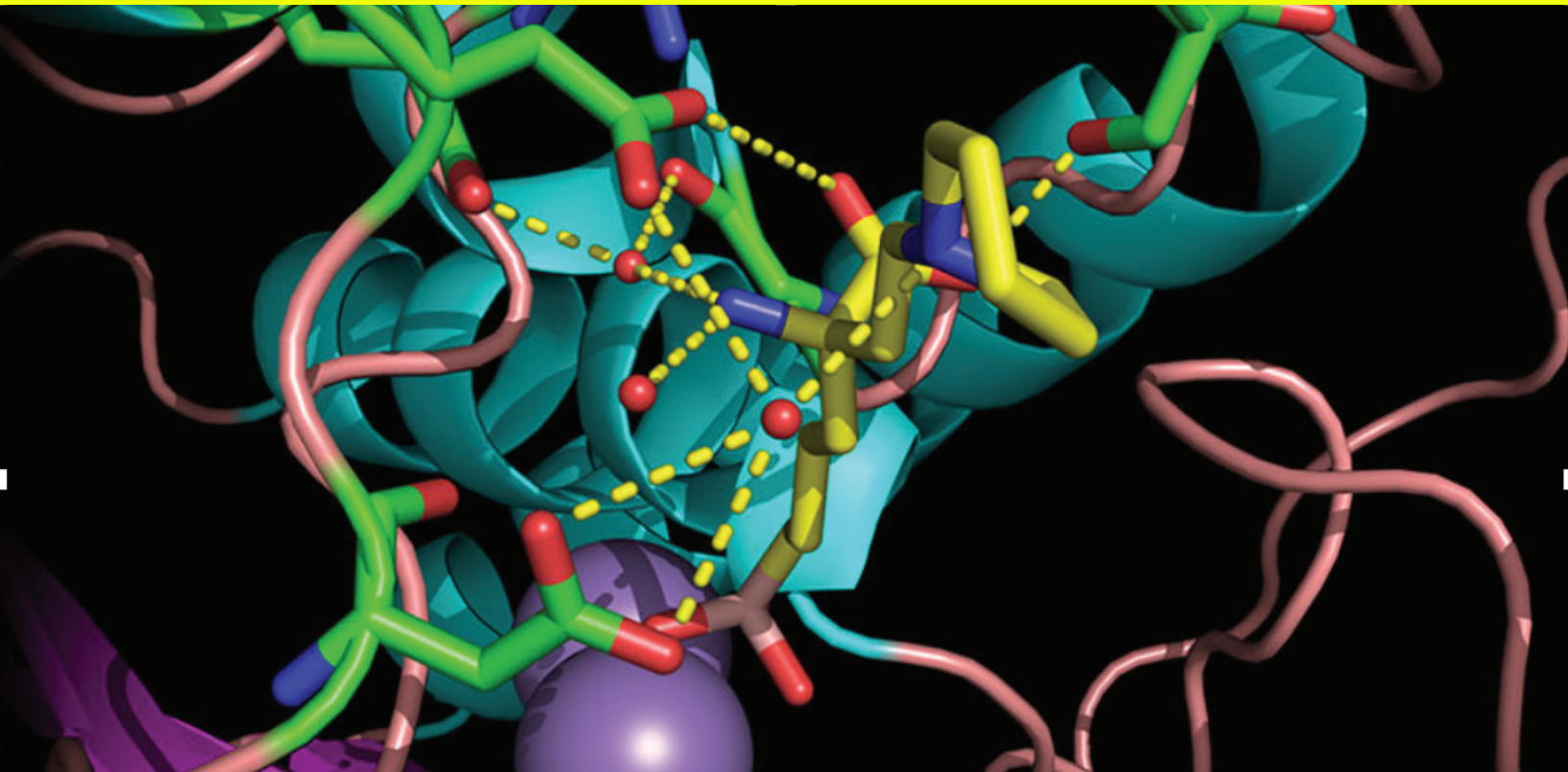
NEDP®

New England Discovery Partners

A GENESIS DRUG DISCOVERY & DEVELOPMENT COMPANY

OVERVIEW OF SERVICES



GD³ Genesis
Drug Discovery & Development

Chemistry
- Venenum Biodesign Chemistry
- NEDP New England Discovery Partners
- BioBlocks
- Organochem — Accelerate Your Business

