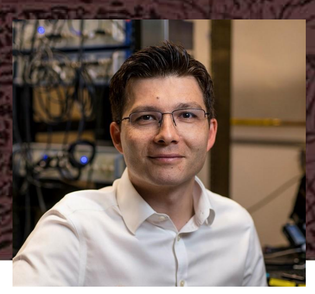
INSTITUTO CAJAL

SEMINARIO PRESENCIAL

Lunes, 11 de Septiembre de 2023
12:30 h. Instituto Cajal - CSIC



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FROM STEM CELLS TO ORGANOIDS TO ASSEMBLOIDS AND TOWARD BUILDINGS HUMAN CIRCUITS IN LIVING SYSTEMS TO STUDY DISEASE

Abstract

A critical challenge in understanding the programs underlying the development, assembly and dysfunction of the human brain is the lack of direct access to intact, functioning human brain tissue for direct investigation and manipulation. In this talk, I will describe efforts in my laboratory to build functional cellular models and to capture previously inaccessible aspects of human brain development and dysfunction. To achieve this, we have pioneered the use of instructive signals to derive, from pluripotent stem cells, self-organizing 3D tissue structures called regionalized neural organoids that resembles domains of the developing central nervous system. We have shown that these cultures, such as the ones resembling the cerebral cortex, recapitulate many features of neural development, can be derived with high reliability across dozens of cell lines and experiments, and can be maintained for years in vitro to capture advanced stages of neural and glial maturation and function. To model complex cell-cell interactions, we developed assembloids and demonstrated their use in modeling cell migration, formation of neural circuits and disease processes. To advance maturation and circuit integration of organoids, we introduced a transplantation paradigm and demonstrated that engrafted human neurons can respond to sensory stimulation in the animal and can drive reward-seeking behavior therefore enabling behavioral readouts from patient-derived cells. Lastly, I will illustrate how these methods can be combined with modern neuroscience tools to study the cellular and molecular consequences of mutations and copy number variants associated with neuropsychiatric disorders.

Related publications with the topic

Revah O, Gore F, Kelley K, Andersen J, Sakai N, Chen X, Li M-Y, Birey F, Yang X, Saw N, Baker S, Amin N, Kulkarni S, Mudipalli R, Cui B, Nishino S, Grant GA, Knowles JK, Shamloo M, Huguenard J, Deisseroth K, and Pașca SP*. Maturation and circuit integration of transplanted human cortical organoids. Nature 610(7931):319-326 (2022).

Andersen J, Revah O, Miura Y, Thom N, Amin ND, Kelly KW, Singh M, Chen X, Thete MV, Walczak E, Vogel H, Fan C, and Paşca SP*. Generation of functional human 3D cortico-motor assembloids. Cell 183(7): P1913-1929.E26 (2020).

Khan T, Revah O, Gordon A, Yoon S-Y, Krawisz A, Goold C, Sun Y, Kim C-H, Tian Y, Li M-Y, Schaepe J, Ikeda K, Neal AD, Sakai N, Yazawa M, Kushan L, Nishino S, Porteus M, Rapoport J, Bernstein J, O'Hara R, Bearden C, Hallmayer J, Huguenard J, Geschwind DH, Dolmetsch RE, and Paşca SP*. Neuronal defects in a human cellular model of 22q11.2 deletion syndrome. Nature Medicine 26: 1888-1898 (2020).

Trevino A, Sinnott-Armstrong NA, Andersen J, Yoon S-J, Huber N, Pritchard J, Howard CY, Greenleaf WJ*, and Paşca SP*. Dynamic changes in chromatin states in a model of human forebrain development. Science 367: 404 (2020).

Birey F, Andersen J, Makinson C, Islam S, Wei W, Huber N, Fan CH, Metzler K, Panagiotakos G, Thom N, O'Rourke NA, Steinmetz LM, Bernstein JA, Hallmayer J, Huguenard JR, and Paşca SP*. Assembly of functionally integrated forebrain spheroids. Nature 545: 54-59 (2017).

Pasca AM, Sloan S, Clarke LE, Tian Y, Makinson C, Huber N, Kim C-H, Park J-Y, O'Rourke NA, Nguyen K, Smith SJ, Huguenard J, Geschwind DH, Barres BA, and Paşca SP*. Functional cortical neurons and astrocytes from human pluripotent stem cells in 3D cultures. Nature Methods, 12: 671-78 (2015).

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