Leasure Hall, Room 13
Thursday, September 21, 2017
4:00 P.M.

Coffee and Cookies
Leasure Hall, Room 13 alcove
3:45 P.M.

Biochemistry & Molecular Biophysics **Seminar**

The complexity of Mdm2 activity

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E3 ubiquitin-protein ligase Mdm2 is a regulator of the p53 tumor suppressor protein. Mdm2 acts by facilitating the conjugation of ubiquitin to p53, which thereby signals nuclear export, leading to p53 destabilization. The interplay between p53 and Mdm2 is more intricate as p53 can bind to and transactivate the promoter of Mdm2 to increase Mdm2 protein levels, which in turn downregulates p53 activity. This interplay has been termed the autoregulatory feedback loop, which is functional when there are low levels of DNA damage/DNA repair in cells. The interplay between p53 and Mdm2 has led to the central dogma that the main function of Mdm2 is to regulate p53 via ubiquitination. This has some fundamental flaws: although p53 is mutated in roughly 50% of human cancers (and this frequency is much higher in recurrent or metastatic tumors, which would be unable to induce Mdm2 gene expression), Mdm2 is still found to be elevated in tumors with mutant p53. In this seminar, we will explore: the novel function of Mdm2 to stabilize and inactivate p53, how the Mdm2 gene is induced in mutant p53 cells, how Mdm2 promotes angiogenesis and metastasis; and the role of Mdm2 in bone metastatic foci to promote lytic disease. This body of work will provide evidence that Mdm2 has important roles in promoting several stages of tumorigenesis independent of mutant p53 function.