Translational “Bench-to-Bedside” Basic and Clinical Research: An Overview
IMMU 7630 Fall 2009
October 6, 2009

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Associate Professor
Psoriasis and Cutaneous Inflammation Research Laboratory
Department of Dermatology, University of Colorado Denver, Anschutz Medical Campus
Aurora, CO 80045 USA
Outline of Presentation

- Introduction
  - My Background in the Biopharmaceutical Industry

- What exactly is Translational Research (and Why)?
  - Where does it get done?
  - Who does it? What kind of training do you need?
  - How is it funded?
  - The FDA Approval Process and the Cost of Getting a New Drug to the Market
  - CCTSI on our campus is a great place to start

- Some Practical Examples of Translational Experiments

- Conclusions
Carl K. Edwards, III, Ph.D.
Background – October 6, 2009

**Training:**
- Immunology (University of Colorado Health Sciences Center)
- Immunophysiology (University of Illinois, Urbana-Champaign)
- Immunology and Infectious Diseases (Indiana University Medical Ctr, Indianapolis, IN)

**Research Interests:**
- Cutaneous Inflammatory and Joint Diseases (Psoriasis, Psoriatic Arthritis, RA)
- Transgenic and Knockout animal models of autoimmune disease
- Soluble TNFα and IL-1 Receptors/IL-1ra
- Molecular and Cellular Regulation of Proinflammatory Cytokines (TNFα, IL-1β, IL-32γ)
- Activation, Co-Stimulation, and Immunological Synapses of Human T-cells
The Coming Epidemic of ARTHRITIS

THE BAD NEWS: Research shows that the disease starts attacking your joints long before middle age
THE GOOD NEWS: The latest treatments are more effective than ever

21 Million Americans Suffer From Arthritis

New Drug Warnings & Alternative Treatments: What You Should Know
**Enbrel® (etanercept)**
Moderate-to-severe rheumatoid arthritis
Approved

**Enbrel® (etanercept)**
Ankylosing spondylitis (arthritis of the spine)
Approved

**Enbrel® (etanercept)**
Psoriatic arthritis Approved

**Enbrel® (etanercept)**
Moderate-to-severe juvenile rheumatoid arthritis
Approved

**Enbrel® (etanercept)**
Chronic moderate-to-severe plaque psoriasis
Inflammation
Approved

---

**Kineret® (anakinra)**

**How it works:** Kineret® is a recombinant form of a naturally occurring protein that regulates interleukin-1 (IL-1), a protein that is present in excess in patients with rheumatoid arthritis. By blocking IL-1, Kineret® inhibits the inflammatory response in rheumatoid arthritis.

**Related Link:**
Kineret® Prescribing Information
www.kineretrx.com

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**Pegsunercept®**

Research Highlights
*Nature Clinical Practice Rheumatology* (2006) 2, 121
doi:10.1038/ncprheum0107

**Pegsunercept is a safe and efficacious treatment for rheumatoid arthritis**
Katherine Sole

Preclinical studies have indicated that pegsunercept, a polyethylene-glycol-modified soluble tumor-necrosis-factor receptor type 1, is effective in treating rheumatoid arthritis (RA). Pegsunercept has also been shown to be well tolerated in a clinical trial. Investigators in the US have conducted a prospective, double-blind, randomized, placebo-controlled, multicenter, phase II trial, assessing the safety and efficacy of this treatment for RA.
What exactly is Translational Research?

- The “application of a basic or clinical discovery to medical practice”...
- “Pharmacogenomics” perhaps led the way to the new term of Translational Medicine over the last decade
- Examples of Questions include:
  - Who is at risk of developing cancer?
  - How aggressive is the tumor?
  - Will it metastasize?
  - To which organ?
  - How should the patient be treated?
  - How is the patient responding?
  - Why has the tumor become resistant?
  - What is the prognosis?
  - Is there a biomarker?
  - Is there a target therapy?

- Any observation made in the basic or applied laboratory that can expedite a novel idea or drug or process to the clinic for testing provided
  - Have shown adequate proof-of-concept in vitro, in vivo, or ex vivo
  - Clinically relevant!
  - Safety is always a concern, especially to the FDA
Why Translational Research?

