February 24, 2026

Dear Editor,

We submit for your consideration the manuscript entitled "**A 12-Tissue Atlas of Circadian Gene Coupling: Genome-Wide BMAL1 Predictor Screening Reveals Universal and Tissue-Specific Clock Connections**" for publication in *Molecular Systems Biology*.

Summary. We present a systematic atlas of BMAL1 (Arntl) statistical coupling across 12 mouse tissues and genome-wide in mouse liver. Using AR(2)+exogenous predictor modeling, we identify 63 BMAL1-coupled genes genome-wide (180-fold enrichment over random predictors, $p < 10^{-10}$) and 85 significant coupling events across 33 genes in the 12-tissue atlas. Wee1 is coupled in 10/12 tissues (the most broadly conserved circadian output), and Nampt in 8/12 tissues.

Significance. This work provides the most comprehensive statistical coupling atlas of the core circadian transcription factor BMAL1 across mammalian tissues. The decisive falsification test (180-fold enrichment over housekeeping and random gene predictors) rules out statistical artifact. Seven predictions are independently confirmed by published wet-lab experiments. Ten novel predictions—including circadian coupling of the stem cell marker LGR5—await experimental validation.

Clinical relevance. The near-universal coupling of Wee1 across tissues predicts that Wee1 inhibitor efficacy (e.g., adavosertib, in active clinical trials) should be strongly time-of-day dependent. Tissue-specific coupling programs suggest that chronotherapy strategies must be tailored to target tissue.

This manuscript has not been submitted elsewhere and all work is original.

Sincerely,

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