**Protein Homeostasis in Biology and Disease**

October 17-21, 2016

Professor Richard Morimoto, Department of Molecular Biosciences,

Northwestern University, Evanston, IL 60201, r-morimoto@northwestern.edu

<http://www.biochem.northwestern.edu/ibis/morimoto/index.html>

Proteins convert genetic information into diverse shapes and forms by replicating and transcribing the genome and translating mRNA into proteins, that in turn, fold and assemble into a myriad of structures with diverse function. This course will examine how the dynamics of proteome stability are achieved by the Proteostasis Network (PN) that determines the synthesis, folding, and clearance of proteins. The PN ensures optimal cellular function in development, but fails in aging and diseases of protein conformation. This link between faulty proteostasis in aging has been proposed to contribute substantially to the pathology of many degenerative diseases including neurodegeneration, cancer and metabolic diseases. The opportunity to reset proteostasis therefore offers a promising therapeutic approach.

In this class, we will examine: (1) the physical biochemical properties of the nascent chain and the function of molecular chaperones in protein folding, (2) the complex cellular events that determine protein folding in the cell and how triage processes detect and sort damaged molecules for refolding, disaggregation, or clearance, (3) how aging and stress promote proteome mismanagement leading to the accumulation of misfolded species and aggregates that interfere with cellular function to cause disease, and (4) how cell stress responses detect improperly folded species and induce the Proteostasis Network (PN) to prevent protein damage, restore cellular health and lifespan.

This course is based on primary readings from the scientific literature on protein biology. Papers for each lecture will be provided prior to the discussions where we will examine the basis for the tested hypothesis, analyze the results, interpretations, and implications. On the last day of the course, the class will give oral Powerpoint presentations based on selected papers. Students, in teams of two, will select one or two key papers that will be used as the basis for presentations in a “Journal Club” format. Each team presentation will be 12 minutes presentation will use PowerPoint will be followed by 3-5 minutes of questions. The oral presentations should identify the key question/hypothesis of the paper, present and analyze the data critically with an emphasis on novel methods or approaches, and summarize the conclusions and overall contribution of the work. The analysis should also attempt to identify potential issues or concerns with each paper when appropriate. The list of papers (and pdfs) that will be discussed in the Literature critique session on Friday will be made available and the class will be expected to read these papers and prepared to ask questions.

**Syllabus: Protein Homeostasis in Biology and Disease**

Oct. 17 (Mon.) 9-11am: ***Dynamic properties of proteins from folding in vitro to folding***

***and clearance in the cell*** *–* physical biochemical properties of proteins and the function of the proteostasis network comprised of chaperones, proteasome, and autophagy to regulate proteome stability, functionality, and clearance in the cell.

Oct. 18 (Tue.) 9-11am: ***Proteotoxic stress in aging and disease***– examination of underlying

mechanisms by which misfolded proteins cause cell stress, interfere with the function of the proteostasis network, promote cellular damage and dysfunction, and alter the aging program.

Oct. 19 (Wed.) 9-11 am: ***Infectious proteins***– the physical biochemical and cell biological

properties of amyloid proteins, how amyloid seeds propagates by transmission between cells, the basis of prion and prion-like diseases, and therapeutic strategies to prevent seeding and amplification.

Oct. 20 (Th.) 9-11am: ***Cell stress responses: Stress sensing transcription factors and***

***networks that control expression of the proteostasis network*** *–* Transcriptional networks regulated by the heat shock response and organellar unfolded protein responses to sense misfolded proteins and to activate cellular and organismal level responses to stress and damage.

Oct. 21 (Fri.) 9-11am: ***Student Presentations*** *-* 12-minute team Powerpoint presentations on

 papers selected by the class