
Supplementary information

**Developmental xenocortication using
human-derived organoids in mice**

In the format provided by the
authors and unedited

Summary of ethical oversight

Our work is motivated by the need to develop improved human models of brain disease and, ultimately, therapeutic approaches. Existing models, whether animal or human cellular, remain insufficient for capturing key features of many brain disorders, particularly those that depend on the maturation of human neurons within circuits and their consequences at the network and behavioral levels. The rationale for transplanting human cortical organoids into a depleted rodent cortex emerged from the recognition that conventional transplantation paradigms involve substantial competition between the rapidly maturing rodent cortex and the neonatal human graft, thereby limiting the emergence of certain circuit level and behavioral readouts. The present approach is intended to create a more permissive *in vivo* context in which disease relevant properties of human cells can be studied. Importantly, we provide proof of concept that this model can be used to examine aspects of human disease *in vivo* that would otherwise be difficult to address *in vitro*.

Prior to starting experiments, we sought approval from the Stanford Administrative Panel on Laboratory Animal Care (APLAC). Beyond this conventional review procedure, we requested higher-level consultation from two bioethicists at Stanford University who provided an extensive overview of implications. Soon after, we consulted with the Stanford Neuroscience Institute's Executive Committee that included leading neuroscientists. The committee consulted with ethicists, extensively discussed the project, and concluded that we are "complying with all pertinent regulations", and the work "has potential significance for curing human diseases", and that the committee "sees no credible conceptualization of these experiments as creating organisms with human-like behavioral or cognitive capacities that would lead to elevated ethical concern."

As we initiated these experiments and established the apallial model in the laboratory, we also sought feedback systematically and confidentially from several neuroscientists around the world. In parallel, Stanford University School of Medicine convened an external committee composed of neuroscientists, legal scholars, ethicists, and patient advocates to develop a framework for oversight of these studies. All aspects of the experiments were shared transparently and discussed, including the scientific rationale for the work and sequence of studies, laboratory practices and safeguards, ethical dimensions of study design, methods, and data interpretation, and potential social, medical, and ethical implications of the work. We presented this work to the committee on multiple occasions, and their feedback substantially informed our approach.