DRUG DELIVERY EXPERTS

CHANGING LIVES THROUGH DELIVERY TECHNOLOGY

www.ddelabs.com
• Specialists in injectables and combination product development

• From solution injectable to complex formulation design and device integration

• Drug product development from research to commercialization

• Extensive experience in biologics drug development and delivery technologies

• Highly-qualified Ph.D. scientists working in state-of-the-art R&D lab in the heart of San Diego biotech
• Leveraging a deep understanding of molecular properties, formulation, and device
  • Integrating delivery system R&D projects into your development program
    • Optimizing target product profile to enhance value proposition

**Discovery Support**
- Lead molecule profiling
- Clinical candidate evaluation
- Biologic half-life extension

**Drug Product Development**
- Formulation design
- Drug product development
- Analytical methods

**Device Selection**
- Device identification
- Integration with formulation
- Combination product development
Pharmaceutical R&D Laboratory
• Formulation, analytical, process, chemistry, device development
• Specialists in complex drug product development
• Peptide and small molecule chemistry, conjugation (e.g., PEGylation)
• Lead candidate selection, optimizing pharmaceutical properties

Drug Product Development Strategic Partnership
• Strategic product development and hands-on technical support
• Participation in CMC teams (analytical, formulation, chemistry, device)
• Translation of innovative technologies from research to clinic

Partnering to Develop New Delivery Technologies
• Sustained release injectable delivery technology
• Self assembling delivery technology
• Oral capsule device for targeted delivery
LEADERSHIP WITH EXTENSIVE PHARMA/BIOTECH EXPERIENCE

Chris Rhodes, Ph.D.
President & CEO
Founded Drug Delivery
Experts in 2014 after 20
years in biotech and drug
delivery companies in both
technical and executive
leadership roles.

Sharon Lee Rhodes, Ph.D.
Executive Vice President
Sharon is a proven strategic
leader with a potent
combination of skills in the
technical, corporate, academic
and non-profit arenas.

Dave Litzinger, Ph.D.
Scientific Advisor
Dave has over 22 years of
drug discovery and
development experience,
including technical and
leadership roles.

Jui-Chen Lin, Ph.D.
Formulation, Drug
Product Development,
Aseptic Manufacturing
Chemical engineer with
broad formulation and
delivery system
experience.

Lawrence D'Souza, Ph.D.
Discovery, Chemical
Development,
Formulation
Organic chemist with
discovery and early
development experience
in small molecule,
peptide, and protein
synthesis.

Shu Fen Wen, Ph.D.
Drug Product
Development,
Manufacturing
Microbiologist with
many years of
product development
experience in device
integration.

Laxma Reddy, Ph.D.
Formulation, Small
Molecules, Biologics
Biochemist with
experience in
sustained-release
drug delivery product
development.
Our Leaders Have Worked at These Companies

Our Leaders Developed These Products
SUPPORT AT EVERY STAGE

LEAD MOLECULE SELECTION
- Peptides
- Small Molecules

SOLUTION FORMULATION
- 5C in a Vial
- Lyophilized
- Frozen Solution

DEVICE INTEGRATION
- Pre-filled Syringe
- Cartridge
- Pen
- Auto-Injector

LIFE-CYCLE MANAGEMENT
- Reformulation
- Long-Acting System
- Non-Injectable Delivery (Oral, Nasal, Pulmonary)
32 LAB PROJECT CLIENTS IN 5 YEARS
| PRECLINICAL | Small Organic Formulation | • Topical Ocular Formulation for a Diagnostic, Analytical, PK |
| LEAD SELECTION | Protein PEGylation | • Process, Formulation, Analytical, Tech Transfer • CMC and Drug Development Team Consulting (Mfg, Reg, Tox) |
| PHASE 1 | Small Organic Formulation | • IV Injection Formulation, Analytical, CMC |
| PHASE 2 | Peptide Formulation | • Optimize IV Aqueous Formulation Stability • CMC Consulting |
| PHASE 3 | Peptide Re-formulation | • Life Cycle Support, Immediate Release to Extended-Release Injection • CMC Consulting |