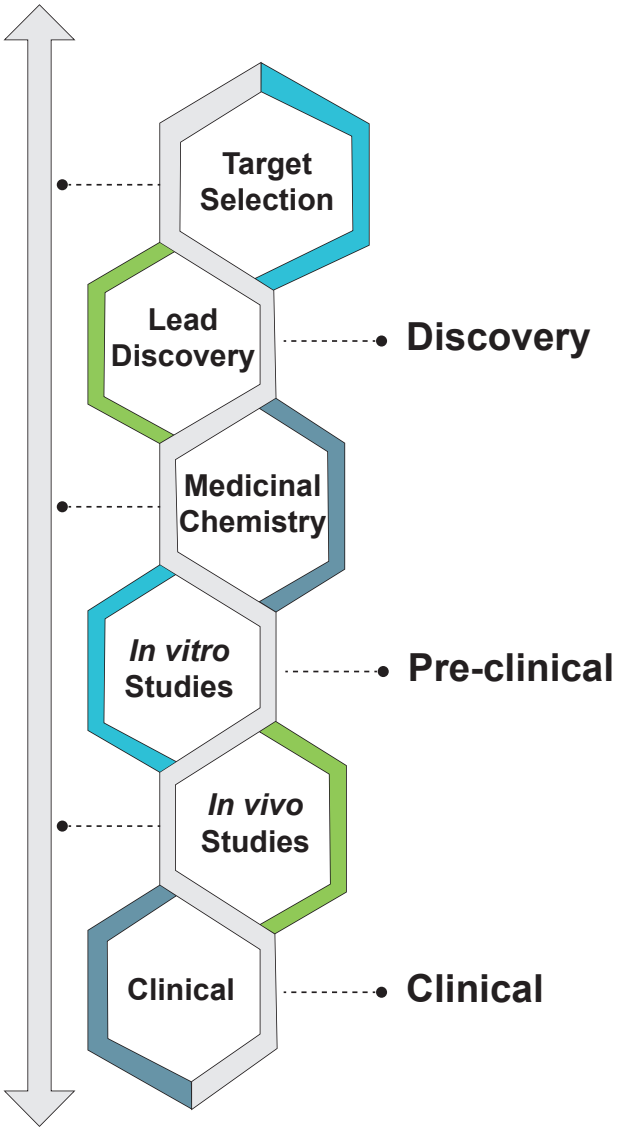
Biology/ Bioanalytical
- ias integrated analytical SOLUTIONS
- Venenum Biodesign Biology
- Pharmoptima
- Ingenio Diagnostics

Disease Modeling
- Invivotek
- nexus pharma

Preclinical-Toxicology
- Comparative Biosciences Inc.

Clinical
- STATKING Clinical Services
- JSS RESPONSIVE RELIABLE RESULTS

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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NEDP

Making Molecules that Matter

New England Discovery Partners (NEDP) was founded in 2012 to meet the growing demand for highly-skilled synthetic organic and medicinal chemists. Staffed with a diverse team of experienced industry professionals, we understand the necessary steps required to identify and develop new clinical compounds. Our pharmaceutical scientists have managed drug discovery programs from early lead identification to clinical development.

As a premier service provider, NEDP delivers a wide range of high-value chemistry services to further the drug discovery programs of academic investigators, pharmaceutical and biotechnology companies, nonprofit and government institutions.

We understand the importance of maintaining a consistently high level of productivity and scientific rigor throughout every project. We're flexible. We adapt personnel as necessary to meet specific program objectives and insist on open and honest communication. Our labs are well-equipped, and we maintain the highest standards for security and confidentiality.

The NEDP Difference

We're highly-skilled synthetic organic and medicinal chemists who love what we do – creating and developing new compounds to change lives for the better.

Services

New England Discovery Partners is a contract research organization (CRO) specializing in synthetic organic and medicinal chemistry.

