Growing Human Brains in Space

Alysson Muotri: I'll share a little bit of the work that we do in the lab, basically sending brain tissues or brain organoids to space, and there is a reason for that. My lab focus on neurological conditions. Most of them neurogenetic conditions such as autism. You are born with autism. You don't get autism after you are born. Everything happens in uterus, inside the uterus, and this inaccessibility of the brain tissue is one of the things that makes the sign so hard.

It's different from cancer, from heart, from blood, where you can have biopsies. You can see what's happening. In the brain, it starts in uterus and keeps inside that is core to your life. Really hard to study. Despite the fact that we know that these conditions have a strong genetic factor, we don't know exactly how the genes plays into behavior and neuroscience. The interface between the genetics and neurobiology, that's exactly where my lab is. We start developing tools to actually create better models to understand the human brain.

As I mentioned, because this always starts in uterus so I turn into stem cells. That's when the brain tissue start to become what we have today in our heads. It always start with stem cells. I was inspired by the first observation that stem cells when growing suspension and neutralize can form these clusters of cells that we now call brain organoids. Over the years, my lab have been improving these protocols to create something that is more robust, cheaper, easy accessibility, and also a protocol that produces neurons that can fire and connect to each other forming networks.

This is an example of what we call a semi-guided brain organoid where we transiently expose progenitor cells to specific factors that guide the cells towards the cortical tissue. It's a simple protocol where you neuralize the pluripotent stem cells. Again, in suspension induce the proliferation of the precursor cells, and afterwards, you just withdraw these factors and the cells will mature over time, forming these spheres that contains about five million cells, 2.5 million neurons in each one of them. If you've never seen one, this is how we grow them in these six well dishes. Each one of these white dot is the beginning of a brain organoid that will grow up to 2.5 centimeter in diameter.

The cool thing about these organoids is that you can measure the electrical activity, and we have been following how these networks rearrange and connect over a year, and this is more or less what we learned that it takes about two months for them to have a robust electrical activity. Before that, you can see neurons firing, but they are not connecting to each other. They're just firing in a random fashion. After two months, they start to get organized and start to form some circuitries that might generate what we call neural oscillation. These neural oscillations will develop through the next month or two, and will become quite robust and stereotype. After that, these oscillations will become more complex over time, and this is all due to the emergency of specific cell types in this population such as astrocytes that helps with the synaptogenesis or inhibitory neurons that help to modulate this network.

The cool part of this model is that it recapitulates the early stages of neurodevelopment quite well. Even the timing it's quite well reproduced in our dishes. It takes about nine months for the human brain to start showing these complex neural oscillation. The model is perfect to study conditions such as autism.

The problem is that we don't want to just focus on the preembryonic stages, but we want to also understand what happens when our brains are 1, 2, 10, 9-years-old. We start getting into the age factor of the model, which is not currently possible. I was looking to ways of doing that. How can I speed up? How can I accelerate neurodevelopment in the lab, and that's when I came across some of the NASA literature suggesting that cells from the astronauts returning from the space actually show signs of accelerated senescence, something that might be seen as an accelerated aging, and even more importantly, signs of cognitive decline has also been reported, and this cognitive decline cannot be fully

restored even six months after the flights. This is also a concern for long flights into space, but we can actually think about leveraging this phenomenon here to earth to understand age-related conditions.

Starting in 2019, we actually have several missions to the International Space Station by sending brain organoids in an autonomous platform together with Space Tango, our implementational partners. These organoids have specific payloads that changes the media, keep them alive in a similar way as we would do it here. Because these platforms are quite autonomous, the astronaut doesn't need to do too much. Basically plug these boxes inside the cabinets in there, and then we have immediately access to the experiments inside.

What did we learn with these experiments? Most of the experiments are kept at the International Space Station for about 30 days. Upon their return, what we learned was that some of the cells show signs of cellulated aging or extreme maturation, and this is seen in the transcriptomics. This is just comparing space and ground controls. Several molecular pathways related to senescence is also highlighted. On the proteomic side, this was done by Lynn and Paolo at the Ice Core, where they compare the overall proteomic changes that happens after these 30 days in space, reaching a specific age of about 10-12 years on average. Thirty days in space when the cells return, they'll have a proteomic profile of a neuron or a brain cell that is equivalent of a 10, 12-year-old person.

