AN ORGAN SYSTEMS APPROACH TO EXPERIMENTAL TARGETING OF THE METABOLIC SYNDROME

Funded by the National Institutes of Health (GM-086771)
Lecture Outline

• Introduction and Business
• NIGMS: Short Course Program
• Outline of Vanderbilt Short Course
• Responsible Conduct in Research
Who are we?

- Owen McGuinness (Course Director)
- Masakasu Shiota (Associate Director)
- Fiona Harrison (Associate Director)
- Fran Tripp (Course Coordinator)
Housekeeping Items

• Parking
• Accommodations
• Food
• When you work with animals
  – Wear gloves and a disposable gown
• Course web site:
  • http://www.mc.vanderbilt.edu/diabetes/msshortcourse/index.php
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Background

• **NIGMS-Sponsored Integrative and Organ Systems Pharmacology: Short course**
  – demand for researchers with experience in the use of isolated organ systems and whole animal methods in pharmaceutical industry
  – Limited training using isolated organ systems and animal methods in core graduate student curriculum
  – Lack of physiological training limits ability to translate to human disease
  – NIGMS funded four Courses in 2005
Other Short Courses

• Michigan State University
  – June 3-15
  – autonomic, renal, gastrointestinal, computer modeling, cardiovascular, respiratory, and neuropharmacology

• University of Nebraska
  – June 4-15
  – Neuro and cardiovascular pharmacology

• University of North Carolina at Chapel Hill
  – June 10-15
  – Preclinical skills with emphasis on rodents

www.aspet.org/public/public_affairs/pa_NIGMS_shortcourse_awards.html
Vanderbilt Short Course

• Disease focus
  – Obesity Epidemic
  – Disease that crosses multiple disciplines
    • Hypertension (cardiovascular system)
    • Diabetes (endocrinology and metabolism)
    • Behavior
    • Dyslipidemia and atherosclerosis
    • Cancer
  – Many coexist
    • Metabolic syndrome
Metabolic Syndrome

Risk Factors
• Insulin resistance
• Central obesity
• Dyslipidemia
• Hypertension
Vanderbilt’s Core

• Diabetes Research and Training Center (DRTC)
  – Metabolic Physiology Shared Resource Core (Human, Rat and Dog)
  – Islet Procurement and Analysis Core
• Mouse Metabolic Phenotyping Center (MMPC)
  – Metabolic Pathophysiology Core
  – Subcore: Lipids, Lipoproteins, and Atherosclerosis
• Murine Neurobehavioral Laboratory (MNL)
• Institute of Imaging Science
  – Small animal imaging
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Our course

• Lectures
• 10 Laboratories
• 9 Group Discussions
Outline (Week 1)

• Monday –Tuesday
  – Animal behavior (rat and mice)
  – Animal care
• Wednesday –Thursday
  – Glucose metabolism
  – Glucose tolerance tests (mice and dog)
• Friday
  – Islet physiology
  – Islet isolation and Characterization
  – Load Animals into CLAMS
• Saturday
  – Cardiovascular/renal system
  – CV and glucose lab
Outline (Week 2)

• Monday
  – Lipid metabolism
  – Student presentations

• Tuesday
  – Pharmacology 101
  – Liver perfusion lab
  – Group Dinner at “Wildhorse Saloon”

• Wednesday
  – Energy balance

• Thursday
  – Advanced Imaging Technology
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Adnan Hajj’s Smoking City Photo

• Data Manipulation in 2006

Computers and Data

• The number of reported ethical problems involving publications of American Physiological Society (in 14 separate journals) rocketed from an average of less than one a year before 1999 to more than 50 a year in 2004, when all of the society’s publications became available online

Responsibility comes with authorship

- A paper in *Nature* co-authored by Nobel prizewinning scientist Linda Buck has been retracted after the researchers were unable to reproduce the results. The authors now report that they have found “inconsistencies” between the original data and the data published in 2001.

“Too good to be true”

“Nature ...(1 April 2009) is retracting a 2000 paper that promised an advance in diabetes treatment using gene therapy.”

- We used a recombinant adeno-associated virus (rAAV) that expresses a single-chain insulin analogue (SIA), which possesses biologically active insulin activity without enzymatic conversion, under the control of hepatocyte-specific L-type pyruvate kinase (LPK) promoter, which regulates SIA expression in response to blood glucose levels. Here we show that SIA produced from the gene construct rAAV-LPK-SIA caused remission of diabetes in streptozotocin-induced diabetic rats and autoimmune diabetic mice for a prolonged time without any apparent side effects.
- a patent was pending
It takes a long time to purge fraudulent material.

- Thioridazine and withdrawal dyskinesias on workshop performance of mentally retarded young adults Brunning SE
- After nearly 20 years citations still exist

Scientific Record Keeping

- Collection
- Storage
- Ownership
- Sharing
DATA COLLECTION

• Why do we need to keep good records?
  – To record our progress
  – To build upon for new research
  – To support our claims in grants and papers
  – For audit purposes
  – For the approval process of new drugs or medical devices
  – To establish intellectual property claims
  – To establish that appropriate authorization was granted
Good data books:

- Are sufficiently legible
- Are mostly organized
- Are up to date
- Allow repetition of your experiments
- Are compliant with granting agency and institutional requirements
- Are accessible to authorized person, stored properly, and appropriately backed up
- Are the ultimate record of your scientific contributions
- Stay in the lab
DATA STORAGE

• Raw data, notebooks and computer files
  – Safe place
  – Back ups
  – Prevent sample degradation
  – Risk of fire, flood etc

• Confidentiality

• Retention periods
  – *What is a reasonable period of time?*
  – NIH: 3 years after final financial report
  – Know individual organizations’ rules
WHO OWNS WHAT?

• Those who provide money for research
  – Government agencies
    • grants (institution)
    • Contracts (government)
  – Private sector (generally the funding source)
  – Philanthropic organizations (Varies)
DATA SHARING

• Intuitive in the scientific tradition
• Supports open scientific inquiry
• NIH:
  – Data should be made as widely and freely available as possible
  – Grants usually must contain plan for sharing of data, animals and reagents
• Special circumstances:
  – Complexity of projects
  – Multi-site investigations
  – National security
Scientists are INTERESTED in

- Advancing knowledge
- Discoveries that benefit society
- Professional advancement
- Personal gain and satisfaction

- However these often can be **in conflict**!
Types of conflict

• Financial Conflict
• Intellectual conflict
  – Grant or manuscript review
• Conflict of Commitment
  – Percent Effort
  – Teaching/Advising
  – Paid Consultant
CONFLICT OF INTEREST

- Exists when an individual (appears to) exploits his position for personal gain or for profit of his immediate family
- Undue use of position or exercise of power to influence decisions (VU guidelines)
- Rule of thumb: if an educated outsider could perceive there is a conflict, then there is likely a conflict
Today

8:40-9:30 An overview of the metabolic syndrome in humans: Owen McGuinness PhD

Break

9:45-10:50 What is normal animal behavior? Fiona Harrison PhD

11:10-12:00 How to measure animal behavior and perform a neurological screen: Examples of therapeutics which alter behavior Fiona Harrison PhD

12:00-1:00 Lunch:

1:00 Tour animal facility (MMPC and then walk over to Neurobehavioral core)

1:30-4:30 Lab I: Working with mice: Murine Neurobehavioral Laboratory