Drug / Contrast Agent Discovery, Imaging Modalities and Kinetic Analysis

Course: Biomedical Engineering (BME) 522, Cancer Biology 522, Medical Pharmacology 522, Optical Sciences 522, and Pharmacology & Toxicology 522

Semester: Spring 2025

Unit Credit: 3 units

Instructors: Terry Matsunaga Pharm.D., Ph.D.; Professor, Research Track, Biomedical Engineering, Russell Witte, Professor of Medical Imaging, Optical Sciences, Biomedical Engineering and Director of the Experimental Ultrasound and Neural Imaging Laboratory; Lars Furenlid Ph.D., Director, Center for Gamma-Ray Imaging and Professor, Department of Medical Imaging and Optical Sciences; Beth Hutchinson, Ph.D. Assistant Professor, Biomedical Engineering; Matthew Kupinski Ph.D., Professor, Optical Sciences, Medical Imaging, and Applied Mathematics, Ali Bilgin, Ph.D., Associate Professor of Biomedical Engineering, Electrical and Computer Engineering, and Medical Imaging, Craig Weinkauf, MD, PhD. Professor, Dept. of Surgery, Loi Do, Post-Doctoral Scholar, Dept. of Surgery.

Class Meeting Time: Tues - Thurs 11:00 am- 12:15 pm, (75 min.)

Location: MRB 201.

Required Text: None

Prerequisites: All graduate student status in Biomedical Engineering, Chemistry, Cancer Biology, Pharmacology, Optical Sciences, 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 journal presentations (2 x 20), one midterm (20%), class participation (5%) and the final written project (35%) which will comprise writing a 6-page proposal similar to a R21 NIH grant proposal. 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, newer imaging methodologies, how the biodistribution of these agents affects their efficacy and dosing. In addition, all methods will be complemented by lectures discussing clinical applications for all methods described. A description of the topics are provided below:

Contrast Agent and Drug/Vaccine Discovery: A lecture will be devoted to drug and vaccine discovery with examples of new developments for Covid-19 vaccines and new methods used for drug 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. This will include MRI, ultrasound, PET, photoacoustic imaging, SPECT. 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 (Absorption, 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.

Clinical Application: Clinical faculty in Medical Imaging will offer presentation highlighting the clinical use of the various imaging modalities.

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.

Grant Writing and Submissions: A lecture will be devoted to discussing how NIH grant proposals are written and reviewed to give the student an understanding of the peer-review process.

Learning Objectives:

By the end of the semester, students will;

1. be able to summarize new therapeutic and contrast agent development from initial discovery to approval by the Food & Drug Administration (FDA);
2. be able to describe mechanistic strategies for contrast agents, therapeutics and theranostics including how they work, why they are efficacious, and why they have toxic profiles.
3. be able to compare and contrast the key imaging modalities and associated analysis methods that are useful in drug discovery.
4. Be able to present critically reviewed scientific literature with regards to scientific merit and significance.
5. Be able to identify key components of a NIH R21 grant proposal and write a 5-page mock proposal emphasizing significance, innovation, and approach with literature precedence.

Please also refer to the University of Arizona reference to syllabus-policies as they all pertain to this course. Policies can be referred to in the following URL:

https://catalog.arizona.edu/syllabus-policies

Enrollment: Those interested in enrolling, please contact Dr. Terry Matsunaga at 626-6689 or 982-5688 or Andrea Anduaga (Graduate Academic Advisor, Biomedical Engineering, at 626-9134).

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

Accessibility and Accommodations: At the University of Arizona, we strive to make learning experiences as accessible as possible. If you anticipate or experience barriers based on disability or pregnancy, please contact the Disability Resource Center (520-621-3268, https://drc.arizona.edu) to establish reasonable accommodations.

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**

Week 1

Jan. 16, 2025 Overview of Drug Discovery I Dr. Matsunaga

a) Course Overview
b) Brief hx of drug development.
c) Vaccines
d) Covid Therapies
e) Current Trends: Immunotherapy.

Week 2

Jan. 21, 2025 Overview of Drug Delivery Systems, Nanotechnology biodegradable Matrices, emulsions. Dr. Matsunaga

a) Nanotechnology/ Nanoparticles
b) Emulsion/Suspension Technology
c) Device-Mediated Delivery
    i) Ultrasound-mediated
    ii) Sensitizers

Molecular Imaging

Jan 23, 2025 Ultrasound Contrast Agents Dr. Matsunaga

a) Theory
b) Microbubbles
c) Echogenic liposomes
d) Phase-change contrast agents

Week 3

Jan. 28, 2025 Theranostics Dr. Matsunaga

a) Rationale for combined therapy/diagnostic agent(s)
b) Limitations for theranostic therapy
c) Examples: Nuspions, targeted microbubbles

Jan. 30, 2025 Ultrasound Imaging Methods Dr. Matsunaga

a) Ultrasound methods to enhance sensitivity
b) Ultrasound methods to increase signal : noise (2^{nd} harmonic imaging, Phase inversion)

Week 4

Feb. 4, 2025 Clinical Applications for Imaging Dr. Weinkauf

Feb. 6 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.

Week 5

Feb. 11, 2025 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

Feb. 13, 2025 Energy Medicine: History and Future. Dr. Witte

Week 6

Radionuclide (High Sensitivity) Molecular Imaging

Feb. 18, 2025 Principles of radioactivity and radiochemistry: I Dr. Furenlid

a) Isotopes
b) Decay schemes
c) Particle and photon emissions
d) Half lives
e) Dosimetry

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

Feb. 20, 2025 Radionuclide imaging Methods: Autoradiography, Dr. Furenlid

SPECT.

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

Week 7

Feb. 25, 2025	Radionuclide imaging methods: PET	Dr. Furenlid
Feb. 27, 2025	Journal Review Presentations	

Week 8

March 4, 2025	Journal Review Presentations	

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

March 6, 2025.	Pharmacokinetics	Dr. Kupinski

Week 9

Mar. 8 -16, 2025: Spring Recess. No class

Week 10

March 18, 2025	Pharmacokinetics	Dr. Kupinski
Mar. 20, 2025	Overview of NIH grants. R21, R01, F-30 – 32, SBIR. Strategies for Navigating through them.	Dr. Matsunaga

Week 11

Mar. 25, 2025	Image Processing	Dr. Bilgin
Mar. 27, 2025	Metabolic Pathway Abnormalities and Imaging	Dr. Matsunaga

Week 12

April 1, 2025	MRI Physics	Dr. Hutchinson
April 3, 2025	MRI Physics Part 2	Dr. Hutchinson

Week 13		
Apr. 8, 2025	MRI Clinical Applications	Dr. Do
Apr. 10, 2025	MRI Clinical Applications	Dr. Do
Week 14		
Apr. 15, 2025	**Midterm Exam Preparation**	Faculty
Apr. 17, 2025	**Midterm Exam,**	
Week 15		
Apr, 22, 2025	**Journal Review Presentations (2)**	
April 24, 2025	**Journal Review Presentations (2)**	
Week 16		
April 29, 2025	Final Exam prep: Written R21 preparation discussion.	Dr. Matsunaga
May 1, 2025	The Nobel minute and choosing a career. (optional)	Dr. Matsunaga
Week 17		
May 6, 2025	**Last Day to Submit Final Exam.**	