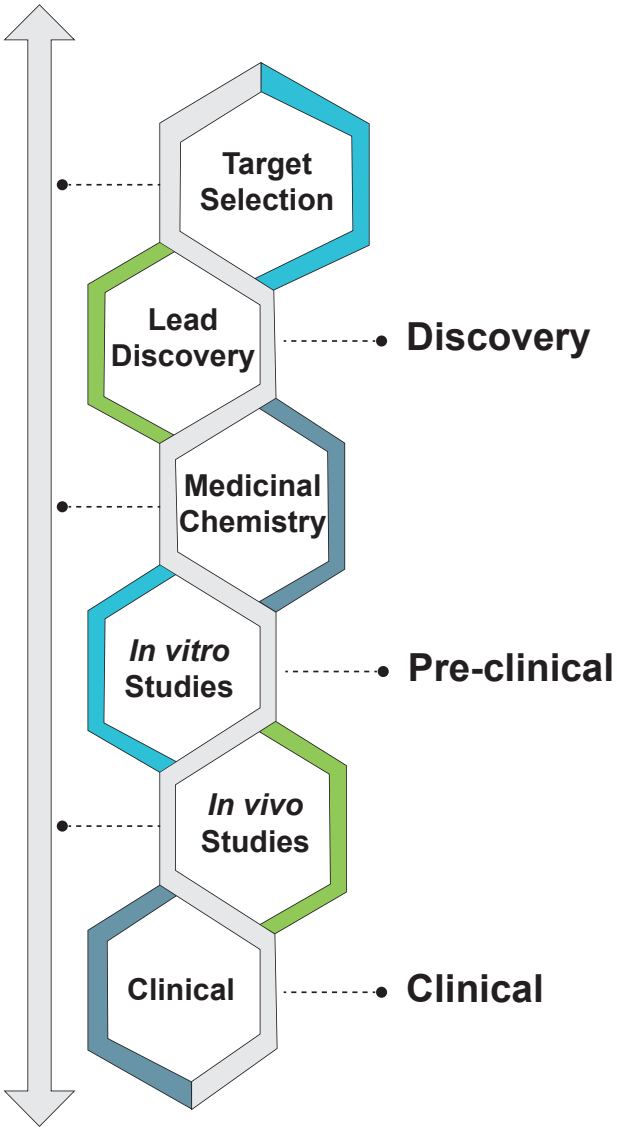
A GENESIS DRUG DISCOVERY & DEVELOPMENT COMPANY

OVERVIEW OF SERVICES





Genesis Drug Discovery & Development (GD³) is is a fully integrated CRO providing services to support drug discovery programs of our clients from target discovery through IND filing and managing Phase I-IV clinical trials. GD³ portfolio includes services for HTS and assay development, synthetic organic and medicinal chemistry, DMPK/in-vivo pharmacology and safety pharmacology, toxicology as well as clinical trial services for the regulatory approval of novel drug and medical device products.



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Venenum Biodesign

Discovery is our mission

Venenum Biodesign is a drug discovery company focused on discovering innovative new medicines for treating diseases. Using our propriety ECLiPS screening technology, in combination with state-of-the-art HTS assays, we have a proven track record of success in identifying multiple novel chemotypes from which compounds were optimized and progressed into *in vivo* studies.

Services

Venenum Biodesign is a contract research organization (CRO) specializing in drug discovery services.

We provide expertise in:

- **Biology**
    - o Assay Development
    - o Compound Profiling
- ECLiPS Compound Collection
- **Chemistry**
    - o Hit-to-Lead
    - o Lead Optimization
- Protein Expression and Purification
- Structural Biology & Molecular Modeling
- ADME Assays & Bioanalytical Services

Biology

Our biology team develops a wide range of biochemical assays for ultra-high-throughput screening (uHTS) and compound profiling to support drug discovery projects from hit-to-lead to lead optimization stages. For uHTS, we develop *in vitro* and cell-based biological assays suitable for screening our 5.5 million ECLiPS compound collection in 1536-well format in 4-8 µL volumes. The compound profiling assays are typically in low-volume 384-well format and allow for the implementation of a fully-integrated critical path that extends beyond primary compound testing to include selectivity and ortholog profiling.

