The hidden biology of the human brain

Sergiu Pașca is a faculty member at Stanford University, where he is also the Uytengsu Director of the Stanford Brain Organogenesis Program. He is a pioneer in developing 3D brain-region-specific organoids, assembloids and cellular models of neuropsychiatric disease from stem cells.

Sergiu P. Pașca

My laboratory is interested in asking two questions: What are the unique principles underlying the assembly and maturation of the *human* brain? How do neuropsychiatric disorders arise at the molecular and cellular level? To address these issues, we developed (3D), self-organizing preparations known as brain-region-specific organoids. More specifically, we generate and manipulate human stem cell–derived neural tissue over months to years in vitro to understand how neurons find their position, how they mature and how they communicate.

I grew up in the western part of Romania known as Transylvania, in the last years of Ceausescu's communism. My early interest was in chemistry, but when I was a medical student, an encounter with a patient with autism, now a talented musical composer, switched my interests toward the biology of neurodevelopmental disorders. I started by studying blood from patients using biochemistry methods. Resources were limited, and my mentor frequently purchased reagents using her own money. I often had to convince myself that there must be some grain of truth in Gerald Edelman's 'refrigerator principle' stating that great scientific ideas sometimes come from the ready availability of reagents. A turning point for me was an internship at the Max Planck Institute, where I was awed by the power of electrophysiology when we recorded from neurons in the cat visual cortex. This made me realize that understanding brain disorders would require direct access to patient brain cells. As I was graduating from medical school, reprogramming of somatic cells into induced pluripotent stem cells (iPS cells) was demonstrated. Joining Ricardo Dolmetsch at Stanford as a postdoc was a second, critical turning point. I lacked formal training in basic science, and it was in his lab that I really learned how to systematically tackle scientific problems.

Over the next few years, I developed methods for differentiating stem cells into human neurons and glial cells, and built some of the initial cellular models of neuropsychiatric disease. These efforts helped uncover the effects of mutations in neural cells and demonstrated the promise of this platform. Studies in human neurons also led to surprising biological findings. For instance, we found that calcium channels can influence fate decision during corticogenesis. These methods had, however, significant limitations—neural cultures derived on plastic surfaces had to be re-plated regularly. Moreover, corticogenesis is an incredibly long process, and conventional cultures could not advance beyond certain stages. Around 2011, these issues prompted me to attempt a different approach—namely, to move cultures onto low-attachment plates and guide their differentiation in 3D. This change enabled a surprising level of self-organization into structures recapitulating more complex features of the developing brain. As I was starting my lab at Stanford, this work led to our establishing brain-region-specific organoids, which represented a third turning point. Unlike undirected organoids, regionalized organoids resemble parts of the nervous system, such as the cerebral cortex or ventral forebrain. They continue to mature over hundreds of days (to years) and resemble later stages of development, something that had not previously been achieved. To capture complex cell–cell interactions, my lab also subsequently developed a novel paradigm called assembloids. This represents a modular system for generating brain regions from stem cells and then fusing them in 3D to allow the assembly and interrogation of neural circuits.

Credit: Steve Fisch for the Wu Tsai Neurosciences Institute

I think I became a tool developer by necessity, because human brain tissue is largely inaccessible for investigation. Nevertheless, the technology we developed is already helping us, and the numerous labs around the world who have implemented it, make discoveries about the hidden biology of the human brain. Focusing on capturing previously inaccessible features of neurodevelopment and function, such as interneuron migration or astrocyte maturation, and then reverse engineering the molecular programs behind these processes may ultimately serve as a more powerful approach to discover novel therapeutics for neuropsychiatric disorders.

I am truly fortunate to have an amazing group of trainees. I anticipate that they will continue to ask ever more daring questions and contribute to developing a new psychiatry—one based on a more complete neurobiological understanding of the human brain. ❐

Sergiu P. Pașca
Department of Psychiatry and Behavioral Sciences & Human Brain Organogenesis Program, Stanford University, Stanford, CA, USA.
e-mail: spasca@stanford.edu

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