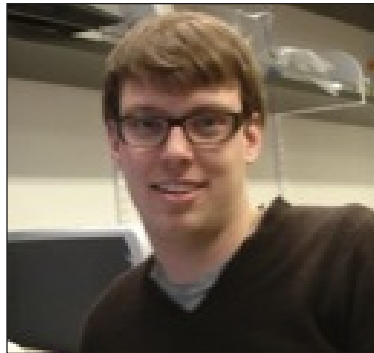
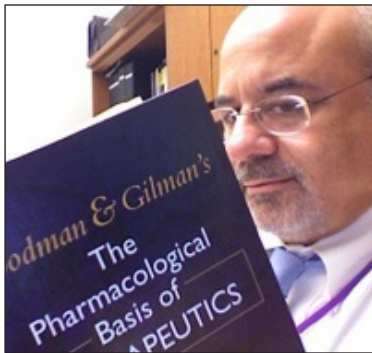


NORTHWESTERN INSTITUTE ON COMPLEX SYSTEMS PRESENTS

# Wednesdays

# @NICO

## *“SHIP-less in Myelodysplastic Syndromes - A Mathematical Solution”*



**Seth Corey, MD & Zak Whichard, BA**  
Pediatrics, Feinberg School of  
Medicine

**Wednesday, October 7, 2009**

**12:00 - 1:00 PM**

**(Refreshments served at 11:45)**  
**Chambers Hall, 600 Foster Street**  
**Lower Level Classroom**

The myelodysplastic syndromes (MDS) are characterized by exaggerated apoptosis in their earliest stages but loss of apoptosis in their late stages during transformation to acute myeloid leukemia. The molecular basis for this change is not known. PI 3'kinase critically regulates cell survival through effectors such as Akt. Two lipid phosphatases, PTEN and SHIP1, dephosphorylate phosphoinositides, resulting in the loss of signaling by PI 3'kinase. Immunoblotting and immunohistochemistry of bone marrow specimens from patients with MDS show increased levels of phospho-Akt, variable levels of PTEN and uniformly decreased SHIP1 expression. Expression of SHIP1, but not a phosphatase-deficient mutant, inhibited myeloid leukemic growth. We found increased miR-210 and miR-155 transcripts in CD34+ MDS cells compared to normal CD34+ cells. Direct binding of miR-210 to 3'UTR of SHIP1 was confirmed by luciferase reporter assay. Transfection with miR-210 resulted in loss of SHIP1 protein expression. SHIP1 expression increased with transfection of its antagomir. Informed by experimental results we assume that complex formation is an elementary reaction obeying mass action kinetics and that miRNA is recycled upon the directed degradation of mRNA transcripts. Our model was validated by showing that it was able to reproduce experimentally known patterns of miRNA-induced gene regulation. More importantly, sensitivity analysis revealed that, among the kinetic parameters considered, protein concentration is most sensitive to changes in miRNAs synthesis rate. Thus our model supports the development of miRNA-based therapies to downregulate particular genes associated with cancer, inflammation, and metabolic disorders.

**NICO Coffee Hour will follow for questions, networking, and collaboration.**

<http://www.northwestern.edu/nico/>



**NORTHWESTERN**  
UNIVERSITY