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Alysson Muotri: Modeling the human brain with stem cells and organoids, from disease paradigms to neanderthoids, space brains, and beyond

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Dr. Alysson Muotri is a Professor at the University of California, San Diego (UCSD), holding appointments in both the Department of Pediatrics and the Department of Cellular & Molecular Medicine. His leadership extends across several cutting-edge research initiatives at UCSD, where he serves as Director of the Sanford Stem Cell Education program, the Integrated Space Stem Cell Orbital Research (ISSCOR) center, the Archealization Center (ArchC), and the Gene Therapy Initiative, as well as Associate Director of the Center for Academic Research & Training in Anthropogeny (CARTA). Dr. Muotri's academic journey began in Brazil, where he earned a BSc in Biological Sciences from the State University of Campinas (Unicamp) in 1995 and a Ph.D. in Genetics from the University of São Paulo in 2001. He then moved to the Salk Institute in 2002 as a Pew Latin America Fellow for postdoctoral training in neuroscience and stem cell biology. At the forefront of neuroscience research, Dr. Muotri's work focuses on brain evolution and the modeling of neurological diseases, employing cutting-edge techniques such as human-induced pluripotent stem cells and brain organoids. We are honored to feature Dr. Muotri in the Genomic Press Interview series, offering our readers a unique opportunity to gain insights into both his personal journey and professional achievements. His contributions to the field of neuroscience and stem cell research continue to shape our understanding of brain development and disease, making his perspectives invaluable to the scientific community and beyond.

Figure 1. Alysson R. Muotri, Ph.D., University of California, San Diego, USA.

Part 1: Alysson R. Muotri – Life and Career

Could you give us a glimpse into your personal history, emphasizing the pivotal moments that first kindled your passion for science?

I was preoccupied with how things work even as a child. I remember my first deep thought around age seven, when I tried to figure out how a lightbulb works. My idea was that the lightbulb was not there to illuminate things but to suck up the darkness. I took a while to work on that hypothesis. As a teenager in São Paulo, Brazil, I often immersed myself in nature, capturing fireflies in jars so I could have light forever. I created a time-lapse series of photos of flickering light from fireflies—one of many projects that earned the nickname 'The Scientist' from my family members.

We would like to know more about your career trajectory leading up to your most relevant leadership role. What defining moments channeled you toward that leadership responsibility?

When I moved from Brazil to the United States to train as a neuroscientist, I was shocked to discover that most of our 'knowledge' about the human brain came from another species: the mouse. This struck me as pretty strange. After all, it was not the mouse brain that put us on the Moon or decoded the human genome. In all its complexity, the human brain generated our understanding of life and the laws that govern the Universe.

Nonetheless, I learned how to dissect mouse brains as a postdoctoral researcher. I hoped to find out more about the significant regions and essential structures associated with mental and neurological disorders such as autism and epilepsy—and, ultimately, how to fix them. I practiced and practiced until I was finally an expert in the anatomy of the mouse nervous system. However, it was bloody work, and I paid the price at night. In my dreams, I replayed the vivid experience of removing the brains from tiny skulls and slicing them up. Something about these nightmares was telling me not to continue down this road. Eventually, I mustered the courage to challenge my colleagues: what if the diseases we want to cure and the answers we want will not be found in the mouse brain? This was when I decided to create a human brain from scratch using human pluripotent stem cells, which can make all tissues in our body, including the brain. Our research relies on brain organoids, structures created from stem cells that can be derived from human embryos or reprogrammed from somatic cells obtained from living persons. These brain organoids capture the development *in vitro* outside the womb and more closely resemble human brain development than relying on a mouse model. It wasn't easy since almost nobody was doing it. However, despite the difficulty in the early days, I am glad I did. This experience pivoted my career and put me in my current leadership position.

Please share with us what initially piqued your interest in your favorite research or professional focus area.

When we pause to think about the significant problems that the world faces today or will face in the future, they include a discouragingly mounting list of seemingly far-ranging issues such as climate change, poverty, sustainable development, mental health, and many more. What strikes us first is not only the enormity of the challenge but also how diverse they seem to be. Identifying problems is one thing, and finding solutions is another. However, upon closer inspection, it becomes clear that there is only one source for their solution—to use the human brain, especially the cortex, with its powers of cognition. The problem is that we do not fully understand how the brain works and how it is formed. To do that would require examining the brain *in utero*. Unfortunately, that is an insurmountable barrier. We lack sufficient non-invasive tools to follow brain development with high definition in looking for the emergence of the first

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synapses, neurons to fire, or networks to form. All these changes occur within the womb, and our tools, such as MRI and ultrasound, lack sufficient magnification or power to focus on these structures or even at the molecular level. Due to these and other limitations, the precise way in which the human brain forms during gestation is a black box. Bridging this gap to understand human brain development was the impetus to start my lab at UCSD, focusing on human brain organogenesis.

What impact do you hope to achieve in your field by focusing on specific research topics?
The ultimate impact I hope to achieve is on people's lives, both on patients and family members. Conditions such as profound autism or Alzheimer's Disease can be devastating to the family and society since treatments are highly specialized and expensive. The human model system we developed can complement current neuroscience tools to advance treatments.

Please tell us more about your current scholarly focal points within your chosen field of science.
I am focused on several exciting projects. We are employing strategies such as ASOs (allele-specific oligonucleotides), gene therapy approaches, or even genome editing capabilities to correct the mutation in the genome of patient-derived brain organoids to unlock the potential of several genetic conditions. We are also looking at ways to take this technology to other applications. One idea was to grow brain organoids at the International Space Station to understand the space environment's impact on human brain cells, including radiation and microgravity. We know that the nervous system has not evolved to cope with the very harsh environment of outer space; for that reason, finding ways to mitigate the environmental effects on cells will be essential to help astronauts with future long-term interplanetary missions and space colonization. There are also crucial implications on Earth. Because organoids are great neurodevelopmental models, they are not ideal for helping us find better treatments and cures for late-onset diseases. We are learning that we can leverage microgravity exposure to speed up the aging of brain cells so that we can model the adult-aged human brain, including conditions such as Alzheimer's, Parkinson's, and Dementia.