**LAB CASE STUDIES — PRE-MARKET**

**PRECLINICAL**

**PHASE I**

**PHASE II**

**PHASE III**

**COMMERCIAL**
<table>
<thead>
<tr>
<th>Category</th>
<th>Type</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ANDA</td>
<td>Peptide Formulation</td>
<td>• Process, Analytical, and Tech Transfer</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• CMC and Drug Development Team Consulting (Mfg, Reg, Tox, BD)</td>
</tr>
<tr>
<td>COMMERCIAL</td>
<td>Protein Re-formulation</td>
<td>• Analytical, PK/BA, Solution, Particulate Suspension, ISR Improvement</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Defined Product Life Cycle Plan as Consulting Team</td>
</tr>
<tr>
<td>COMMERCIAL</td>
<td>Oligonucleotide Re-formulation</td>
<td>• Nanoparticle Development, Process Development, Analytical, Scale-Up for Delivery Improvement</td>
</tr>
<tr>
<td>COMMERCIAL</td>
<td>Small Molecule Re-formulation</td>
<td>• Long-Acting Injectable, Small Molecule, Particle Suspension Formulation</td>
</tr>
<tr>
<td>Client</td>
<td>Type of Project</td>
<td>Scope of Lab Work</td>
</tr>
<tr>
<td>---------</td>
<td>-----------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
</tbody>
</table>
| SENSULIN| DDE is responsible for full R&D Program | • Develop liposomal glucose-responsive insulin drug delivery system  
• Formulation, Process, Analytical, PK / BA  
• Drug Development Team Leadership (Mfg, Reg, Tox, Clin, BD) |
| DIAVACS | DDE runs Product Development Program | • Develop oligonucleotide nano-particle drug delivery system  
• Formulation, Process, Analytical, In vitro cell culture model, in vivo POC |
| ABVANCE | DDE runs Product Development Program | • Develop Insulin Pump Co-Formulation, Process, Analytical, PK/BA |
42 CONSULTING CLIENTS IN 5 YEARS

Area of Consulting
- Due Diligence
- Life-Cycle Planning
- Delivery Technology Assessment
- CMC Support

Client Size
- Size of Client Based on Valuation & Market Cap

Project Type
- Consulting Only
- Consulting & Lab Work

Years With DDE Labs (1 - 5)
Scope of Consulting Project(s)
<table>
<thead>
<tr>
<th>Project Type</th>
<th>Program</th>
<th>Scope</th>
</tr>
</thead>
<tbody>
<tr>
<td>DUE DILIGENCE</td>
<td>Peptide Phase 1 Asset</td>
<td>CMC Due diligence for VC investment</td>
</tr>
<tr>
<td></td>
<td>Peptide/Microneedle Phase 3</td>
<td>CMC Due diligence for company acquisition</td>
</tr>
<tr>
<td></td>
<td>Biologics Oral Delivery</td>
<td>Due diligence for VC investment</td>
</tr>
<tr>
<td>LIFE CYCLE PLANNING</td>
<td>Protein in Commercial Product</td>
<td>Recommend life cycle options for product improvement</td>
</tr>
<tr>
<td>DELIVERY TECH ASSESS</td>
<td>Biologics Polymer Delivery</td>
<td>Evaluate drug delivery polymer applications to biologics</td>
</tr>
<tr>
<td></td>
<td>Cell Penetrating Peptide</td>
<td>Evaluate therapeutics applications for CPP delivery</td>
</tr>
<tr>
<td></td>
<td>Small Molecule Oral Delivery</td>
<td>Recommend therapeutics for oral delivery system</td>
</tr>
<tr>
<td></td>
<td>Biologics Oral Delivery</td>
<td>Evaluate oral delivery as leader of advisory board</td>
</tr>
<tr>
<td></td>
<td>Biologics Ocular Delivery</td>
<td>Evaluate ocular drug delivery technologies for biologics</td>
</tr>
<tr>
<td>CMC SUPPORT</td>
<td>Biologics Ocular Delivery</td>
<td>Advise R&amp;D program for biologics ocular drug delivery</td>
</tr>
<tr>
<td></td>
<td>Peptide R&amp;D Project</td>
<td>Evaluate formulations and guide R&amp;D program</td>
</tr>
<tr>
<td></td>
<td>Peptide Drug Delivery</td>
<td>Advise CMC team for delivery system development</td>
</tr>
<tr>
<td></td>
<td>Long-Acting Injectable</td>
<td>Advise CMC team for delivery system development</td>
</tr>
</tbody>
</table>
OVERVIEW OF LAB CAPABILITIES