Our team has years of pharma and biotech experience developing and validating cell-based and biochemical assays designed to measure ligand binding, enzymatic activity, and cell function. Assays can be configured with either kinetic or endpoint detection. Ideal detection technologies include, but are not limited to:

- Fluorescence
- Fluorescence resonance energy transfer (FRET)
- Time-resolved fluorescence (TRF)
- Homogeneous time-resolved fluorescence (HTRF or TR-TRET)
- Absorbance
- Luminescence
- AlphaScreen®
- SPA

Our technology platforms are comprised of both industry-standard and innovative technologies to support your studies with precise, robust, and efficient assays. We utilize state-of-the-art liquid handling and detection technology for assay optimization to deliver high-quality, consistent, cost-effective assay data with high reproducibility and sensitivity. We establish CVs, z-factors and work with reference compounds to ensure assay quality. We employ a combination of custom microliter liquid handlers along with commercial instruments such as the JANUS, Multidrop Combi, and ATS-100 acoustic dispenser. Our detection instrumentation includes Envision multimode plate readers and FLiPR-Tetra.

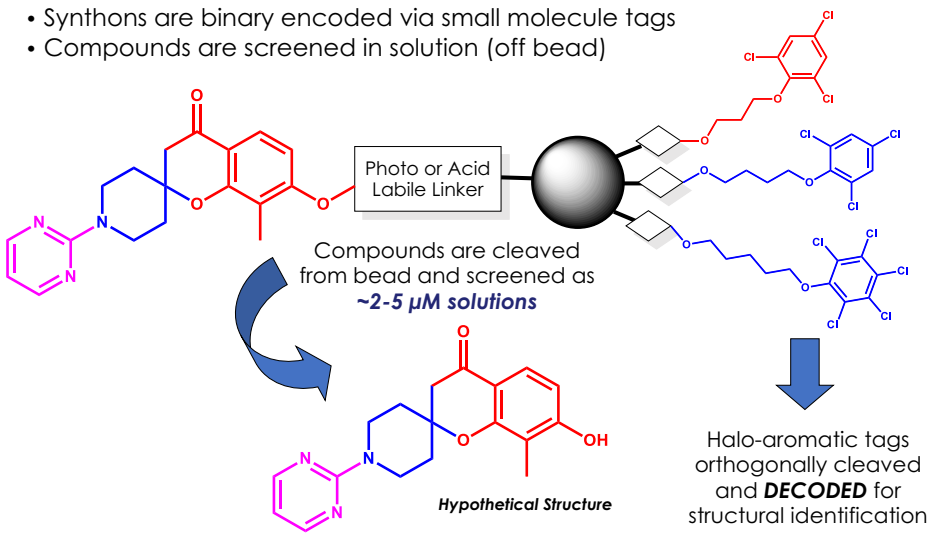
ECLiPS Compound Collection

Venenum Biodesign's ECLiPS collection of small molecule compounds contains large diverse discovery libraries. This collection was designed by experienced medicinal and computational chemists to maximize the probability of lead compound generation. Our ECLiPS collection is comprised of 5.5 million small molecules with drug-like properties. It is a proven deck for uHTS with a success rate of ~70% across pharmaceutical targets, including GPCRs, enzymes, NHRs, transporters, and ion channels. This small molecule collection, one of the largest in the world, combined with state-of-the-art uHTS capabilities, provides a powerful tool to generate quality platforms for drug discovery.

ECLiPS technology is an integrated synthesis and screening technology implemented by Pharmacopeia. ECLiPS was used successfully by Pharmacopeia to identify hits, drive lead optimization, and nominate Development Candidates (DC) in collaborations with multiple pharmaceutical and biotech companies. Ligand Pharmaceuticals acquired Pharmacopeia in 2008, and Venenum Biodesign acquired the ECLiPS technology from Ligand Pharmaceuticals in 2010.

Venenum Biodesign chemists and molecular modelers have continued constructing and synthesizing a series of new libraries to target challenging protein-protein interaction (PPI) and protein–DNA interaction (PDI) targets. Both the Venenum Targeted Libraries (sets of 500-700 compounds) and larger (20,000- 30,000 compounds) ECLiPS libraries have been synthesized based on in-house design ideas.

