Hitting the Moving Target in Circadian Rhythm: The Application of Systems Pharmacology Model in the Development of a CK1 Inhibitor

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Objectives: The correction of circadian rhythm dysregulation represents a plausible mechanism for pharmacological intervention for neurodegenerative disorders, including sundowning syndrome in Alzheimer’s disease (AD). In order to consider the oscillating target concentration and interference by light, a systems pharmacology model is valuable in trial design in order to achieve desired effect.

Methods: A single cell systems pharmacology model that integrated over 60 years’ of circadian rhythm knowledge and extensive information from preclinical pharmacological modulation of a key enzyme casein kinase 1 (CK1) was developed. The model is capable of describing both the effect of light and CK1 inhibition as well as their interaction in preclinical species. Subsequently, the model was expanded into an ensemble model by implementing an intercellular connectivity module.

Results: Simulations based on the single cell model enabled early phase clinical development of a CK1 inhibitor by providing specific guidance on the dose, time of dosing, time of pharmacodynamic endpoint measurement, and duration of dosing. The ensemble model provided a quantitative framework to evaluate the entrainment hypothesis of CK1 modulation in AD circadian dysregulation and assisted the design of a subsequent efficacy trial.

Conclusions: The systems pharmacology model-based drug development strategy was successfully applied in the clinical development of a compound with novel mechanism of action.

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