Lead Molecule Selection

- Analytical Research
- Development Assessment
- Lead Molecule Design

Delivery System Selection

- Analytical Development
- Delivery System Feasibility
- Formulation Development

Formulation Development

- Preformulation
- PK Screening
- Process Development Scale Up
- Device Selection and Development

Analytical Methods Qualification

- Development Stability

Drug Product Development

- Technology Transfer GMP Mfg.

Molecule Design

- Peptide/Protein Variants
- Conjugates for Half-Life

Delivery System Design

- Aqueous or Non-Aqueous Vehicle
- Sustained Release Formulation
- Triggered or Targeted Systems

Drug Product Design

- Pen/Auto-Injector
- Pre-Filled Syringe
- Nasal/Ocular Drops/Spray
Contracted Fee for Service

Developability Assessment

Pharmaceutical Development
  Solutions and Suspensions
  Aqueous and Non-aqueous systems
  Scale from 1 ml to 10 liter batch size
  Stability and Preclinical Supplies

Analytical Development
  HPLC Stability Indicating Methods
  Content assay and impurity profiles
  Various drug product specific QC tests

Delivery Systems
  PLGA Microspheres and Implants
  Nanoparticles
  Liposomes
  Extended-release Suspensions

Proprietary Delivery Technology

SubQ Biologics™
  Modulate solubility & dissolution
  Alter subcutaneous absorption
  Improve PK profile and ISR

Long-Acting Technology
  Proteins
  Peptides
  Oligonucleotides
  Antibodies

IP License Agreement
EXTENDED-RELEASE INJECTABLE APPROACHES

Liposome for Drug Delivery
- Protective layer against immune destruction
- DNA
- Homing peptide
- Drug crystallized in aqueous fluid
- Lipid bilayer
- Lipid-soluble drug in bilayer

<table>
<thead>
<tr>
<th>Daily</th>
<th>Weekly</th>
<th>Monthly</th>
<th>Quarterly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suspension</td>
<td>Liposome</td>
<td>In Situ Gel-Forming System</td>
<td>Microsphere</td>
</tr>
<tr>
<td>Non-Aqueous Solution/ Suspension</td>
<td>Implant</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Compound Type</td>
<td>MW (kDa)</td>
<td>Injection Frequency</td>
<td>Liposome</td>
</tr>
<tr>
<td>------------------------</td>
<td>----------</td>
<td>---------------------</td>
<td>----------</td>
</tr>
<tr>
<td>Small Molecule</td>
<td>&lt;1</td>
<td>Monthly</td>
<td></td>
</tr>
<tr>
<td>Peptide</td>
<td>1</td>
<td>Weekly to Monthly</td>
<td></td>
</tr>
<tr>
<td>Peptide</td>
<td>2</td>
<td>3 to 4 Months</td>
<td></td>
</tr>
<tr>
<td>Peptide</td>
<td>3</td>
<td>Daily</td>
<td></td>
</tr>
<tr>
<td>Peptide</td>
<td>4</td>
<td>Daily</td>
<td></td>
</tr>
<tr>
<td>Peptide</td>
<td>4</td>
<td>Weekly to Monthly</td>
<td></td>
</tr>
<tr>
<td>Peptide</td>
<td>5</td>
<td>Weekly to Monthly</td>
<td></td>
</tr>
<tr>
<td>Insulin</td>
<td>6</td>
<td>Daily to Weekly</td>
<td></td>
</tr>
<tr>
<td>Oligonucleotide</td>
<td>8</td>
<td>Daily to Weekly</td>
<td></td>
</tr>
<tr>
<td>Oligonucleotide triple combination</td>
<td>10</td>
<td>Daily to Weekly</td>
<td></td>
</tr>
<tr>
<td>Protein</td>
<td>15</td>
<td>Weekly</td>
<td></td>
</tr>
<tr>
<td>Protein</td>
<td>50</td>
<td>Weekly</td>
<td></td>
</tr>
</tbody>
</table>
EXPERIENCED IN MANY ROUTES OF ADMINISTRATION