Binary Encoding via Stable Small Molecule Tags



Chemistry

Hits via screening or structure-based design are assessed for their chemical and biological properties. Our biology and chemistry teams progress promising compound series through hit-to-lead and lead-to-development candidate studies.

Our medicinal chemists have significant experience at pharmaceutical and biotech companies and in academia. We have solved the challenges of synthesizing and optimizing compounds across many different protein target classes and therapeutic indications including, Cardiovascular disease, diabetes, infectious diseases, oncology, inflammation, CNS, and respiratory diseases. Our new laboratories are state-of-the-art with the highest standard of instrumentation. In addition, we employ world-class computational chemistry to aid in our compound library designs and medicinal chemistry optimization programs.

We utilize an integrated drug discovery platform, where early leads are profiled through a panel of ADME assays, quickly optimized based on potency, selectivity, and desired properties. The lead compounds can be quickly advanced into pharmacokinetic studies to generate candidate compounds for *in vivo* efficacy studies.

Our Instrumentation includes:

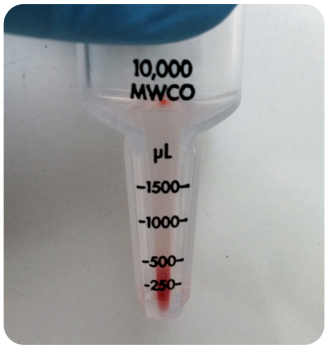
- 400 MHz NMR
- LCMSs
- MS-directed Purification System
- GC
- HPLCs
- ISCO Purification Systems
- Biotage Microwave Reactor
- Genevac Evaporation Systems
- Lyophilizer

Protein Production and Structural Biology

Venenum Biodesign has the expertise and technologies to provide a full range of services from gene to structure and beyond.

1

Protein Expression & Purification



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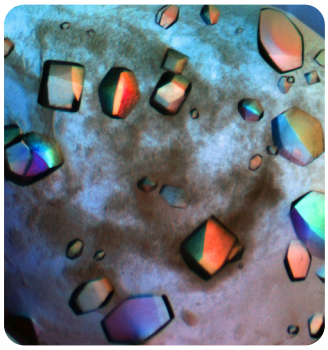
Crystallization



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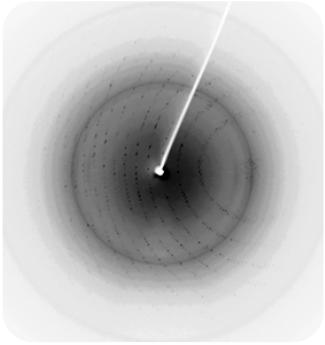
X-Ray Data Collection



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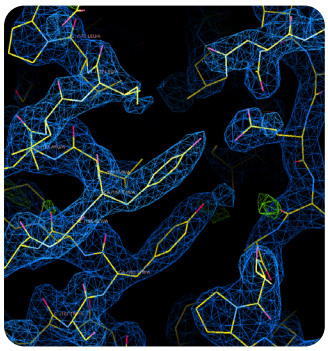
Phasing & Refinement



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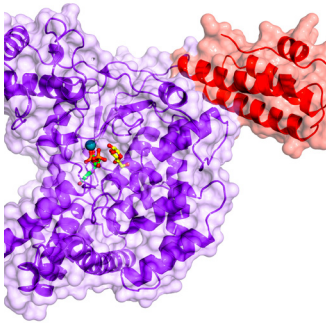
Structure-Function Analysis & Molecular Modeling



Protein Expression and Purification

Venenum Biodesign has years of experience in producing recombinant proteins for our own R&D purposes, as well as for external customers acting as a full service CRO. Our list of equipment includes state of the art platforms such as Sartorius Biostat bioreactor and a set of AKTA FPLC chromatographic purification systems. We are highly proficient in associated methodology ranging from recombinant DNA techniques to the most up-to-date protein purification approaches and supporting analytical technology.