• **Elias A. Zerhouni** (Arabic: إلياس زرهوني) M.D. (born 12 April 1951 in Algeria) was the 15th director of the National Institutes of Health, appointed by George W. Bush in May 2002.

• On September 24, 2008 he announced that he will step down as NIH Director at the end of October 2008. He joined the board of trustees for KAUST when the school opened in September, 2009.

• His accomplishments at the NIH have included the establishment of a research program into the problem of widespread obesity, and supporting the reduction of healthcare disparities.

• In April 2006, he told a Congressional subcommittee, "We can now clearly envision an era when the treatment paradigm of medicine will increasingly become more predictive, personalized and preemptive. We will strike disease before it strikes us with the hope of greatly reducing overall costs to society."
Reasons for Translational Approaches Biomedical Research

It is just plain “tough” conducting Federally-funded biomedical science today…
Still Another Reason for Translational Approaches Biomedical Research

The NIH is leading the way for funding Translational Basic and Clinical Studies so that there is more accountability for the research being conducted.....

<table>
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<th>Challenging Times for All Researchers</th>
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*RO1 Equivalents: RO1, R20, R37
Source: National Institutes of Health
Still Another Reason for Translational Approaches
Biomedical Research

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*RO1 Equivalents: R01, R20, R37
Source: National Institutes of Health
How Much Does it Cost to Get a New Drug Approved Today?
Fixing the drugs pipeline

Drug design: The more pharmaceutical companies spend on research and development, the less they have to show for it. What has gone wrong—and how can it be fixed?

The Economist

Rethinking Drug Discovery

When we last presented a special issue on Drug Discovery (17 March 2000), our focus was mainly on the deluge of information that genomics, proteomics, combinatorial chemistry, and rapid analytical methods would provide. That information revolution is in full swing, but data alone are not enough. In recent years, the number of new drugs approved annually by the U.S. Food and Drug Administration has been stagnant. Despite large increases in R&D investment, industry analysts, meanwhile, have expressed concern over a growing dependence on blockbuster drugs, as Science reports (p. 1796). Has the blockbuster syndrome itself become an obstacle to progress? Or are we simply seeing the normal lag that crosses before newly introduced methods bear fruit?

Research, at least, continues to suggest ways out of the deadlock. Walsh (p. 1803) focuses on the modular protein machinery that constitute polyketide and nonribosomal peptide antibiotics. Genetic engineering of the machinery might result in novel antibiotics, and at Science's STKE (www.stke.org), Shen describes how a synthetic pathway can be engineered in bacteria. Noble et al. (p. 1800) discuss the contribution of structural genomics to drug design for the protein kinase family, and at S1K, kinase disorders whether such single-target approaches are likely to be effective against genetically complex disorders. Also at STKE, Phillips describes antisense therapies that target enzymes that process RNA rather than the enzyme itself. Chait and Monji discuss how an increased understanding of the underlying pathways could lead to novel potential therapies for treating depression.

MacCoss and Baille (p. 1816) outline how the synthesis of more effective analogs of lead compounds now takes many cues from the more readily obtained data on bioavailability and toxicity. Jorgensen (p. 1813) reviews how computational methods address these concerns as well as guide the design and screening of compounds for binding to potential biomolecular targets. Allen and Collins (p. 1816) review how drug delivery systems can improve targeting and reduce toxicity, especially for anticancer and antifungal agents. At SAGE KE (www.sagenet.org/ke/drag), Ruben describes the role of information-dependent interactions in drugs with immunological and immune receptors in the progression of Alzheimer's disease. Gilbody discusses the state of antiviral drug discovery in the context of aging and neurodegenerative diseases.

What is clear is that the "pipeline" problem is not caused by a lack of research effort or even funding. Science's Next Wave (www.sciencemag.org/nextwave) explores the career potentials and pitfalls of drug discovery. Overcoming the obstacles in drug discovery will likely require continued efforts to provide insights into disease pathways and greater diversity of candidate drug molecules.
The FDA Approval Process

- The drug development and approval process is a systematic approach that ensures a drug receives thorough testing and scrutiny before becoming available for public use.

