

\_.png \_bb\_.png height

Contribution ID: 303

Type: Oral Presentation

## Mathematical modelling for pharmacological manipulation of primate's circadian rhythm and precision medicine for advanced sleep phase disorder

Thursday, 12 July 2018 12:00 (30 minutes)

Circadian (~ 24 h) rhythms can be synchronized to the earth's 24 h periodic environment through external cues such as light - dark (LD) cycle. The misalignment of circadian timings with the external environment can lead to crucial physiological problems, such as jet lag, bipolar disorders and cancer. To treat the misalignment problem, we investigate the pharmacological manipulation of circadian phase of primates, *Cynomolgus* monkeys using the casein kinase1  $\delta/\epsilon$  inhibitor, PF-670462. Surprisingly, we observed that the PF-670462-induced phase shift of primates (diurnal species) is less than that of mice (nocturnal species) under LD while that of primates is larger than that of mice under DD. To understand this unexpected phenomenon, we used mathematical modelling and found that the light sensitivity of primate's circadian rhythm depending on circadian phase is different to that of mouse's circadian rhythm. Furthermore, the PF-670462-induced phase shift is dramatically different depending on dosing amount and timing, light condition and chronotype. Thus, it is challenging to identify the dosing amount and timing to induce a desired phase shift. Here, we found a simple strategy to identify personalized dosing amounts and timing regardless of season and chronotype to treat advanced sleep phase disorder using mathematical modelling.

- [1] Jae Kyoung Kim *et. al.*, Modeling and Validating Chronic Pharmacological Manipulation of Circadian Rhythms, *CPT: Pharmacometrics & Systems Pharmacology* (2013)
- [2] Jeffrey Sprouse *et. al.*, Inhibition of casein kinase1 $\epsilon/\delta$ , produces phase shifts in the circadian rhythms of *Cynomolgus* monkeys, *Psychopharmacology*, pp. 735-742 (2009)
- [3] Caroline H.Ko *et. al.*, Molecular components of the mammalian circadian clock, *Human Molecular Genetics*, Vol. 15, pp. 271-277 (2013)
- [4] Jae Kyoung Kim *et. al.*, A mechanism for robust circadian timekeeping via stoichiometric balance, *Molecular Systems Biology* (2010)
- [5] Florian Geier *et. al.*, Entrainment in a Model of the Mammalian Circadian Oscillator, *Journal of Biological Rhythms* (2005)

**Primary authors:** KIM, Daewook (Korea Advanced Institute of Science and Technology); CHEN, Xian (Worldwide Research and Development, Pfizer Inc.); DEMARCO, George J. (University of Massachusetts Medical School); WAGER, Travis (Worldwide Research and Development, Pfizer Inc.); GAUDREAULT, Francois (Worldwide Research and Development, Pfizer Inc.); CHANG, Cheng (Worldwide Research and Development, Pfizer Inc.); KIM, Jae Kyoung (Korea Advanced Institute of Science and Technology)

**Presenter:** KIM, Daewook (Korea Advanced Institute of Science and Technology)

**Session Classification:** Multiscale modelling of sleep and circadian systems

**Track Classification:** Minisymposium: Multi-scale modelling of sleep and circadian systems