Moreover, on the proteomics, we can also take advantage of single cell proteomics to understand different cell populations and what happens inside each one of these cells. So complicated is lies, and I believe Aline might detail this more. But again, I mean, we see several molecular pathways that are age related conditions, increasing some pathoys that are quite interesting, for example, the derepression of retro elements. These are endogenous retrovirus inside the genome. But also mitochondria is affected. Oncogenes, your telomeres are affected. Several of these molecular pathways that we see only in more adult, older postmortem tissues. Even more importantly, once these cells return or the brain organoids return to earth, we can actually measure the electrical activity by placing them on top of multi electrode array. What we are learning is that over time, different from the ground control, there is indications that the networks start to get fragmented. Instead of starting getting more connected as you would expect, if a linear development here on Earth, we see fragmentation of the network, something that will be related to dementia or an Alzheimer's network.

Is there any useful of all this information? In one of those missions, we start sending patient derived brain organoids to space, and we start with Rett syndrome is a neurological condition that I have been studying for a while. It's quite severe. The kids develop quite normal for the first 18 months. You even didn't notice that there is a problem there. But after that, there is a decline and the kids start losing their motor abilities, their verbal capabilities, basically all their skills, and end up in a wheelchair for the rest of their life. What happens in these 18 months that the system their brains crash. We don't have good models for that. I told you that the brain organoid model just recapitulated the pre-embryonic phase, and the mouse model doesn't survive that long. We really don't know what happens to the brain when it reached that stage.

By sending Rett syndrome brain organoids, we learned something new. We learned that brain cells, specifically glia cells or astrocytes from the organoids accumulate the endogenous retrovirus that I mentioned to you that has been related to aging. The accumulation of the retrovirus leads to an increase in inflammation. Rett syndrome was never proposed to be an inflammatory condition, so it's only in this model that we could actually see elevation of certain cytokines such as IL-6. If the accumulation of endogenous retrovirus is related to aging, there's tons of evidence in the literature indicating that these specifically line elements could actually accumulate in the cytoplasm and trigger some of these pro-inflammatory pathways. If we were able to target that using reverse-transcriptase inhibitors, for example, antiretroviral drugs, perhaps we could eliminate the inflammation and help with the brains with Rett syndrome.

Sounds weird treating a neurological condition with an antiretroviral, HIV drugs that are already FDA approved, cheap drugs. I mean, would that be possible? Then we turn back into our preclinical models here on Earth both mouse and human models. I'll show you just one example of the mouse models here, where we treat the animals just before they die with reverse-transcriptase inhibitors, and the animals increase the survival and start to reacquiring their motor skills again. This was, to the best of our knowledge, something that was never seen before for this specific model for Rett syndrome. Not only the behavior, but we actually see changes in the morphology of the neurons. They recapitulate the spine density, even the size of the neurons could be restored. That was enough for the FDA to approve the clinical trial for Rett syndrome and we start treating these patients. Hopefully, in six months from now, we're going to know if antiretrovirals are useful for the treatment of Rett syndrome.

But what about age related conditions more towards the end of your life, such as Alzheimer's and dementia? This is a big market, and we also wanted to focus on that. We have a postdoc in the lab that is focusing on Alzheimer's. That's Natalia Sherman. She's been sending brain organoids derived from Alzheimer's to the space station. Again, I will not give you too much details here, but just to say that there are specific pathways, especially related to the synopsis that seems to be affected in Alzheimer's disease. We are still trying to understand how these networks are affected. But nonetheless, having a model for Alzheimer's is really helpful because, again, I mean, where would you get older human neurons to test potential treatments? There is no model for Alzheimer's. We think that this might be like a value opportunity for us to test potential therapeutics.

I decided to team up with the largest pharmaceutic in the world, which is my friends in the Amazon. In the Amazon, there is about 300,000 species in there, and certain plants do contain neuroactives that has never been studied by modern science. The idea was team up with the original tribes and search for their ancestral knowledge to find what are the plants. I'll play a quick video that illustrate more or less how this is done. We start by the identification of these plants. Again, in collaboration with these original tribes, they point us to the plants that might be neuroprotective for the human brain. They have been using this for thousands of years, actually. Some of these plants are not so easy to get. They are embedded inside of the Amazon.