- This process can be quite lengthy:
  - A typical compound discovered today may not become FDA approved for general use for *12-15 years or more*. [1]
  - It is during this extended period that the FDA requires a drug to undergo clinical trials to prove the safety and efficacy of the drug.
  - The average new drug application (NDA) for a new prescription drug compound is based on nearly 70 clinical trials, which may involve over 4,000 patients [2]


The FDA Approval Process

- A drug considered safe does not necessarily mean that the drug is free of adverse effects; it only means that the drug has a positive risk-to-benefit ratio.
- A positive risk-to-benefit ratio means that the benefits of the drug outweigh any known risks of using the drug.
  - For example, the non-steroidal anti-inflammatory drugs (NSAIDs) (naproxen, ibuprofen, aspirin, indomethacin, etc.) are known to cause gastrointestinal ulcerations; however, these drugs are a very beneficial to millions of arthritis sufferers who depend on them to lead productive, normal lives.
  - The NSAIDs also cause many deaths annually due to allergic reactions, but this risk is far outweighed by the potential benefit of this class of drugs to the public.
Steps in the FDA Approval Process

- The drug approval process evolves through various steps and takes an average of 15 years to complete the entire process.

- These steps can be defined as follows:

  1. The Discovery Process (2-10 years) Avg 6.5 years
  2. Preclinical Testing (2-4 years) Preclinical testing
  3. Phase I Clinical Trials (1-2 years) Avg 1.5 years
  4. Phase II Clinical Trials (1-3 years) Avg 2 years
  5. Phase III Clinical Trials (2-5 years) Avg 3.5 years
  6. FDA Review/ Approval (1-2 years) Avg 1.5 years
  7. Phase IV/ Post-Marketing Review ongoing
The great challenge faced by the pharmacogenomics industry at this point is the systematic correlation between normal versus disease patterns of gene expression in a statistically meaningful way.

Nature Biotechnology. 2004
Conclusions

Drug approval standards in the United States are considered by many to be the most demanding in the world.

By law, all new drugs must first be shown to be safe and effective before they can be approved by the Food and Drug Administration (FDA) for marketing.

Discovering a new drug, and shepherding it through FDA’s review process, can take many years, and cost hundreds of millions of dollars.

- To a large degree, these costs are mostly associated with the clinical testing that must be done to convince the agency that the new product is safe and effective for its intended medical use.

Once a new drug’s clinical testing is complete, the sponsor submits a New Drug Application (NDA) for FDA evaluation. During the application’s review, agency officials examine the drug’s safety and efficacy data, assay samples, and conduct factory inspections to be sure the finished product will be manufactured properly.

Typically, when FDA finishes its review, it notifies the applicant by letter stating that its NDA is either approved, would be approved if changes are made, or cannot be approved due to unresolved problems.
Please distribute this information to your faculty.

TO: Departmental Funding Contact
FROM: John W. Moorhead, Ph.D., Associate Dean, Research Affairs

“What Can the CCTSI Do For You?”
Presenting the Nuts & Bolts of the CCTSI Cores

The CCTSI “Nuts and Bolts” series is open to K Club members and the greater campus community to introduce the offerings of the CCTSI and clarify how these resources can be leveraged to accelerate your research. These sessions provide an overview of the CCTSI cores including: Discovery Translation, Communication Translation, Translational Technology, Child and Maternal Health, Community Engagement Research and Translational Informatics. Three short sessions are planned during the 2009-2010 academic year.

**Topics covered**
- Biostatistics, Epidemiology, Research & Design (BERD)
- Regulatory and Ethical Issues
- Participant and Clinical Interactions Resources (PCIR)

**Monday, October 12, 2009**
3:00 – 5:00pm
Academic Office 1, L15-7000 Board Room

Coffee and snacks will be provided
Emerging Trends in Inflammation and Autoimmune Disease Biomedical Research

- Identification of immune cells causing destruction in the skin and synovial joint(s)
- Characterization of the anti- and pro-inflammatory cytokines and other molecules that communicate intracellularly within cells and extracellularly between cells
- Distinction between inflammation and tissue/joint destruction
- Development of newer treatments that prevent tissue/joint destruction with minimal side effects
Who is Performing Translational Research Today?