We provide expertise in:

- **Discovery Chemistry**
  - o Medicinal Chemistry
  - o Structure-Based Drug Design
  - o Organic Synthesis
  - o Process Chemistry
- **Analytic Services**
  - o NMR
  - o Optical Rotation
  - o Infrared and UV-Visible Spectroscopy
- Antibody Drug Conjugates
- Process Chemistry and Scale-up Capabilities

Medicinal Chemistry

Medicinal chemistry is the iterative process of optimizing early lead compounds into viable clinical candidates. Complex structure-based data from various sources such as enzyme activity, drug metabolism, and physicochemical properties are used to design new analogs that are potent, safe, and effective. Scientists at New England Discovery Partners are highly experienced and have worked on diverse programs in various therapeutic areas, each with specialized target profiles. As a result, we work closely with our research partners, delivering scientific excellence in a highly efficient, effective, and collaborative manner. Specific services include:

- Optimization of early lead compounds into viable clinical candidates: design and synthesis of new analogs to optimize potency, selectivity, efficacy, bioavailability, metabolism, and safety.
- Structure-based drug design
- Parallel synthesis
- HTS Hit confirmation and expansion (confirm structure and activity of hit clusters). Synthesis of selected analogs to evaluate scaffolds and select lead series
- Small molecule patent strategy development and implementation
- Project management and consulting

Intellectual Property

As medicinal chemists and business executives with decades of experience in the pharmaceutical industry, we understand that intellectual property is the primary value driver for drug discovery research. We work closely with our clients and patent attorneys to develop effective patent strategies to ensure the broadest, most complete patent coverage.

Structure-Based Drug Design

The use of X-ray crystallography and molecular modeling to understand enzyme-inhibitor binding interactions can dramatically accelerate the process of optimizing early lead compounds, transforming them from leads with weak activities into highly potent and selective clinical candidates. Whenever possible, we incorporate these technologies into our drug discovery collaborations to maximize our effectiveness. Specific services include:

- Protein production and purification
- X-ray crystallography of small molecule inhibitors bound to protein targets
- Molecular modeling for lead optimization
- Biophysical analysis of protein-inhibitor interactions

Organic Synthesis

Making the molecules that matter

Modern organic synthesis is the ever-evolving science of building complex molecules. Specific objectives for synthetic methods vary depending on the application. Cost, scale, ease of purification, and target flexibility are often considerations. At NEDP, we take great pride in our ability to solve the most complex chemistry challenges. Our scientists have extensive experience working on diverse projects, each with its unique synthetic challenges.

We provide custom synthesis services to pharmaceutical, biotechnology, consumer product companies, academic, governmental, and nonprofit institutions.

From rapidly optimizing chemical templates in drug discovery programs to asymmetric synthesis, heterocyclic compounds, natural products, amino acids, we have the capabilities and experience to tackle the most difficult chemistry challenges. Specific areas of expertise include:

- Asymmetric synthesis
- Parallel synthesis
- Process development
- Carbohydrates
- Heterocyclic compounds
- Amino acids
- Fluorophores
- Phospholipids
- Peptides
- Boronic acids
- Arachinoids
- Biotinylated products
- Structure identification and characterization
- Natural product synthesis
- Metabolite synthesis (Phase I and II)
- Stable isotopically labeled compounds (2H, 13C, 15N)

Analytical Services

Superior data and outstanding service

Timeliness and accuracy are hallmarks of our Analytical Services team. As a chemistry CRO, we understand the time-sensitive nature of analytical data and strive to complete all samples within 24 hrs of receipt.

Spectra are provided as PDF documents via email or fax. A completed sample submission form must be included with all samples. Pricing is based on a per-sample or hourly rate, depending on the type of analysis and number of samples submitted.

Nuclear Magnetic Resonance Spectroscopy (NMR)

NEDP provides one and two-dimensional NMR spectra of common nuclei (1H,13C, 19F and 31P) using a Bruker 400 MHz spectrometer. Typical analysis includes the basic spectrum with expansions, integration and peak listing, but a more in-depth analysis with interpretation is also available.

Spectra are provided as PDF documents via email or fax. A completed sample submission form must be included with all samples. Pricing is based on a per-sample or hourly rate, depending on the type of analysis and number of samples submitted.

Optical Rotation

NEDP provides optical rotation measurements using a Perkin Elmer PE-341 polarimeter equipped with both Na and Hg source lamps.

Infrared and UV-Visible Spectroscopy

NEDP provides Infrared and UV-Visible Spectroscopy measurements using a Thermo-Nicolet 6700 FTIR and Varian Cary 3E UV-Visible Spectrophotometer, respectively.

