To illustrate the role of the Per's (period) and Cry's (cryptochrome). So what we have here are BMAL and CLOCK which are the positive activators actually of a set of at least 5 genes. All three Per genes and both Cry genes appear to be under the regulation of CLOCK based on genetic experiments. And these are activators of all of these proteins. To simplify the animation, we've reduced it to just per and cry, and as we saw in drosophila what happens is once the per and cry genes are turned on their RNA's accumulate, proteins are made, but in this case a number of different dimer combinations can be formed. Per-per dimers, cry-per dimers, and different variations of the various cry and per proteins. They then translocate into the nucleus, where they interact directly with CLOCK and BMAL to then turn off the per and cry genes. Then as time progresses these negative factors, per and cry, turn over and disappear, or degraded, and then the inhibition is relieved, the activation begins in the start and the cycle begins again. So in the next animation we're just going to add casein-kinase 1 (CK1) here as a new member of this CLOCK gene family. And as we saw before we have CLOCK and BMAL regulating per and cryp and CK1ε will start with its role in the cytoplasm, which we believe is very similar to what has been found in drosophila, and that is to phosphorylate the per protein and make it less stable, so that it degrades. Unless the per forms a dimer with either itself or CRY. Another role that's been identified in mammals is that CK1ε may also be involved in either cellular retention or translocation into the nucleus is the second role. A third role is that CK1 is also involved in the turnover of the inhibitory complex in nucleus as Michael Rosbash illustrated. Once those inhibitory molecules degrade, the cycle starts over, and we see the beginning of a new cycle. Now if I could go back to the next slide this shows you a wildtype as compared to a mutant hamster in this case, and what we see is the per genes are produced, but because the mutant enzyme is less effective at phosphorylated per, we would suggest that per accumulate faster in the cytoplasm then translocate into the nucleus earlier, which leads to an earlier shut off. The negative feedback occurs earlier as compared to wildtype. Now this is in contrast to the actual example that Michael showed where the casein kinase effect was primarily in the nucleus. So we think the Tau mutation is working primarily in the cytoplasmic location and we're getting opposite effects of the per.