Biochemistry 673 **Your Name:** _____

Regulation of Metabolism **Assoc. Prof. Jason Kahn**

Midterm Exam (100 points total) **October 19, 2007**

You have 50 minutes for this exam.

Explanations should be concise and clear, but there is extra space on the last page.

You do not need a calculator for this exam, and no other study aids or materials are permitted.

Generous partial credit will be given, *i.e.*, if you don't know, guess.

Honor Pledge: At the of the exam time, please write out the following sentence and sign it, or talk to me about it:

"I pledge on my honor that I have not given or received any unauthorized assistance on this examination."

1. Nuclear Hormone Receptors and Hsp90 (50 pts):

(a; 10 pts) How is it that some nuclear hormone receptors can bind to their DNA sites even when the sites are wrapped in histone octamers? Why is this important for the function of NHRs?

(b; 5 pts) Give a one-sentence summary of the Métivier paper on estrogen receptor signalling.

(c; 5 pts) Briefly describe how the RXR-TR heterodimer switches from being a transcriptional repressor to an activator upon thyroid hormone binding.

(d; 10 pts) Briefly describe one stage in the development of cancer, and the means by which Hsp90 unfortunately acts to potentiate passage through that stage.

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(e; 10 pts) What is the proposed means by which Hsp90 acts as a "genetic capacitor?" Briefly describe one experiment that supports that proposal.

(f; 10 pts) We discussed the Hsp90 inhibitor AAG (related to geldanamycin), which is in clinical trials as a chemotherapy agent. On the face of it, it is surprising that inhibition of a universally conserved protein would be sufficiently selective. What is the proposed explanation for AAG's specificity for cancer cells (i.e. why does it kill cancer cells and not normal cells)? We also discussed that Hsp90 inhibition could be a double-edged sword: what is one conceivable downside of Hsp90 inhibition in advanced cancers?

2. Chemotaxis (50 pts):

(a; 10 pts) What does bacterial chemotaxis look like? In other words, what does one see in observing bacteria moving up an attractant gradient? What is the evidence that bacteria respond to temporal signals rather than spatial ones, and why does this make biophysical sense?

(b; 10 pts) Chemotaxis is characterized by amplified responses to small concentration changes, over a wide range of initial concentration, followed by exact adaptation. Which of these properties must be explained by cooperative interactions among MCPs? Briefly describe some of the biochemical evidence for inter-receptor interactions (more space on next page if you need it).

(c; 6 pts) We talked about the difference between robust and fine-tuned mechanisms for regulation. What is the difference? Which property of chemotaxis is believed to be robust, and what aspects of that same property are fine-tuned?

(d; 5 pts) Barkai and Leibler proposed a mechanism for robust exact adaptation. What is the fundamental proposed property of CheB that confers exact adaptation in their model? How has it been partially tested?

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(e; 15 pts) We know that attractant binding to a receptor ends up suppressing the activity of CheA. In other words, it stabilizes the "off" state of the MCP receptor. Diagram why it must be true that the off state has a stronger affinity for attractant than the "on" state. Qualitatively, extend this idea to explain how bacteria can respond at a very wide range of attractant concentrations. How does the structural work that we discussed in class relate to this ability? (Hint: someone is always listening.)

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(f; 4 pts) What was the most confusing concept we covered in these two sections, and how could it have been better explained?

Page	**Score**
1	_____/10
2	_____/20
3	_____/20
4	_____/20
5	_____/11
6	_____/15
7	_____/4
Total	_____/100

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