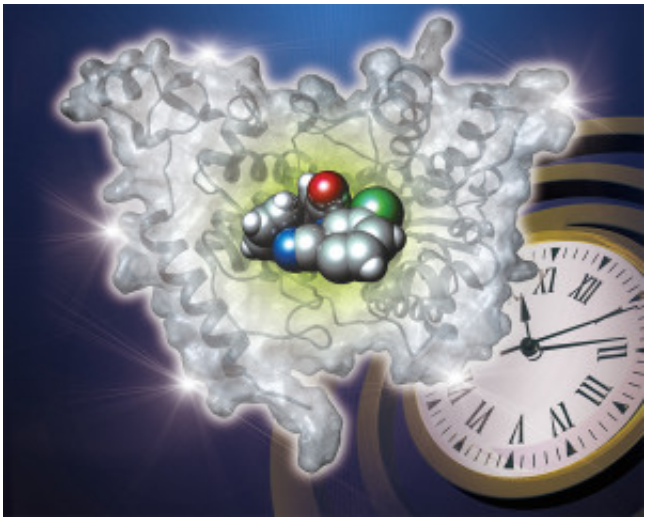
Design principle of CRY-acting compounds for regulation of the circadian clock

Almost every aspect of our life varies over time: we wake up in the morning, sleep at night, and become hungry at about the same time every day. This is called the circadian rhythm; an approximately 24-hour cycle regulated by the circadian clock, which is an interplay among genes and proteins in every cell of the body. The circadian clock regulates many physiological processes, such as body temperature, metabolism and hormone secretion. Various environmental factors, including sunlight and temperature, affect the circadian clock. Therefore, the circadian clock can be disturbed by modern lifestyle changes, such as shift works or long distance flights, which in turn can lead to sleep or metabolic disorders. Understanding how the circadian clock works and how it affects our physiology is therefore vital to understand and find treatments for these disorders.



We previously discovered a small molecule compound named KL001 that binds to the CRY protein, an essential component of the circadian clock. KL001 prevents degradation of CRY and slows down the speed of the circadian clock. In this study, we developed derivatives of KL001 to understand which parts of the small molecule are effective in controlling the circadian clock. Biological activities of the compounds were tested, and a model was built using the 3D structure of CRY-bound KL001 as a template. In this fashion, the structure-activity relationship of the small molecules was examined at the atomic level. With this approach, we were able to understand the structural basis of CRY-acting compounds: which parts of the small molecule can be modified to make it more effective, for example, making it bigger or smaller in certain directions. Also, the model provided explanation for why certain compounds were not effective. Eventually, we discovered a 10 times more potent derivative KL044. Using this information will enable us to virtually screen a relatively large collection of compounds with the computer and test the most potent molecules in the lab.

Through a combination of organic synthesis, biological screening and computational modeling, we

were able to find the most potent CRY-acting molecule so far. This knowledge will guide us in the search for even more effective molecules, which will potentially lead to the discovery of new drugs for circadian clock-related diseases.

Publication

Development of Small-Molecule Cryptochrome Stabilizer Derivatives as Modulators of the Circadian Clock.
Lee JW, Hirota T, Kumar A, Kim NJ, Irle S, Kay SA
ChemMedChem. 2015 Sep