- **Small Molecules**
  - IV, SC
  - Nasal
  - Oral

- **Peptides**
  - SC
  - Inhalation
  - Nasal
  - Ocular
  - Oral

- **Proteins**
  - SC
  - Nasal

- **Oligos**
  - SC

- **Antibody**
  - SC

~ 1K Da
~ 10K Da
~ 100K Da
Non-invasive delivery for small molecule, peptide, protein
• Painless, no needles or injections
• Easy administration by patient or caregiver

Formulation and analytical development
• Dosage forms: solution, suspension, and dry powder
• Chemical and physical stability

Drug product device assessment
• Dose delivery/content uniformity
• Particle/droplet size distribution
• Spray pattern
• Plume geometry
• Leachable and extractable
Technologies for Controlled Release of Drugs
Small Molecule and Peptides Dosage Forms Created

**Tablets**
- Bi-layer Tablets
- Mini Tablets

**Capsules**
- Powder blends
- Microparticle-filled
- Microsphere-filled

**Tablet Processes**
- Direct compression
- Dry granulation
- Wet granulation
- Enteric coating

**Oral Controlled Release**
- Instant release
- Sustained release
- Enteric or delayed release

**Topical**
- Transdermal cream
- Topical Spray
Chemical Instability
- Deamidation – Asn and Gln residues
- Oxidation – Met residues
- Degradation, ligation (adduct formation)

Solubility Issues
- pH, temperature, buffer composition, ionic strength, etc.

Gelation Issues
- pH, temperature, buffer composition, ionic strength, etc.

Injection Site Reaction Issues
- Precipitation, extreme pH, osmolality, needle size, etc.
PARTNERSHIP OPTIONS

Project Specific Work
- Shorter well-defined projects
- Typically 3 to 9 months
- Confidential project definition
- Payment milestones

Dedicated R&D Team
- Longer term and broader projects
- Typically 1 to 3 years
- Dedicated resources for program
- Regular quarterly or monthly payments
Client publications, patents and applications

- Peptidomimetic macrocycles and formulations thereof
  - US 20160101145 A1 (Aileron Therapeutics)
- Systems, compositions, and methods for treating diabetes
  - US 2018/016647 (Vanderbilt – Abvance Therapeutics)
- Emolient topical disinfectants
  - WO 2018/017645 A1 (Iogen LLC)

Client applications not yet published

- Chemical responsive formulation
- Sustained release peptide formulation
- Co-formulation of peptides
Analytical Development

- 17 HPLC with diode array UV Vis, fluorescence, ELSD, RID detectors
- Molecular weight determination for polymers, proteins characterization
- UV/Vis fluorescence plate readers nanodrop for concentration, plasma compatibility, and solubility
- Particle size analyzer (laser diffraction) for micron-sized particles
- Dynamic light scattering with zeta potential for hydrodynamic radii estimation
- Stability Chambers certified and monitored (ICH conditions 25°C/60RH, 40°C/75RH, 2-8°C, -20°C, -80°C)
- SEM for microsphere visualization

Formulation Development

- Osmometer and Viscometer for characterization
- Microfluidizer, homogenizer, stirrers
- In vitro release testing for extended-release injectables
- Injection force measurement using Instron

