

# **Molecular Interventions in Human Disease (Biochem 230) - 2006**

Julie Theriot, Pehr Harbury.

“Molecular Interventions in Human Disease” is a literature discussion course designed to teach students how to critically evaluate research at the frontiers of modern medicine. The course will meet between 10:00-11:00 A.M. on Mondays and between 9:00-11:00 on Wednesdays in Beckman B402. The format of the course is:

## **1) Seven weeks of specific topics including an introductory presentations, primary literature reading and discussion:**

On the Monday of each week, either Julie or Pehr will present background material related to the papers to be discussed the following Wednesday. On Wednesdays, students will lead discussions of a paired set of papers: one from the primary basic research literature and one from the primary clinical literature (see attached schedule). The goal of the discussion is to learn how to read and think critically about different experimental approaches in medicine. Topics will cover everything from forests (what are they studying, why this system, would another approach be better), to trees (what is that extra band in the southern blot, do the dissociation constants make sense given the concentration of molecules in cells, etc.). Wednesday presenters can contact Julie and Pehr for additional background literature.

## **2) The last week will be an open forum discussion of student-selected papers:**

Each student should nominate a paper in the basic science/medical literature that they've read recently and thought was cool. Please provide a short summary of the paper and explain why you think it would be an interesting topic for the group to discuss. The nomination deadline is Monday, November 13. Votes will be due on Thursday, November 16, and the winning papers will be discussed on November 27 and 29.

### **Contact Information:**

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### **Course Web Site:**

<http://biochem.stanford.edu/biochem230>. The paper PDF's are posted on the web site. Printing facilities for course materials are available in the Biochemistry Department.

## Methods and Logic for BC230:

1. Given a human disease, how does one identify the molecules/pathways involved?
2. Given a traditional medicinal therapy, how does one identify the molecules/pathways involved? Off-targets?
3. What's the best point in a pathway to choose for intervention?
4. How does one pilot an intervention (before investing a huge amount of time and \$'s)? What constitutes good evidence that an intervention strategy is likely to succeed?
5. What constitutes proof that you understand the mechanism by which a medicine acts? How would you find out if you were wrong? What kinds of mechanisms are at play with the medicines we think we understand?
6. How do therapies fail? How should we cope with the problems that result?
7. How does one deal with genetic heterogeneity in human populations when thinking about medicine in molecular terms? Can we exploit variation?
8. Where are the new therapeutic targets and strategies coming from?

## MOST IMPORTANT TIPS FOR EFFECTIVE READING

### **Read actively!**

- Think about the problem before reading their method for solving.
- Look at the data before reading the model figure at the end.
- Understand how the experiments are done.
- Take your own notes instead of just highlighting on the paper copy.

### **THERE ARE ONLY A FEW EXPERIMENTS:**

The following 3 types of experiments exist in all fields, and together provide the evidence needed to prove that A does B.

#### **1) Association experiments (what components are at the right time, place, and concentration to be able to function in a particular process):**

- What components are present?
- When are they expressed?
- Where are they expressed ?
- How big are they ?
- What do they interact with?
- How tightly do they bind?
- How quickly do they act?

#### **2) "Necessary" experiments (various ways of eliminating a component from a system, and asking if that component is necessary for the system to function):**

- Search for mutants.
- Drip in inhibitors.
- Add monoclonals or antisense DNA.
- Adsorb out a population of cells or specifically kill subgroups.
- Fractionate an in vitro system (genetics with salt)

#### **3) "Sufficient" experiments (various ways of adding a component to a system and asking whether that component is sufficient to trigger particular events)**

- Make transgenics.
- Microinject cells or messages or proteins.
- Move regulatory sequences from one gene to another.
- Express genes at different times and places to check effects.
- Add purified components together in an in vitro system.

## **THE SYSTEMS THAT WE UNDERSTAND THE BEST ARE THOSE WHERE IT HAS BEEN POSSIBLE TO USE BOTH GENETIC AND BIOCHEMICAL TECHNIQUES:**

### **Genetic approaches:**

- Mutants.
- Hierarchies and pathways.
- Suppressors.
- Enhancer traps.
- Knockouts.
- Transgenics.

### **Biochemical approaches**

- Proteins and antibodies.
- Radiolabeling, pulse-chase.
- Fractionation.
- Purification.
- Direct tests of interaction.
- Reconstitution
- Structural and mechanistic studies.

**These approaches give complementary information.**

Genetics needs biochemistry to explain what hierarchies are really doing in physical terms. Biochemistry needs genetics to test function of identified components in living system.

**For in vivo experiments:**

Could you reinterpret as some animals or cells being sick in a nonspecific way?

Could the observed phenomenon be an Nth order effect?

Can you imagine a way of pulling the system apart using genetics? Using simpler in vitro systems?

**For in vitro experiments**

Have all components been defined?

Has carry over been eliminated?

What is signal to noise ratio?

Have all possible rate limiting steps been separately considered?

Can you see dose response?

How does in vitro level compare to in vivo? Are concentrations within physiological range?

How does in vitro rate compare to in vivo? Are they reasonable?

Can you change interpretation by assuming that different members of the population act differently than population as a whole?

Can you use genetics to verify importance of components in vivo?

**For any genetic analysis:**

More than one example of each complementation class?

Dominance been examined?

Null phenotype established?

Time of action established?

Place of action established?

Number of genes required known?

Order of genes known?

Nature of genes known?

What components may have been missed because of redundancy, pleiotropy, or maternal masking?

**General:**

What is the positive control? What is the negative control?

What can you tell for sure?

What is only correlation or consistency? Could correlation be reversed, with different cause and effect?

What other models can you make?

Could a positive effect really be an anti-negative, or a negative effect an anti-positive (activators vs. repressors of repressors)

What are the advantages of this system over others?

Is there a better system for the same phenomenon?

What was the key technical breakthrough? What is the main handicap to further progress?

Could techniques, materials, or conclusions have applications to other problems?

**What would you do next with this system?**