Chem 162/262 (Kahn, 2005) Assignment #3: Due Mon, Oct 24th

Target Validation Techniques

In the following assignment, you should focus on target validation techniques that could, in principle, allow finding relevant drug targets. Note that while in some cases the target validation work has been published, you are not required to find or understand this literature. In fact, I have occasionally slightly "re-dressed" the factual material to impede finding the answer from the research literature. However, careful analysis of required reading should give you more or less direct hints on how to answer these questions.

1. Sanfilippo syndrome type A is a genetic disorder that leads to delayed mental development due to accumulation of heparin sulfate in affected individuals. Genetic analyses of most patients with this disorder have identified mutations in a gene called SGSH in chromosome 17 but a small number of Sanfilippo patients have normal SGSH gene and normal chromosome 17. Several hypothesis have been proposed to explain the occurrence of Sanfilippo syndrome in patience with normal SGSH gene. Your task is to suggest experimental approach to test the validity of each of these hypothesis

   Hypothesis a): SGSH gene has nothing to do with the accumulation of heparin sulfate.

   Hypothesis b): The patients with normal SGSH gene do not transcribe the gene properly.

   Hypothesis c): The patients with normal SGSH gene cannot translate the SGSH mRNA into the protein.

   Hypothesis d): The patients with normal SGSH gene lack ability to carry out required post-translational modifications of the protein encoded by the SGSH gene.

2. Assuming that the rare form of Sanfilippo syndrome with the normal SGSH gene arises from the lack of ability to post-translationally modify the SGSH protein, propose an experimental approach that allows identification of a protein that is mutant or lacking in this patient population.

3. Apoptosis (see http://users.rcn.com/jkimball.ma.ultranet/BiologyPages/A/Apoptosis.html for more details) is a complex and tightly controlled processes by which certain cells commit suicide. The commitment to suicide is determined by the balance of between survival signals and death signals. Mammalian cells have surface receptors (such as TNF-α, and Fas receptors) that can bind death activators (such as tumor necrosis factor-α and the FasL); binding of these ligands would normally induce apoptosis. However, in some infectious diseases and cancers the apoptosis of infected cells is prevented by expression of anti-apoptotic genes. The strategy is used, for example by the virus that causes "the kissing disease", or mononucleosis. Propose an experiment that allows identifying which virally encoded gene allows infected cells to escape apoptosis.