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Small molecule modulators of the circadian clock function

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In mammals, circadian rhythms are generated through transcriptional regulatory networks of the clock genes. To search for novel clock modifiers, we applied chemical biology approaches. From hundreds of thousands of small molecules with diverse structure, we identified a number of compounds that potently change the period of the circadian clock in human cells. Among the period lengthening compounds, we previously discovered the first small molecule targeting the core clock protein CRY. The compound KL001 interacts with FAD-binding pocket of CRY and inhibits FBXL3-dependent degradation. By analyzing KL001 derivatives, we found 10 times more potent compound KL044. KL001 and KL044 share carbazole group and act on both CRY1 and CRY2. We further identified novel period lengthening compounds KL101 and TH301 that do not have carbazole group. Surprisingly, we discovered that KL101 is selective against CRY1 while TH301 shows much higher effect on CRY2. To understand molecular basis of the CRY1/CRY2 selectivity, we determined the X-ray crystal structures of CRY1-KL101, CRY1-TH301, CRY2-TH301, and CRY1-KL044 complexes. In this presentation, I will discuss these unique compounds that will enable atomic-level dissection of the functional difference between CRY1 and CRY2 proteins and their selective manipulation.