Name: Yang Xiao
PI Name: Kam Leong

Email: yangxa@umich.edu
PI Email: kam.leong@columbia.edu

Chronic Opioid Treatment Arrests Neurodevelopment and Alters Synaptic Activity in Human Midbrain Organoids

Hye Sung Kim[#1,2,3], Yang Xiao[#1], Xuejing Chen[1], Siyu He[1], Jongwon Im[1], Moshe J. Willner[1], Michael O. Finlayson[4], Cong Xu[1], Huixiang Zhu[5], Se Joon Choi[5,6], Eugene V. Mosharov[5,6], Hae-Won Kim[2,3,7], Bin Xu[5]*, and Kam W. Leong[1,8]*

[1]Department of Biomedical Engineering, Columbia University;
[2]Institute of Tissue Regeneration Engineering (ITREN), Dankook University;
[3]Department of Regenerative Dental Medicine, Dankook University;
[4]JP Sulzberger Columbia Genome Center, Columbia University Irving Medical Center;
[5]Department of Psychiatry, Columbia University Medical Center;
[6]Division of Molecular Therapeutics, New York State Psychiatric Institute;
[7]Department of Nanobiomedical Science, Dankook University;
[8]Department of Systems Biology, Columbia University Irving Medical Center

Understanding the impact of long-term opioid exposure on the embryonic brain is critical due to the surging number of pregnant mothers with opioid dependency. However, this has been limited by human brain inaccessibility and cross-species differences in animal models. Here, a human midbrain model is established that uses human iPSC-derived midbrain organoids to assess cell-type-specific responses to opioids. This study establishes a highly scalable and sensitive framework for transcriptomic profiling of brain tissues to investigate fentanyl exposure and withdrawal. Single-cell mRNA sequencing of 25,510 cells from organoids in different treatment groups reveals that chronic fentanyl treatment arrests neuronal subtype specification during early midbrain development and alters synaptic activity and neuron projection. In contrast, acute fentanyl treatment increases dopamine release but does not significantly alter gene expression related to cell lineage development. These results provide the first examination of the effects of opioid exposure on human midbrain development at the single-cell level. (Advanced Science, 2024)