Antibody-Drug Conjugates

Targeted Therapy for Cancer

Antibody-drug conjugates, or ADCs, are an important new class of biopharmaceutical drugs engineered to deliver potent anti-cancer agents directly to the target tumor. ADCs are composed of a tumor-specific antibody connected via a chemical linker to a biologically active drug or cytotoxic compound. By combining the exquisite targeting capabilities of an antibody with potent drug molecules, these innovative therapeutics are highly efficacious without the side effects of traditional chemotherapeutic agents.

Bioconjugation

NEDP offers bioconjugation services for Antibody Drug Conjugates (ADCs) utilizing the following general methodologies:

- Conventional cysteine conjugation: reduction of interchain disulfides followed by conjugation to electrophilic linker payloads (e.g., maleimide, haloacetyl)
- Site-specific cysteine conjugation: deprotection of mutant cysteine followed by conjugation to linker payloads
- Lysine conjugation: conjugation to lysine residues via activated ester-containing linker payload

ADC Process Research

Conjugation optimization employs a "design of experiments" (DOE)-based approach for rapid and efficient screening of all relevant reaction parameters such as linker-payload stoichiometry, concentration of solubilizing agents, reducing agents, oxidizing agents, pH of reaction medium, reaction temperature, agitation rate, addition rate, effect of co-solvents, etc. Using this approach, optimized processes are developed in a highly efficient manner.

Purification and Analytic Services

Purification is conducted use chromatography (HIC, IEX, mixed-mode, affinity) and/or ultrafiltration/diafiltration (UF/DF). ADC characterization including Drug Antibody Ratio (DAR), Unconjugated antibody (UmAb%), aggregation percentage, endotoxin level, and residual drug and related species levels are provided.

Design and Synthesis of Linker Payload

NEDP provides the linker payload services, including linker design, synthesis of linker payload, and related building blocks.

Process Chemistry

The NEDP process chemistry group works closely with medicinal chemists and chemical engineers to efficiently develop robust chemistry solutions for clients. This collaborative approach facilitates a smooth transition from bench to reactor, minimizing any risk of late-stage process issues that can negatively impact the time to clinic.

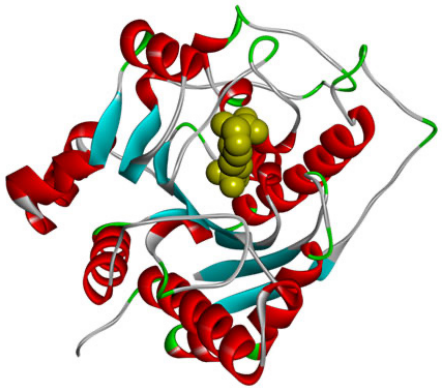
Our new state-of-the-art facility is well-equipped with chemical reactors ranging in size from 5 to 30 L (-65°C to 200°C), suitable for convenient preparation of most APIs on a kg scale. With a decade of experience in the pharmaceutical industry, we have the expertise to solve the most complex chemistry challenges and understand the importance of delivering results on time and within budget.

Services provided:

- Route discovery, selection, and development
- Process improvement and optimization
- Analytical method development
- Reaction feasibility determination
- Rapid lot preparation for proof-of-concept studies
- Preparation of discovery chemistry intermediates and analogs preparation (milligram to kilogram scale)
- Custom synthesis
- Process limits testing
- Synthesis of analytical reference standards
- Process impurity isolation, identification, and synthesis
- Impurity profile development
- Solid-state chemistry –salt selection, polymorph screening, amorphous dispersions, crystallization development
- Freedom to operate assessment
- Hazard evaluation

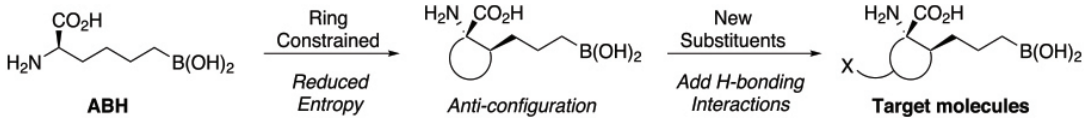
Case Study

Design and synthesis of highly potent third generation inhibitors of Arginase I and II



