1. No.
   2019Y006

2. Title
   Screening for the clinical drugs preventing the nicotine-induced disruption of circadian clock by the use of genetically modified zebrafish

3. Period
   2019-2021

4. Summary
   Circadian clocks are a naturally selected intrinsic time-keeping system that regulates various biochemical and physiological processes with an approximately 24-h periodicity, even in the absence of external cues. They exist in almost all organisms on earth and enhance the physiological efficiency and survival of an organism by processes which organize its behavior and body functions. It has been reported that treatment of animals with excess amount of nicotine induces disruption of circadian clocks. Using zebrafish, which share a common circadian clock with humans, I has identified clock molecules (zPER2, zCRY1a, and zCRY2a) whose expression is affected by nicotine. I have generated genetically modified [zPer2/zCry1a double KO (DKO) or zPer2/zCry1a/zCry2a triple KO (TKO)] zebrafish, in which these molecules are disrupted. This study aimed to select drugs that restore the circadian clock of DKO or TKO zebrafish. I also simultaneously searched for intracellular signaling pathways targeted by zPER2, zCRY1a, or zCRY2a by metabolomic analysis. As a result, this study found that the clock molecules whose expression is affected by nicotine target signaling molecules that regulate the redox state in the cell. Future analysis will proceed with compound screening using genetically modified zebrafish, as originally planned. Based on the results of metabolome analysis, I will also focus on drugs that regulate the intracellular redox state and examine the restoration of the regulation of the circadian clock in genetically modified zebrafish by these drugs.