Our protein production services incorporate:

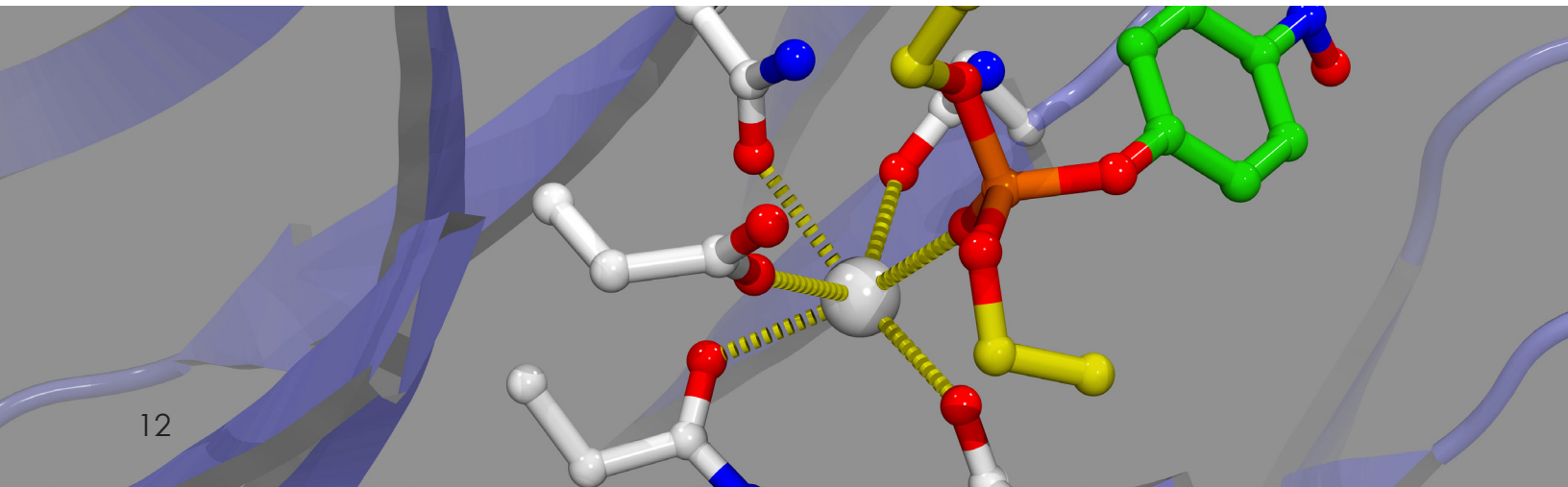
- Developing the best strategy based on risk assessment, solubility/stability analysis, amino acid composition and 3D structure (if available) of the target protein
- Designing the most relevant expression construct that contains all required modifications such as truncations, point mutations, solubility and purification tags, functional fusion peptides (e.g. cell-penetrating and receptor-specific), etc.
- Cloning into a vector of choice, transforming an appropriate host
- Running an analytical scale expression to establish an optimal format
- Designing and performing a production scale expression based on previously optimized conditions and particular needs for the amount of purified protein
- Designing, developing, and performing extensive chromatographic purification with various methods including affinity, ion exchange (IEX), hydrophobic interaction (HIC), and size exclusion (SEC) chromatography
- Performing a purity analysis via electrophoretic (SDS-PAGE or native gel), immunochemical (Western blot), and chromatographic (analytical size exclusion) techniques
- Untagging, concentrating, and adjusting a final formulation according to specific requirements of the finished product

Structural Biology & Molecular Modeling

Structural Biology has proven to be a highly effective tool for a small molecule target identification, drug design, and optimization. It provides key insights for understanding the specific nature of the interaction between a target protein and its potential inhibitor or activator. At Venenum Biodesign, we have a solid expertise in utilizing structural biology techniques for a high precision visualization of a drug binding mode and guiding our medicinal chemistry optimization efforts.

Our capabilities include:

- Rational design-based protein engineering for improved stability, solubility, and propensity to crystallize
- A broad screening for initial crystallization conditions of target proteins and their complexes with drug candidates
- Optimization (if necessary) of initially identified conditions in order to obtain high quality crystals
- Re-purification of a protein sample to a crystallization grade purity level (in necessary)
- X-ray data collection using synchrotron radiation
- Crystal structure determination and refinement
- Engineering a protein for a specific use
- Homology-based molecular modeling
- Analysis of function-related conformational changes and structural basis of molecular recognition
- Structure-based and ligand-based analysis of structure-activity relationships
- Modeling of protein-ligand interactions
- Computational discovery of novel leads including virtual screening, lead hopping, and de novo design using both structure-based and ligand-based techniques
- Rapid exploration of large virtual libraries around leads and follow up prioritization for synthesis
- ADME and property analysis and modeling



ADME Assays & BioAnalytical Services

We have established a suite of *in vitro* ADME assays to determine drug-like properties.

