BRIEF HISTORY OF KEY EXPERIMENTAL TOOLS USED IN PHARMACOLOGY

• 1700-1975: Whole animal systems
  Development of rodent models

• 1975-1985: Intact organ systems
  Isolated perfused liver and kidney; in situ perfused brain

• 1985-1995: Isolated cellular systems
  Hepatocytes for metabolism, transport

• 1995-2005: Isolated protein systems
  Expression systems for enzymes, transport proteins, and receptors
RESULTS OF THESE EVOLUTIONARY CHANGES

• Excellent understanding of discrete molecular mechanisms
• Excellent understanding of the contribution of genetics to drug response
• Diminished understanding of how multiple mechanisms interact
• Diminished understanding of modulation of genetic predisposition to environmental factors
ADDITIONAL FACTORS DRIVING THE SHIFT AWAY FROM INTEGRATED BIOLOGIC SYSTEMS

• Increasing costs associated with animal-based research
• Increasing regulatory complexity associated with animal-based research
• Increasing political complexity associated with animal-based research
EXPERIMENTAL PROCEDURES IN ANIMALS

Development of animal use in the 20th century

SKILLS THAT HAVE BEEN “LOST”

- Technical aspects of animal experimentation
  *Substrate administration; sample collection; biologic measurements*

- Approaches to experimental design
  *Animal models of disease; inter-animal variability; design optimization*

- Philosophy of animal experimentation
  *Research ethics; animal-to-human predictions; interpretation of effects of multiple mechanisms*
COURSE PREMISE

The overall result of the shift away from integrated biologic systems is an acknowledged deficiency in expertise in whole animal and intact organ experimentation.
**COURSE OVERVIEW**

- Consists of a six-day intensive experience
- Emphasizes routine rodent procedures, isolated organ systems, and neuropharmacology
- Includes lectures, demonstrations, and hands-on laboratory exercises
- Animal models consist primarily of mice and rats, with some introduction to higher models (rabbits, dogs, pigs, nonhuman primates, horses)
COURSE OBJECTIVES

- Introduce basics of animal handling
  - Aspects of animal housing and care
  - Exposure to a variety of species
  - Principles of surgical anesthesia
  - Post-surgical care
COURSE OBJECTIVES

• Introduce basics of animal handling

• Introduce methods of whole animal pharmacokinetic experimentation
  • Vascular access
  • Modes of drug administration
  • Techniques for sample collection
COURSE OBJECTIVES

• Introduce basics of animal handling

• Introduce methods of whole animal pharmacokinetic experimentation

• Illustrate methods of intact organ pharmacokinetic experimentation
  • Isolated perfused liver
  • Isolated perfused kidney
  • *In situ* perfused brain
  • *In situ* intestinal loop
COURSE OBJECTIVES

• Introduce basics of animal handling

• Introduce methods of whole animal pharmacokinetic experimentation

• Illustrate methods of intact organ pharmacokinetic experimentation

• Introduce methods of whole animal pharmacodynamic experimentation
  • Behavioral techniques
# COURSE SCHEDULE (2011)

<table>
<thead>
<tr>
<th>Time</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
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<tbody>
<tr>
<td></td>
<td>June 19th</td>
<td>June 20th</td>
<td>June 21st</td>
<td>June 22nd</td>
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<td>Sunday</td>
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<td>Wednesday</td>
<td>Thursday</td>
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<td>8:30am - 9:00am</td>
<td>BREAKFAST</td>
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<tr>
<td>9:00am - 10:00am</td>
<td>Mouse Handling</td>
<td>Non-Human Primate Models</td>
<td>Canine Models</td>
<td>Francis Owen Blood Research Laboratory (Porcine)</td>
<td>Rotations</td>
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<td>10:00am - 11:00am</td>
<td>Rat Handling</td>
<td>Surgery</td>
<td>Handling</td>
<td>Research Laboratory</td>
<td>Rotations</td>
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<td>11:00am - 12:00pm</td>
<td>Aseptic</td>
<td>IACUC</td>
<td>Bellinger</td>
<td>Godfrey, Bellinger</td>
<td>Rotations</td>
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<td>4:00pm - 5:00pm</td>
<td>DINNER</td>
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<td>Group Dinner</td>
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<td>5:00pm - 6:00pm</td>
<td>Overview of Course</td>
<td>NIH Video - Surgical Techniques</td>
<td>Mouse Handling</td>
<td>Equine Handling</td>
<td>Rotations</td>
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<td>6:00pm - 7:00pm</td>
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<td>Paine, Everitt</td>
<td>IACUC</td>
<td>Godfrey</td>
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<td>Carolina Brewery</td>
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</tbody>
</table>

**POSSIBLE ROTATIONS:**
DAILY SCHEDULE

Sunday – Day 1

• Registration begins late afternoon
• Overview of course – M. Paine
• Animal models in pharmaceutical industry – J. Everitt
• NIH video on surgical techniques
• Group dinner
DAILY SCHEDULE

Monday – Day 2
• Mouse handling
• Rat handling
• Aseptic technique
• Surgical techniques

Tuesday – Day 3
• Nonhuman primate lecture
• Mouse handling
• Mouse necropsy
**DAILY SCHEDULE**

**Wednesday – Day 4**
- Dog, rabbit, pig lecture
- Dog and rabbit handling
- Rotations*
- Group dinner at local restaurant

**Thursday – Day 5**
- Pig necropsy
- Horse handling
- Ice-cream!

**Friday – Day 6**
- Rotations*

*Jugular vein cannulation, femoral vein cannulation, portal vein cannulation, metabolic cages, isolated perfused liver, isolated perfused kidney, *in situ* brain perfusion, brain slicing, *in situ* intestinal loop, osmotic minipumps, microdialysis, behavioral techniques
COURSE OBJECTIVES

• Seek participant feedback for continued success.
• Continue interactions between course faculty, instructors, and participants.
Next course at **UNC** planned tentatively for mid-late June, 2012

ACKNOWLEDGEMENTS

- Former Principal Investigator: Gary Pollack, PhD
- Course Coordinator: Kristina Wolf, PhD
- Lead Teaching Assistant: Christina Won, PharmD
- Strategic assistance: Arlo Brown
  - Kristina Wolf, PhD
  - Adam Persky, PhD
- Host institution: UNC at Chapel Hill
- Funding: National Institutes of Health