- Ongoing standard programs at most Biotechnology and Pharmaceutical Companies
  - Very expensive to conduct Translational Clinical Research and then have it become “validated”
  - Biomarkers

- Many Clinical Research Operations
- Clinician Researchers
- Basic Researchers who conduct Clinically-based research
“YOU’VE GOT TO FEAR MCCOVEY MORE THAN YOU DO A .340 OR .350 HITTER WHEN HE’S IN POSITION TO BAT IN THE WINNING OR TYING RUN. I THINK YOU COULD HURT THE GIANTS IF YOU WALKED MCCOVEY EVERY TIME HE CAME UP.”

SPARKY ANDERSON
THE SPORTING NEWS, 1973
Baseball Hall of Famer
Willie McCovey
July 2004
PLAY NOW, PAY LATER

can no longer use his right hand.
Like so many former NFL players, he is doomed to a life of pain and disability.
“...Scientists will discover that a single peptide from a protein found in human joints is the target of the autoreactive T cells that initiate rheumatoid arthritis in more than half of the cases of this disease. Clinical trials in which the peptide is given in various forms to prevent the disease will be started in the year 2005 and ended in 2050 for lack of patient enrollment...”

Philippa Marrack
Howard Hughes Medical Institute
Denver, Colorado
Cytokine Fun Fact:
The original Tumor necrosis factor binding proteins were described by David Wallach at the Weitzmann Institute in 1987
*these proteins were isolated from nearly 600 liters of urine obtained from nuns living near Turin, Italy
*this material is still being used to today to isolate new cytokines and soluble cytokine receptors (IL-18, IL-18BP, IL-32, IL-36, especially by Charles Dinarello, M.D.)
Development of Anti-TNF Therapy for Chronic Inflammatory Diseases

Feldmann 2002
Structure of TNF Inhibitors

sTNF-RI is a Novel, High-affinity Soluble TNF Receptor
It takes “Teamwork” to get a Therapeutic Agent to the Clinic!

PEG r-metHu-sTNF-RI Therapeutic Product Team-Amgen, Inc. Boulder, CO
Investigational New Drug Application Filing - March 31, 1998
Swollen Joint Count Change from Baseline by Treatment Group-Weekly Cross-Sectional Analysis
Comparison of Patient Population in sTNF-RI vs. Enbrel®

- Improve upon Current Standard of Care
- Broad patient population

**Amgen - ph 2A/B study**
- sTNF-RI + DMARD Failure (no DMARDs)
- sTNF-RI + MTX
- sTNF-RI + MTX + 1 > DMARD
- sTNF-RI + other single DMARDs

**Immunex - Enbrel MTX ph 2 study**
- Enbrel + MTX
Phase 2 Weekly Dosing Results Suggests that sTNF-RI has Similar Efficacy to Twice-Weekly Dosed Enbrel in the No DMARD Subgroup
ACR Component Scores

![Graphs showing changes over time for various ACR component scores](image)

**Results**

- TP Joint Count
- SW Joint Count
- Physicians Assessment of Disease Activity
- Patients Assessment of Disease Activity
- Patients Assessment of Pain
- HAQ
- CRP (mg/dL)
- ESR (mm/hr)

**Legend**

- Treatment Group: ● Placebo (N=61) ● 400 µg/kg (N=67) ● 800 µg/kg (N=66)

**Notes**

* p < 0.05, ** p < 0.01, † p < 0.001, TP = tender/painful, SW = swollen, HAQ = health assessment questionnaire, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate. Absolute baseline values are given in Table 3.

_Furst et al. 2004_
The Six Phases of a Drug Development Project

1. Enthusiasm
2. Disillusionment
3. Panic
4. Search for the guilty
5. Punishment of the innocent
6. Praise and honors for the nonparticipants
brave new PHARMACY

By MICHAEL D. LEMONICK

INSIDE AN OLD FACTORY BUILDING IN Cambridge, Mass., a remarkable machine with the improbable name Zeus is hard
The great challenge faced by the pharmacogenomics industry at this point is the systematic correlation between normal versus disease patterns of gene expression in a statistically meaningful way.

*Nature Biotechnology. 2000;18:IT40/IT42*
Figure 1: An ultimate clinical goal of pharmacogenomics. 

