Drug / Contrast Agent Discovery, Imaging Modalities and Kinetic Analysis

Course: Biomedical Engineering (BME) 524, Cancer Biology 524, Pharmacology 524

Semester: Spring 2011

Unit Credit: 3 units

Instructors: Terry Matsunaga Pharm.D., Ph.D. (Research Professor, Radiology Research), Russell Witte (Assistant Professor of Radiology and Director of the Experimental Ultrasound and Neural Imaging Laboratory). Lars Furenlid Ph.D. (Associate Director, Center for Gamma-Ray Imaging and Professor, Department of Radiology and Optical Sciences), Eric C. Clarkson Ph.D. (Associate Professor, College of Optical Sciences and Radiology Research), Evan C. Unger, M.D. (Professor of Radiology and Biomedical Engineering), Ted Trouard Ph.D. Associate Professor Biomedical Engineering and Radiology
Class Meeting Time: Tues - Thurs 11:00 am- 12:15 pm, (75 min.)

Location: Medical Research Building 302 or to be announced.

Required Text: None

Prerequisites: 1st, 2nd or 3rd year graduate or 4th year undergraduate status in Biomedical Engineering, Chemistry, Cancer Biology, Pharmacology, or other Physical or Biological Sciences and a minimum of one year of undergraduate Calculus. An understanding of chemical kinetics is desirable.
Grading: Based upon class participation, midterm (1) journal review presentations (2), and final written project. Students will provide publications that will be reviewed in class. There will be a 40% weighting between presentations (2 x 20), one midterm (20%) and the final written project (40%) which will comprise writing a 6 page proposal similar to a R21 NIH grant proposal. In addition, the participant will be required to critically review a journal publication for discussion during class. The final project report (minimum of 6 pages, single space, 11 point) will be due at the end of the semester the week before final exams. Topic recommendations will be discussed and approved during the semester.

Description: Current Topics in drug discovery and molecular imaging involve the integration of a series of research modalities. The Pharmaceutical Industry uses these modalities in their developmental and regulatory efforts to attain new indications. As well, the Medical device community is continually developing new techniques to enhance medical imaging for the earliest detection of disease. Furthermore, kinetic ADME studies (absorption, distribution, metabolism, and excretion) are required so as to determine the fate of these agents as an indicator of efficacy and toxicity.

The major objective of this team-taught course is to introduce the student to state of the art methods for drug discovery, contrast agent discovery, the newer imaging methodologies, and how the biodistribution of these agents affects their efficacy and dosing. A description of the topics are provided below:

Contrast Agent Discovery: After comparing the characteristics of each molecular imaging modality as an introduction to the course, the properties of contrast agents for each modality will be presented. Applications of imaging methods and contrast agents will then be discussed, including molecular targeting, responsive detection of molecular biomarkers, assessments of flow, perfusion, and permeability. Finally, these concepts will be combined during a discussion of multi-modality imaging.

Molecular Imaging: Smart Contrast: The purpose of this section will be to teach how molecular imaging is evolving towards selective/specific detection of target cells or landmarks. The first seminar will review terminology and give examples of contrast agents. How can they become "smart" for molecular targeting, functional imaging and therapy? What are the primary design considerations when making a new agent? Two other seminars will discuss application areas of smart contrast agents and focus on the brain and heart. Seminars will reflect on the role of contrast agents in these application areas and limitations of these agents. What imaging and treatment paradigms are on the horizon?

Imaging Applications: This section will provide discussions on the clinical utility of imaging modalities outlining the rationale for utilizing selective imaging applications for particular disease states. In addition, a brief treatise on the research methodologies (high throughput screening) for identifying molecular imaging agents for these applications will be discussed.

Radionuclide Molecular Imaging: These lectures will provide a basic overview of the principles and practice of molecular imaging with radiotracers. After an introduction to the principles of radioactive decay and gamma-ray emission, the lectures will cover the generation and isolation of radioisotopes and the basic techniques of radiochemistry such as labeling reactions and purification. The lectures will then progress into the mechanisms and dynamics of radiopharmaceutical uptake and distribution in the body. Finally, imaging applications using autoradiography, SPECT, and PET will be discussed.

