Chem 162/262 (2005) Assignment #1:

Molecular Mechanisms of Diseases. General Principles of Drug Design.

1. Many cancers are linked to genetic defects in the gene that encodes for a protein known as p53. Based on your own research using available literature and web resources, explain the role of p53 protein of in healthy tissues and outline a plausible mechanism that explains how loss of p53 function leads to cancer.

2. One rational approach to drug discovery that was discussed in the class relied on identification of molecular target, determining its three-dimensional structure, and then proceeding with the design based on the 3D structure of the target protein. However, three-dimensional structures of targets for many important diseases, including osteoporosis, are not known. Discuss:

    a) The prevalence and seriousness of osteoporosis; and which subgroups of population are most affected
    b) What is known about molecular mechanisms behind osteoporosis
    c) What approach has been used, or could be used, to design drugs for the treatment of osteoporosis

3. In early 1990's it was thought that once a molecular target for a given disease has been identified through a good understanding of molecular mechanism of the disease, in vitro screening of random combinatorial libraries against the target could easily lead to discovery of new drugs. Explain why this strategy may produce lead compounds that have reasonable in vitro activity but are likely to show low potency in vivo.