(a) Current state of drug development research

Proportion of patients who respond to drug

Population of patients with given disease

Patients receiving drug

(b) Ideal future objective of drug development research

Population of patients with given disease

All or nearly all respond to different drugs according to genotype

At present, only a limited number of patients are treated with a specific drug for any given disease due to adverse events. Of those patients who are receiving the drug, not all respond.

One ideal goal that is anticipated from pharmacogenomics is to personalize or "taro" therapies, so that, on the basis of pre-genotyping, all patients who have a given disease will receive different drugs and respond to therapy with less risk of adverse events.
Objectives of Predictive Medicine

- Identify patient subpopulations that may be more responsive to one drug versus another
- Identify surrogate markers that can be utilized to determine if the drug is efficacious
- Identify novel gene targets that can be utilized for drug discovery
<table>
<thead>
<tr>
<th>Role</th>
<th>Description</th>
<th>Examples</th>
</tr>
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<tr>
<td>Disease biomarkers</td>
<td>Indicate the presence or likelihood of a particular disease in patients or in animal models.</td>
<td>High blood levels of proteins (troponin, C-reactive protein) associated with risk of stroke or heart disease, genotypes and gene expression profiles linked with cancer.</td>
</tr>
<tr>
<td>Surrogate endpoints</td>
<td>Accepted by the FDA in support of drug approval as a substitute for desired clinical outcome, and often can be measured months or even years before meaningful clinical endpoints like mortality or morbidity.</td>
<td>Blood pressure, tumor shrinkage, psychometric testing, pain scales, CD4 blood count for HIV AIDS.</td>
</tr>
<tr>
<td>Efficacy or outcome biomarkers</td>
<td>Correlate with the desired effect of a treatment, but do not have as much validation as surrogate endpoints.</td>
<td>Pain scales, lung function tests, electrocardiogram readings, bone density, blood or urine levels of proteins and other analytes associated with disease.</td>
</tr>
<tr>
<td>Mechanism biomarkers</td>
<td>Suggest a drug affects the desired pathway.</td>
<td>Evidence of downstream effects of the drug, such as activation or deactivation of enzymes and receptors.</td>
</tr>
<tr>
<td>Pharmacodynamic biomarkers</td>
<td>Used in early clinical trials to determine the dose that has the highest response. This dose is often below the maximum tolerated dose.</td>
<td>Blood or urine levels of proteins and other analytes associated with disease.</td>
</tr>
<tr>
<td>Target biomarkers</td>
<td>Show that a drug interacts with a particular target in in vitro studies, preclinical studies and, increasingly, in in vivo imaging studies.</td>
<td>PET imaging studies to show residence time on a receptor.</td>
</tr>
<tr>
<td>Toxicity biomarkers</td>
<td>Indicate potentially harmful effects of a drug in cell-based, preclinical or clinical studies.</td>
<td>Q-T prolongation; induction of cytochrome P-450.</td>
</tr>
<tr>
<td>Bridging or translational biomarkers</td>
<td>Can be used in both preclinical and clinical studies and may also be disease, efficacy or toxicity biomarkers.</td>
<td>Any of the above examples that can be assessed in both humans and animal models of disease.</td>
</tr>
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</table>
Mean Log Transformed IL-8 Level Change From Baseline by Treatment Group and Treatment Week ACR20 Responder
Box 2 | Remaining challenges for the treatment of psoriasis

- Understanding the true mechanism of action of new drugs in psoriatic plaques and joints. Open questions include the following: why do the TNF-targeting biologicals behave differently in patients? Why is the onset of the clinical benefit of alefacept relatively slow if it induces apoptosis? What is the mechanism of efalizumab-induced rebound?
- Understanding the predominant mechanisms of pathogenesis in psoriasis and psoriatic arthritis.
- Understanding differing patient response to therapy.
- Predicting clinical response before or early in therapy.
- Reducing the cost of treatment.
- Developing more convenient formulations (oral, inhalation and topical).
- Demonstrating the benefits to society of better treatments for psoriasis.
- Determining whether early treatment of psoriasis prevents psoriatic arthritis.
- Determining whether treatment alters the long-term behaviour of psoriasis in individual patients.
Looked at histology, gene expression and cellular infiltration in a total of 10 patients treated with etanercept for 6 months.