Biodistribution Kinetics (Absorbtion, Distribution, Metabolism, and Excretion): In the first lecture we will describe single-compartment models for pharmacokinetics in both graphical and mathematical terms. We will review in detail the mathematical solution to the resulting differential equation, and discuss its implications in terms of time- activity curves. The mathematics needed to understand this discussion are covered in a first year calculus course. In the second lecture we will discuss two-compartment models as a system of two differential equations and discuss their solution using a matrix formulation. Some familiarity with matrices will be helpful here, but not necessary as we will cover the important concepts in the lecture. Examples, with corresponding time-activity curves, will be provided. In the third lecture we will introduce models with N compartments and discuss in general terms the mathematical form that the time-activity curves take and how they are related to the compartmental matrix. For the fourth lecture we will introduce the concept of an identifiable parameter and show, for the 1, 2 and N compartmental models, what the identifiable parameters are when there is access to a single compartment. Finally, in the fifth lecture we will discuss how imaging can be used to increase the number of identifiable parameters and provide some examples that demonstrate this result.

Regulatory Issues (FDA/EMEA): The purpose of this section will be to provide the student with an introduction to the issues involved when translating technology from the benchtop to the regulatory authorities prior to conducting pre-clinical (animal) and clinical (human) trials. This set of lectures will include such topics as Good manufacturing Practices (cGMP), Chemistry, Manufacturing, and Controls, pre-clinical toxicology, pre-clinical pharmacology (efficacy), Investigational New Drug Submissions (IND), Investigational Review Boards (IRBs), and Clinical Trials (Phase I, II, and III, pivotal trials (IIb)) and post-market surveillance.

Enrollment: Those interested in enrolling, please contact Dr. Terry Matsunaga at 626-6689 or 982-5688 as soon as possible.

Academic Integrity

According to the Arizona Code of Academic Integrity (http://dos.web.arizona.edu/uapolicies/cai2.html), "Integrity is expected of every student in all academic work. The guiding principle of academic integrity is that a student's submitted work must be the student's own." Unless otherwise noted by the instructor, work for all assignments in this course must be conducted independently by each student. CO-AUTHORED WORK OF ANY KIND IS UNACCEPTABLE. Misappropriation of exams before or after they are given will be considered academics misconduct.

Misconduct of any kind will be prosecuted and may result in any or all of the following:
** Reduction of grade*
** Failing grade*
** Referral to the Dean of Students for consideration of additional penalty, i.e. notation on a student's transcript re. academic integrity violation, etc.*

Students with a Learning Disability

If a student is registered with the Disability Resource Center, he/she must submit appropriate documentation to the instructor if he/she is requesting reasonable accommodations. (http://drc.arizona.edu/learn/test-accommodation.html).

The information contained in this syllabus, other than the grade and absence policies, may be subject to change with reasonable advance notice, as deemed appropriate by the instructor.

Course Outline (Dates are Tentative)

Drug and Contrast Agent Discovery:

Date: **Topic** (Each Lecture will be 75 minutes) **Instructor**

Jan. 12, 2012 Overview of Drug Discovery I Dr. Matsunaga
- a) Course Overview
- b) High-Throughput Screening
- c) Phage Display
- d) Biopanning

Jan. 17, 2012 Overview of Drug Delivery Systems, Nanotechnology biodegradable Matrices, emulsions. Dr. Matsunaga
- a) Combinatorial Libraries
- b) Nanotechnology/ Nanoparticles
- c) Emulsion/Suspension Technology
- d) Device-Mediated Delivery
  - i) Ultrasound-mediated
  - ii) Sensitizers

Molecular Imaging

Jan 19, 2012 Ultrasound Contrast Agents Dr. Matsunaga
- a) Theory
- b) Microbubbles
- c) Echogenic liposomes

Jan. 24, 2012 Introduction to Molecular Imaging Dr. Trouard (I will keep this lecture)
- a) Review and comparison of imaging characteristics of each modality---not how they work, but what types of images are expected
- b) Biomarkers and Surrogate Endpoints; validation vs. qualification; theranostics Creative problem solving techniques as applied to molecular imaging

Jan. 26, 2012 MRI I Dr. Trouard
- a) General Principles
- b) T1 relaxation, T2 relaxation (including fundamental equations). Examples of MRI images and the information they contain

Jan 31, 2012 MRI II Contrast Agents
Mechanisms and Images Dr. Trouard

Feb. 2, 2012 Smart Contrast Agents: Introduction Dr. Witte

a) Diverse capabilities of contrast agents and nanotechnology
b) Size and scale: examples
c) Grading contrast agents on an intelligence scale
d) Quantification of "smart" or activatable agents.