- Liver Microsomal Stability
- Hepatocytes Stability
- Plasma Protein Binding
- Plasma Stability
- Plasma Protein Binding with Stability
- Solubility
- MDCK Permeability
- Whole Blood Stability
- Simulated Gastric/ Intestinal Fluid Solubility
- Urine Stability

Except for the routine assays listed above, we are capable of conducting CYP450 binding, hERG binding, and cytotoxicity assays for our collaborators.

Our in-house bioanalytical group collaborates with the discovery biology group to develop *in vitro* assays, and collaborates with our colleagues at Invivotek to study pharmacokinetic profiles of our lead compounds. Efficacy of lead compounds and PK/PD relationships are assessed using predictive *in vivo* models of disease.

Scientific Management

Venenum Biodesign's scientific leadership has significant experience discovering and developing highly successful programs in many therapeutic categories. This includes leadership in developing and deploying pioneering technology in medicinal chemistry, discovery biology, and ultra-high-throughput screening to accelerate the drug discovery process. Our scientific staff has extensive pharmaceutical industry experience and is eager to collaborate.

James R. Beasley, Ph.D.
Director of Biology

Dr. Beasley has over 20 years of experience in early phase drug discovery ranging from assay development and ultra-high-throughput screening to lead identification and lead optimization programs to preclinical development projects. He has previously worked at Ligand Pharmaceuticals, Pharmacopeia Inc., and DGI BioTechnologies. He has planned and managed the discovery critical path of multiple programs with experience in a wide variety of therapeutic areas and target classes. He is also experienced in evaluation and implementation of new assay technologies, new liquid handling instrumentation, and new detection instrumentation. Dr. Beasley is a co-author on over 20 published papers, book chapters, and patents. He has also presented multiple invited oral lectures in the area of drug discovery. He has been a member of the Society of Lab Automation and Screening (SLAS, formerly SBS) since 1999, as well as the Laboratory Robotic Interest Group (LRIG). Dr. Beasley graduated with a B.S. in Chemistry from The University of Texas at Austin. He received his Ph.D. in Chemistry from The University of North Carolina at Chapel Hill in the laboratory of Professor Gary J. Pielak with a focus on protein structure, function, and stability. He was a postdoc at Princeton University in the laboratory of Professor Michael Hecht with a focus on de novo protein design.

Chia-Yu (Joyce) Huang, Ph.D.
Chief Scientific Officer

Dr. Chiayu (Joyce) Huang is a medicinal chemist with 25 years of experience in drug discovery. Her experience spans a variety of therapeutic areas, including Metabolic Disease, Oncology, Respiratory, CNS, and Inflammatory Disease. Dr. Huang joined Venenum Biodesign in May 2010 and started the design and set up of organic chemistry, analytical chemistry and NMR laboratories, a compound management facility, and a chemical stock room. She has led several hit to lead and lead optimization programs at Venenum, targeting metabolic disease, NASH, and cancer. In 1995, Dr. Huang began her career at Pharmacopeia, where she led several lead optimization programs in collaboration with Schering-Plough and Cephalon, resulting in one clinical candidate and two GLP tox candidates for these programs. In addition, she designed and synthesized multiple encoded chemical libraries, which produced hit/lead compounds for many medicinal chemistry programs. From 2009 to 2010, Dr. Huang managed multiple successful Lead Discovery/Lead Optimization programs in a broad range of therapeutic areas for Ligand Pharmaceutical, in collaboration with Schering-Plough. She managed internal and external resources, coordinating with multiple sites internationally, and achieved four milestones in 2010. Dr. Huang received a B.S. in chemistry from National Taiwan University, a Ph.D. in Organic Chemistry from the University of Texas at Austin, and was a post-doctoral research fellow at Duke University. She has co-authored more than 35 papers and patents.

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