

Pharmacology 902—Molecular Characterization of Drug Targets

(offered in the Spring of each year to sequence with Pharmacology 901—4 Credits)

Course Directors— J.C. Garrison and F. Rastinejad

Molecular Characterization of Drug Targets is an advanced course that focuses on the biochemical and molecular aspects of the signaling mechanisms which are known targets for important classes of clinically useful drugs. Potential future targets in diseases such as cancer will also be covered. The course will highlight existing examples of the research critical to important therapeutic agents and draw on the scientific expertise of the Pharmacological Sciences Training Program Faculty to cover important signaling systems and principles. The intent of the course is to focus on how an important drug target can be identified and exploited rather than a complete coverage of pharmacology. We will invite individuals from the Pharmaceutical Industry to participate as appropriate and describe how the Industry develops Drug Targets and Drugs.

The course will meet twice each week for 2-3 hours (Monday and Thursday from 1 to roughly 3:30 PM). Most Pharmacology Graduate Students will take the general pharmacology course (Pharmacology 901) or Medical Pharmacology before this course. However, the course is designed so it can be taken by other students without these prerequisites. The course will include both lectures by the Faculty to introduce topics and presentations by students on selected examples of recent literature relevant to the topics covered. The exam(s) will emphasize design of research projects to advance understanding of certain areas.

Section 1: Basics of Drug Screening, Discovery and Design:

This section will present information on: High Throughput Screening of Chemical Libraries, Rationale and Methods for Drug Design, Methods for Molecular Visualization and Modeling, Proteomics and Analysis of Pharmacological Data (Statistics, Binding Curves, Curve Fitting). Faculty will include Drs. Johnson, Brown and Macdonald.

Jan 16: Course Introduction— Drs. J.C. Garrison and F. Rastinejad

21 Jan-- Strategies for drug discovery— Dr. T.L. Macdonald

24 Jan—Combinatorial Chemistry and High Throughput Screening- M. Geysen

28 Jan-- Rational Drug Design, Molecular Modeling – Dr. Milton Brown

31 Jan-- Lab Session on Molecular Visualization and Modeling- Dr. Milton Brown

4 Feb-- Measurements and Analysis of Ligand Binding Data- Dr. M.L. Johnson

Section 2: G Protein Coupled Receptors for Hormones, Neurotransmitters and Autocoids

This section will present information on the G protein coupled receptor super family including: overview of the receptor family, the structure and function of the receptors, signaling mechanisms used by G proteins, and G protein effectors. The Adenosine receptor family, its biology and ligand design will be the focus. Faculty will include Drs. Lynch, Garrison and Linden.

- 7 Feb—Introductory lecture: Receptor Structure, Ligand Binding and Activation of G proteins –
Dr . J. Garrison
- 11 Feb-- Emerging concepts in Receptors/G proteins (RGS, AGS proteins, Arrestins)-
Drs . J. Garrison/K. Lynch
- 14 Feb-- New Concepts in G Protein Coupled Receptors (RAMPS and Heterodimers) –
Dr . K. Lynch
- 18 Feb-- Drug Development, Agonists, Inverse Agonists and Antagonists. Dr. J. Linden
- 21 Feb-- Pharmaceutical Guest Lecture-

Section 3- Signaling Molecules that Regulate Cell Proliferation, Adhesion and Differentiation

This section will present information on the families of molecules regulating cell growth and related functions in normal and diseased cells. Specific topics will include: signaling cascades including small G proteins, structure and function of protein kinase families (PKC, MAP kinases, insulin activated kinases, tyrosine kinases), and regulatory roles of kinases and phosphatases in cell proliferation, adhesion, differentiation and apoptosis. With this background, drugs intended to disrupt these signaling cascades can be considered. An example might be the farnesyl transferase inhibitors. Faculty will include Drs. Brautigan, Lawrence, Macara, and Sturgill.

- 25 Feb—Introductory lecture: Protein Kinases –Dr. T. Sturgill
- 28 Feb-- Kinase Cascades and MAP Kinase- Dr. T. Sturgill
- 4 Mar-- Insulin Activated Kinase Cascades –Dr. J. Lawrence;
---*Turn in Midterm Exam Topics*---
- 7 Mar-- Protein Phosphatases – Dr. D. Brautigan

----- March 9 – March 17 *SPRING BREAK*-----

- 18 Mar-- Small G proteins, Ras -Dr. I. Macara
- 21 Mar--Pharmaceutical Guest Lecture-

- 25 Mar- MIDTERM PAPERS due
- 28 Mar--MIDTERM EXAM Presentations

Section 4: Ion Channels and Drugs Regulating Channels

This section will present information about the families of Ion Channels that regulate cellular function in health and disease. Topics will include: An overview of the important properties of channels (activation/inactivation, selectivity and conductance); structural regions of channels that confer these properties; mechanisms of channel regulation (ligands, G proteins and phosphorylation), drugs affecting channel function in health and disease. Faculty will include Drs. Bayliss, Guyenet, Perozo and Perez-Reyes.

- 1 Apr – Introductory lecture: Ion Channels –Dr. D. Bayliss and E. Perozo
- 4 Apr – Transmitter effects on Ion Channels: Gating and Modulation–Dr. Bayliss
- 8 Apr – T- and L- type Ca²⁺ channels–Dr. E. Perez-Reyes

11 Apr -- ATP Gated K⁺ Channels – Dr. P. Guyenet

15 Apr-- Pharmaceutical Guest Lecture

Section 5: The Steroid/Hormone/Orphan Nuclear Receptor Family

This section will present information about the steroid receptors the class of receptors that bind to DNA. Topics will include overview of the family, differentiated function of the receptors and the molecular structure of ligand and DNA binding domains. Faculty will include Drs. Rastinejad, Shupnik and Uht.

18 Apr—Introductory Lecture: Nuclear Receptors- Dr. F. Rastinejad

22 Apr-- Protein-Protein Interactions – Dr. P. Shupnik

25 Apr-- Crosstalk with other transcription factors – Dr. R. Uht;

---Turn in Final Exam Topics----

29 Apr. Pharmaceutical Guest Lecture

13 May FINAL EXAM Papers Due

16 May FINAL EXAM presentations