To do that, we create a specific AI to inside a little robot that contains the ancestral knowledge of the Shamans. It's a visual system. These little robots, you're going to see in a moment, can actually fly through the forest and identify the specific plants that we can send like someone to collect. Someone from the tribes will go there, collect the plants, replant more, and bring it back to the lab. Once in the lab, we can isolate the extract and using a several AI type of pipeline, which would take thousands of years to do it five years ago, now we can do it in a week. We can actually point to specific molecules that can bind to specific neuronal receptors. We are scoring these molecules. This would be the first candidate to travel to space to actually be tested directly into brain organoids over there. Once we bring the cells back, the ones that has been exposed to certain of these molecules, if they show reversal of the phenotypes, those are going to be strong candidates for potential therapeutics for Alzheimer's, dementia, and other neurodegenerative disorders.

We are also working better ways to visualize the activity of the neurons, working with fluorescent markers as well as pathophysiology that can be done actually in space. We have real time capabilities through the ascending, the time in space, and also descending. That would be a game changer for us right now, we put the organoids in a box, goes to the space, comes back. We don't know what happens in between. We just know before and after. But this time would allow us to actually follow the entire trajectory of these organoids.

I'm finishing here. These are basically my take home messages. We think that growing these brain organoids in space can teach us about the impact of space into human cognition. We can accelerate aging and use this as a model for aging here on Earth, not only aging, but rejuvenation and treatments

and can be used to test novel neuroprotective molecules or compounds either from Pharma who may have them on their shelves, as well as new drugs that has never been discovered before. I'll end here by thanking the members of Ice Core that participates on that, several of the funding agencies. Thank you.

[APPLAUSE] Speaker 1: Can you tell us a little bit more about your clinical trial that you're doing and where that started? Alysson Muotri: Yeah. Right now because it's FDA approved drug, the clinical trial was immediately approved by the FDA. We also approved that in Brazil. We are starting there in Brazil with a pilot experiment that is going to be, I believe, 13 kids, different ages, and half of them would take placebo, half of them would take the real drug. There is a doctor that specialize in the milestones of these patients to see if we can have either a slow progression through these milestones or any reversal.

Speaker 1: We get to see each other all the time, and yet I have so many questions. Would it be possible to do some of the preliminary extraction and API, active pharmaceutical ingredient development in Brazil closer to where the sources for these new compounds? Alysson Muotri: Oh, for the new compounds. Yeah, absolutely. This is something we're thinking about. It will depend on the molecule. As you know, some of the molecules might be hard to synthesize.

Speaker 2: Truly inspiring. I'm guessing a lot of those compounds that you're screening can relate to a lot of neurodegeneration that is related or not, maybe to DNA damage and things like that. Have you considered also, in your screening an AI base to extend it not only to neuroreceptors, but maybe other things that we know that maybe we can screen, and there are so many people around us that can look, oh, that can be actually a super cool candidate. Alysson Muotri: Yeah. You are absolutely right. That's the ultimate goal is to create a catalog where this would be available. People can mind that, can see if it works in other cell types. Absolutely.

We are also working with not only isolated molecules, but extracts. If we want to start with an extract, might be better chances to find something. Then you funnel out a specific molecule. Speaker 2: That's beautiful. Thank you.

Speaker 3: I think connected to that, not just other cell types or other diseases. What about other plants, not just in Amazon, but other areas of the world? Alysson Muotri: Yeah. Once I start talking about that, other groups start to reaching out to reproduce similar things with different ecosystems. For example, the Saudis have the coral reefs that are bleaching, and before it bleaches, they start collecting bacteria from them and create a chemical library from the coral reefs. That's another thing that is going to get extinct. People will not be able to reproduce that. But finally, I mean, they save at least a part of that and could be used to screen as well. Also, I started working with Bill Panico, who he's retired now, but he was from scripts of oceanography here, where he isolated bacteria from deep sea, also contains lots of molecules that has never been studied before.

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