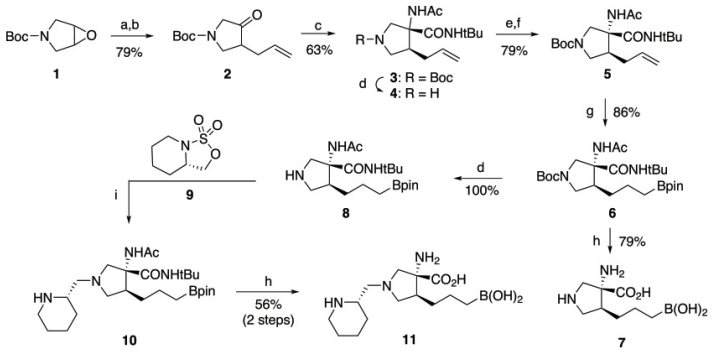
L-arginine metabolism is emerging as a crucial regulatory pathway for a wide variety of oncological,[1] autoimmune, [2] anti-inflammatory [3] and infectious diseases. [4] Arginase, which competes with inducible nitric oxide synthase (iNOS) for L-arginine as a common substrate, is dysregulated in many such diseases. The diverse pathologies associated with increased arginase expression levels arise from both increased production of ornithine, proline and polyamines, the products of arginase-mediated hydrolysis of arginine, and the decreased nitric oxide (NO) production that results from reduced substrate availability for iNOS.

Scheme 1.



Evaluation of ABH and our related second-generation series of analogs [5] co-crystalized with arginase indicated a five-membered ring connecting the amino acid carbon with the first carbon on the butane boronic acid side chain could potentially provide a suitable constraint without introducing negative Van der walls interactions with active site amino acids, provided the amine and boronic acid side chain were positioned in an anti-orientation as illustrated in Scheme 1. In addition to reducing entropy, the atoms used to create the ring constraint could be used as a scaffold to introduce additional substituents that would form hydrogen-bonding interactions with Asp 180 and Asp 182 in a manner analogous to our previous series [5]. A pyrrolidine-based ring system was selected because it would provide convenient access to a versatile late-stage intermediate that would accelerate the lead optimization process.

Scheme 2.



Reagents and conditions: (a) allyl magnesium bromide, ether, 0°C; (b) pyridine-sulfurtrioxide, DMSO, diisopropylethylamine, DCM, 0°C; (c) t-BuNC, NH4Ac, CF3CH2OH, RT, 3 days; (d) TFA, DCM; (e) (2S,3S)-2,3-bis(benzoyloxy)-4-(isopropylamino)-4-oxobutanoic acid, MeOH, IPA; (f) BOC2O, aq NaHCO3, EtOAC; (g) pinicolborane, Ir2Cl2(COD)2, dppe, THF; (h) 9N HCl, AcOH, 100 oC, 12 h; (i) ACN.

Synthesis of these pyrrolidine-based arginase inhibitors was completed using the chemistry outlined in Scheme 2. Addition of allyl magnesium bromide to commercially available boc-protected pyrrolidine epoxide **1** followed by oxidation with sulfur trioxide pyridine complex gives allyl ketone **2** in 79% yield (2 steps). The racemic amino acid moiety **3** is formed via the Ugi reaction using our standard conditions.

The desired anti-diastereomer is separated into its enantiomers using a classical resolution with dibenzoyl-L-tartrate [(2S,3S)-2,3-bis(benzoyloxy)-4-(isopropylamino)-4-oxobutanoic acid]. Using this method, the desired enantiomer **5** is obtained in approximately 77% theoretical yield with an enantiomeric excess of 99.7% as determined by chiral HPLC after reintroduction of the boc-group. Subsequent hydroboration and hydrolysis results in the unsubstituted pyrrolidine **7** in 68% yield (2 step).

Boc-protected intermediate **6** can be selectively deprotected using trifluoroacetic acid to give the corresponding amine **(8)** which is a versatile intermediate for use in reductive amination and alkylation reactions. When the desired aldehyde, such as (S)-piperidine-2-carbaldehyde, contains an adjacent chiral center, the reductive amination reaction conditions give primarily the epimerized product. To avoid this racemization, the substituted ethylamine moiety can be introduced using alkylation chemistry via the corresponding cyclic sulfamate **(9)** which is prepared from (S)-piperidin-2-ylmethanolusing the general method described by Alker6. Alkylation of pyrrolidine intermediate **8** with the desired sulfamate **(9)** in acetonitrile gives alkylation product **10**. Subsequent hydrolysis gives the target amino acid **(11)** as a single enantiomer in 10 steps with an overall yield of approximately 10%.