Process Development

- Tray lyophilizer for cycle development
- Jacketed reaction vessels
- Laminar flow hood, depyrogenation oven, and autoclave in clean for preclinical and stability supply

Bioanalytical Development

- MSD ELISA for bioanalysis
- Gel electrophoresis imager for imaging protein gels

Chemistry

- Organic synthesis reactors
- FPLCs for protein purification
- Rotary evaporator
Test Article Preparation – Research to Toxicity Studies

Restricted Access – Training Required

Suite meets ISO Class 7

Laminar Flow Hoods
  - ISO Class 5 annual certification

Quality System Guidelines
  - Sterile Technique, Cleaning

Documentation System
  - Process Batch Records
Manufactured over 200 batches in the past 4 years

Batch size 800 µL to 2 liters (Capability to go to 10 liter batches)

Batch records and suite preparation signed off ahead of fill

Batch release testing with Certificate of Analysis
  - Concentration, purity, pH, osmolarity, endotoxin, and others

Formulation composition and process
  - Aqueous and non-aqueous solutions and suspensions
  - Liposomes, microspheres, gels, salts, and others

Formulation and fill finish manufacturing
  - 24 month shelf life now supporting phase 2 program
  - Stability studies to support ANDA filing
  - Several development studies for toxicology and clinical formulation selection
STATE-OF-THE-ART
PHARMACEUTICAL R&D LAB
Combination Drug Product Development

- Peptide and protein development
- Lead molecule profiling and half-life extension
- Subcutaneous and ocular formulation design and development
- Sustained release injectable formulations
- Device design and development
- Translation from research through clinical and commercialization
WE THRIVE ON SOLVING YOUR MOST CHALLENGING PROBLEMS
<table>
<thead>
<tr>
<th>Technique</th>
<th>Daily</th>
<th>Weekly</th>
<th>Monthly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acylation (albumin binder)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbohydrate analogues</td>
<td></td>
<td></td>
<td>HESylation, Glycosylation</td>
</tr>
<tr>
<td>Poly Amino Acid Fusions</td>
<td></td>
<td></td>
<td>XTEN, ELP, PASylation</td>
</tr>
<tr>
<td>PEGylation</td>
<td></td>
<td></td>
<td>Various including Reversible PEG</td>
</tr>
<tr>
<td>Albumin or Fc Fusion (FcRn recycling)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Lead Molecule Selection and Molecular Design

- Structural modifications to improve physio-chemical properties and extend half-life
- Amino acid variants for site-specific conjugation
- Mutation series and Fc fusions

Non covalent modifications to alter properties

- Salts and complexes to slow dissolution

Recombinant protein expression, peptide and oligonucleotide synthesis

Structural characterization, stability, and degradation products identification
ADVISORS AND EXPERTS

William Vincek, Ph.D.
President Pharma CMC, formerly SVP Development, Alpharma, Guilford Pharmaceuticals, GSK, Merck

Phil Duffy
Operations consultant in life sciences, previously SVP Pacira, VP at Ligand and Schein Bayer

Solomon Steiner, Ph.D.
CEO Perosphere Inc., previously CEO and Founder of Biodel, Mannkind, and Emisphere Technologies

Will Clodfelter, M.B.A.
Market & Device Development

Mark Longer, Ph.D.
Regulatory Strategy

Nelson Lugo, M.B.A.
Manufacturing

Bill Van Antwerp
Device and Diagnostics R&D
Dan Bradbury  
*Pharma Advisor*  
CEO Equilium, Chairman BioBrit, Former Amylin CEO

Donald Rindell  
*Business Advisor*  
Principal, Camino International, corporate strategy and business development

Eddie Rodriguez  
*Legal Advisor*  
Attorney at Troutman Sanders, corporate and legal advisor

Magda Marquet  
*Contract Services Advisor*  
Founder of Althea and Althea DX, successful sterile manufacturing