Feb. 7, 2012 **Journal Review Presentations (1)**

Feb. 9, 2012 Smart Contrast Agents: Biomedical Applications Dr. Witte
a) Cancer Imaging and Therapy
b) Neural disorders, Blood Brain Barrier, Imaging and Therapy
c) Cardiovascular Imaging and Therapy
d) In-class project: design a smart contrast agent

Imaging Applications

Feb. 14, 2012 Theranostics Dr. Matsunaga
a) Rationale for combined therapy/diagnostic agent(s)
b) Limitations for theranostic therapy
c) Examples: Nuspions, targeted microbubbles

Feb. 16, 2012 Ultrasound Imaging Methods Dr. Matsunaga
a) Ultrasound methods to enhance sensitivity
b) Ultrasound methods to increase signal : noise (2^{nd} harmonic imaging, Phase inversion)

Feb. 21, 2012 MRI III: MR Spectroscopy, non-proton MRI (19F, 13C and 13P) Dr. Trouard
a) Multiple agents in 1 animal in 1 detector: design considerations
b) One (1) agent in multiple animals in 1 detector: design considerations
c) One (1) agent in 1 animal in multiple detectors: design considerations
d) In-class engineering design exercise: which agents, animals, detectors make the best combinations for particular biomedical applications?

Feb. 28, 2012 Photoacoustic Imaging Dr. Witte
a) How does it work?
b) Advantages?
c) Limitations?
d) Sample Applications

Mar. 1, 2012 Computed Tomography Dr. Trouard
Mechanism, contrast and contrast agents

Radionuclide (High Sensitivity) Molecular Imaging

Mar. 6, 2012 Principles of radioactivity and radiochemistry: I Dr. Furenlid
a) Isotopes
b) Decay schemes
c) Particle and photon emissions

d) Half lives
e) Dosimetry

Mar. 8, 2012 Principles of radioactivity and radiochemistry: II Dr. Furenlid

a) Reactor-based activation
b) Accelerator(cyclotron)-based activation
c) Targets
d) Isotope separation
e) Labeling reactions – hot cell techniques
    i) ^{18}FDG synthesis
    ii) Chelation reactions
    iii) Iodination reactions
    iv) Solid-phase reactions
    v) Specific activity

March 13, 15 2011 **No Class – Spring Break**

Mar. 20, 2012 Dynamics and mechanisms of radiotracer uptake and clearance Dr. Furenlid

a) Tracer administration methods
b) Distribution
    i) Specific uptake
    ii) Non-specific uptake
    iii) Biodistribution measurements
c) Clearance
    i) hepatic
    ii) renal
    iii) dynamics
d) Target to background ratios

Mar. 22, 2012 Radionuclide imaging Methods: Autoradiography, SPECT and PET Dr. Furenlid

a) Technique & instrumentation descriptions
b) Calibration methods
c) Data extraction

Mar. 27, 2012 Role of PET and SPECT in Dx/Rx agent discovery Dr. Furenlid

a) Case studies

Mar 29, 2012 **Midterm Exam (1)**

Biodistribution Kinetics (Absorbtion, Distribution, Metabolism, and Excretion)

April 3, 2012 Kinetics: 1 compartment models Dr. Clarkson

a) Exponents and logarithms, derivatives and integrals, assumptions, diagram and kinetic equation, solving the equation, data fitting, area under the curve, half-life.

Apr. 5, 2012 Kinetics: 2 compartment models Dr. Clarkson

a) 2 dimensional vectors and matrices, diagram and kinetic equation, solving the equation, data fitting, parameter determination.

Apr. 7, 2012 Kinetics: N compartment models Dr. Clarkson

a) N dimensional vectors and matrices, diagrams and kinetic equations, solving the equation, data fitting, parameter determination.

Apr. 10, 2012 Kinetics: Identifiable kinetic parameters Dr. Clarkson

a) Kinetic parameters, the concept of identifiability, identifiable parameters from 1 accessible compartment, examples.

Apr. 12, 2012. Kinetics and Imaging: Compartmental models and imaging Dr. Clarkson

a) Localized compartments, identifiable parameters from imaging data, examples.

Regulatory Issues (FDA/EMEA)

Apr. 17, 2010 Regulatory Development Dr. Unger

a) Drug vs. Device, IND vs. IDE
b) Pre-Clinical studies (GLP)
c) IND submissions
d) Phase I, II, III clinical studies
e) NDA
f) Post-market surveillance

Apr. 19, 2010 Translational Research Issues Dr. Unger

a) Transition from bench to clinical

Apr. 24, 2010. **Genomics and Proteomics** Dr. Klimecki

April 26, 2010 **Journal Review Presentations (2)**

May 3, 2010 **Last Day to submit Final Written Project**