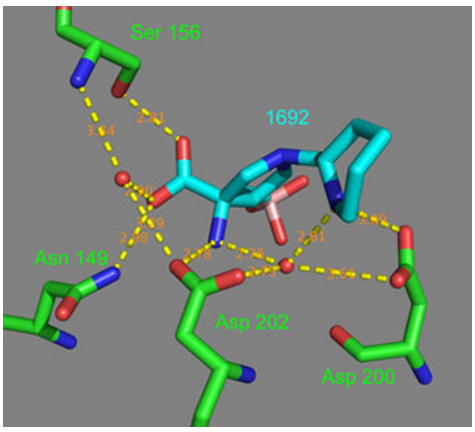
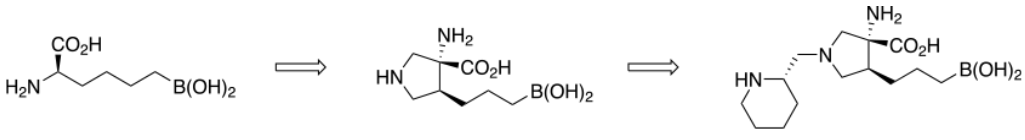


Figure 1.
Example **11** (blue) bound in the arginase II active site pocket (green) with ionic and hydrogen bonds (yellow) and bond distances (salmon).

Analysis of compound **11** co-crystalized with hArg II confirms the hydrogen bonding interaction between the piperidine ring nitrogen and Aspartic acid residues. As illustrated in Figure 1, the piperidine nitrogen forms one hydrogen bond with Asp 200 (3.09 A) and one with Asp 202 through a water molecule (2.73 A).

Consistent with the X-ray crystallography data, screening results for compound **11** indicate strong binding interactions between the inhibitor and active site amino acids. Arg I and Arg II IC50s for compound **11** are 2.6 and 14 nM respectively (Scheme 3).

Scheme 3.



ABH
ArgI IC_{50}: 1,547 nM
ArgII IC_{50}: 2,551 nM

7
ArgI IC_{50}: 110 nM
ArgII IC_{50}: 440 nM

11
ArgI IC_{50}: 2.6 nM
ArgII IC_{50}: 14 nM

The increased potency relative to ABH arises from the added effects of two specific structural changes: introduction of a ring constraint that reduces entropy, and addition of a basic amine side chain that is positioned to form new ionic interactions with aspartic acid residues in the active site pocket. This new class of arginase inhibitors is significantly more potent than any series previously reported. It is hoped that these compounds will help facilitate a better understanding of arginase and the specific pharmacological role it plays so many important diseases.

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The NEDP Team has earned a reputation as a trusted partner. Their experience, dedication, communication, and commitment to excellence make them ideally suited for discovery-stage research programs.

Senior Management

Michael Van Zandt, Ph.D., President & CEO

Michael is an accomplished synthetic organic and medicinal chemist with more than 20 years of experience in large and small pharmaceutical company environments. Before founding NEDP, he was a department head and project leader for The Institute for Pharmaceutical Discovery (IPD) and a medicinal chemist at Bayer's pharmaceutical division. Michael received his Ph.D. in Organic Chemistry with a minor in Biochemistry while working with Distinguished Professor Carl R. Johnson at Wayne State University. Michael, an inventor on more than 40 issued patents and author of more than 30 publications in peer-reviewed journals, is a frequent reviewer for the Journal of Medicinal Chemistry and Bioorganic Medicinal Chemistry Letters.

G. Erik Jagdmann, Jr, Ph.D., Principal Scientist

After receiving his Ph.D. from Princeton University under the guidance of Professor E. C. Taylor, Erik went on to a postdoctoral fellowship with Professor A. I. Meyers at Colorado State University. He has over 25 years of industrial experience in the pharmaceutical and biotechnology industries, including 11 years as a group leader with Eli Lilly, North Carolina Labs. Erik has over 40 publications and patents.

Darren Whitehouse, Ph.D., Principal Scientist

Darren is a highly-skilled synthetic organic and medicinal chemist with over 15 years of experience in large pharma and biotech companies. Before joining NEDP, Darren was a Sr. Staff Scientist, lab head, and project leader at the Institutes for Pharmaceutical Discovery (IPD). Darren received his Ph.D. in natural product synthesis from the University of Manchester, UK, from Professor E. Jim Thomas's research group. To date, he has over 40 issued patents, journal and book publications, and invited presentations.

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