We also leverage human brain organoid networks to improve artificial intelligence (AI). Based on what we learn from organoids, we can propose innovative algorithms to explain how the brain works, which will be fundamental to creating a more human-like AI type. It will be like an organic way to perform AI, using biocomputers created by stem cells to have more humanized AI networks. The energy cost is so low that it is possible to perform several computational analyses simultaneously at a fraction of the price that we currently have with AI. This work also helps us understand the emergence of consciousness in the human brain. Finally, I am also interested in the evolution of the human brain. Our approach is to resurrect extinct genetic variants from Neanderthals using genome-editing enzymes to archealize the human genome in pluripotent stem cells and generate brain organoids from them. We now call these brain organoids 'neanderthoids,' and they reveal unexpected evolutionary steps that would be impossible to discover using fossil records.

What habits and values did you develop during your academic studies or subsequent postdoctoral experiences that you uphold within your research environment?
The most important value is being honest with the data and being persistent. Most of my essential discoveries came from unexpected data that actually contradicted my initial hypothesis. It takes persistence to convince yourself and others about an unusual perspective.

At Genomic Press, we prioritize fostering research endeavors based solely on their inherent merit, uninfluenced by geography or the researchers' personal or demographic traits. Are there particular cultural facets within the scientific community that warrant transformative scrutiny, or is there a cause within science that deeply stirs your passions?
Yes, I am involved with two issues. The first is diversity, with the inclusion of different types of minorities. While this is improving in science, the "neuro" diversity is still behind. I am designing a non-traditional academic path for people with neurodiversity. These individuals might not sit in a regular class but could significantly impact science by working in different environments and with appropriate support. Another aspect that I enjoy is merging Western science with traditional science from ancient tribes. There is so much knowledge in these communities that is being lost, mainly due to prejudice.

Figure 2. Together with my with son (Ivan) and wife (Andrea) on a walk to support better treatments and conditions for autistic individuals (São Paulo, Brazil 2024).

What do you most enjoy in your capacity as an academic or research leader?
I enjoy interacting with different generations of scientists and learning from different disciplines. I love genuinely interdisciplinary research and leading truly transformative projects.

Outside professional confines, how do you prefer to allocate your leisure moments, or conversely, in what manner would you envision spending these moments given a choice?
Family time is significant for me, especially when I am doing outside activities with my son and wife. When alone, I enjoy yoga and surfing, meditating, listening or playing music, and traveling.

Part 2: Alysson R. Muotri – Selected questions from the Proust Questionnaire[1]

What is your idea of perfect happiness?
Doing what I like, while helping others in need.

[1]In the late nineteenth century, various questionnaires were a popular diversion designed to discover new things about old friends. What is now known as the 35-question Proust Questionnaire became famous after Marcel Proust's answers to these questions were found and published posthumously. Proust answered the questions twice, at ages 14 and 20. In 2003 Proust's handwritten answers were auctioned off for $130,000. Multiple other historical and contemporary figures have answered the Proust Questionnaire, including among others Karl Marx, Oscar Wilde, Arthur Conan Doyle, Fernando Pessoa, Stéphane Mallarmé, Paul Cézanne, Vladimir Nabokov, Kazuo Ishiguro, Catherine Deneuve, Sophia Loren, Gina Lollobrigida, Gloria Steinem, Pelé, Valentino, Yoko Ono, Elton John, Martin Scorsese, Pedro Almodóvar, Richard Branson, Jimmy Carter, David Chang, Spike Lee, Hugh Jackman, and Zendaya. The Proust Questionnaire is often used to interview celebrities: the idea is that by answering these questions, an individual will reveal his or her true nature. We have condensed the Proust Questionnaire by reducing the number of questions and slightly rewording some. These curated questions provide insights into the individual's inner world, ranging from notions of happiness and fear to aspirations and inspirations.

What is your greatest fear?
I am free of fears.

Which living person do you most admire?
My son Ivan.

What is your greatest extravagance?
To imagine a novel scientific hypothesis.

What are you most proud of?
Witness the progress of my autistic son Ivan.

What is your greatest regret?
Worrying too much about others' opinions.

What is the quality you most admire in people?
Creativity.

What is the trait you most dislike in people?
Cruelty.

What do you consider the most overrated virtue?
Innate abilities.

What is your favorite occupation (or activity)?
To create and test the most absurd scientific hypothesis.

Where would you most like to live?
San Diego, California.

What is your most treasured possession?
My memories.

When and where were you happiest? And why were so happy then?
Here and now, because I have all I need.

What is your current state of mind?
Energetic.

What is your most marked characteristic?
Optimism.

Among your talents, which one(s) give(s) you a competitive edge?
Creativity and multitasking.

What do you consider your greatest achievement?
To create and test the most out-of-the-box scientific hypotheses.

If you could change one thing about yourself, what would it be?
To become more self-confident earlier in life.

What do you most value in your friends?
Unconditional love and support.

Who are your favorite writers?
Machado de Assis, Jorge Amado, and Oliver Sacks.

Who are your heroes of fiction?
My childhood imaginary friend Fader, who still visits my mind.

Who are your heroes in real life?
My wife Andrea, my mom Vitoria, and my gramma Dona Ana.

What aphorism or motto best encapsulates your life philosophy?
The only certainty in life is maybe.

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