Results showed:

- Rapid and complete reduction of IL-1 and IL-8
- Slow reductions in infiltrating CD11c+ cells and T cells

Molecular mechanism of inhibition was not addressed.
Flow Chart Protocol #06-0303: Sample collection and Processing Flow Chart

Obtain written Informed consent

No → STOP

Yes

Give donor a copy of the informed Consent. Retain a copy of the signed Informed Consent.

Collect 15 ml of whole blood

Collect 1 x 4mm Punch biopsy (Involved Skin); Collect 1 x 4mm Punch biopsy (Uninvolved Skin)

A. 2 x PAXgene Tubes (2.5 mLs each)
B. 1 x VACUTAINER Blood Collection Tube (3.0 mLs each)
C. 3 x 15 mL Falcon Tissue Culture tubes (2.33 mLs each); C1 = RPMI Media; C2 = RPMI + 10 ng TNFα; C3. RPMI + Heat-Killed S.aureus.

Processing of biopsy tissue:
1. Each biopsy divided in half;
2. One half of each biopsy is snap frozen (-70°C);
3. One half of each biopsy is added to OCT solution;

• Snap frozen (-70°C) biopsy tissue sent to Dr. Lisa Sicolfini (SMDx) for Total RNA Processing and Q-PCR Analysis;
• OCT/biopsy tissue sent to Dr. James Fitzpatrick (IF Lab) for Immunohistochemistry

Coded tube Sent to Dr. James Fitzpatrick (CBC Analysis)

Coded tubes (Frozen) sent to Dr. Lisa Sicolfini (SMDx) for Total RNA Processing and Q-PCR Analysis

Sent to Dr. Carl Edwards, Department of Dermatology, UCDHSC; Ex Vivo Whole Blood Assay
We are currently using Precision, Quantitative “Real-Time” PCR Gene Expression Analysis to Determine Patient Subpopulations and Cytokine Biomarkers
Distribution of Gene Expression in Blood Bank Population (N=271)
Inflammatory Loci Show Consistent Standard Deviations for Gene Expression Levels Across the Linear, Measurable Range
The Comprehensive Use of Human Functional Genomics is a Major Focus of The “Biopharmaceutical” Industry Today

3.1 billion bases
30,000 genes

Proteins, their function and connections

-> Proteomics
2003 INVESTING GUIDE

MUTUAL FUNDS FOR THE LONG HAUL

U.S. News & WORLD REPORT

JANUARY 20, 2003

THIS DRUG'S FOR YOU

NEW TARGETED MEDICINES PROMISE BREAKTHROUGH CURES
Summary

Translational Research Appears to Be Catching On:

- Cancer Indications
- New Drugs and Quicker Decisions
- More Human Tissue Systems
  - IRB Issues
- FDA has adopted criteria for Biomarker Validation
- NIH is focused on these types of studies
- Good Opportunities to conduct this work here at UCD
Psoriasis and Cutaneous Inflammation
Research Laboratory Collaborators

David Norris MD  Asokan Rengasamy PhD  Charles Dinarello MD  Mayumi Fujita MD PhD  Elan Eisenmesser PhD  Karen Jonscher PhD

John Mountz MD PhD  Mark Pettrash PhD  Eugene Butcher MD
Collaborators – October 2009

**Dermatology – UCDHSC**

David Norris, M.D.
Mayumi Fujita, M.D., Ph.D.
James Fitzpatrick, M.D.
John Ansel, M.D.
Cheryl Armstrong, M.D.
Cory Dunnick, M.D.
Ling-Jia Hu, M.D., Ph.D.
Li Li, M.D., Ph.D.
Ewen Callaway, M.S.
Hillary Somerset – Medical Student
Karen Helm, M.S.

**Medical Genetics - UCDHSC**

Richard Spritz, M.D.

**Infectious Diseases – UCDHSC**

Charles Dinarello, M.D.
Soo-Hyun Kim, Ph.D.

**Anatomical Pathology**

Kenneth Shroyer, M.D., Ph.D.

**Technology Transfer – CU**

David Allen
Rick Silva, Ph.D.

**External Collaborators**

John Mountz – UAB
Linc Moldawer – UF

Eugene Butcher – Stanford
Robert Modlin – U.C.L.A.