Madeline Lancaster wins Eppendorf Young European Investigator Award 2014

Presented in partnership with *Nature*

The Eppendorf Award for Young European Investigators was established in 1995 to recognize outstanding work in biomedical science. It also provides the opportunity for young European researchers to showcase their work and communicate their research to a scientific audience. *Nature* is pleased to partner with Eppendorf to promote the award and celebrate the winner's work in print and online. Thea Cunningham from *Nature* talks to the 2014 winner Madeline Lancaster about her work — which showed that complex neuronal tissues resembling early states of fetal human brain can be created *in vitro* from pluripotent stem cells — and how it felt to win the award. To listen to the full interview, visit: **nature.com/nature/awards/eppendorf**.

About the Award

Madeline Lancaster is the nineteenth recipient of the Eppendorf Award for Young European Investigators, which recognizes talented young individuals working in the field of biomedical research in Europe. The Eppendorf Award is presented in partnership with *Nature*. The winner is selected by an independent jury of scientists under the chairmanship of Reinhard Jahn, Director at the Max Planck Institute for Biophysical Chemistry, Göttingen, Germany. *Nature* and Eppendorf do not influence the selection. For more information see: **eppendorf.com/award.**

Thea Cunningham: Congratulations on winning the award. How did it feel when you found out?

Madeline Lancaster: It was a big surprise. It's a wonderful opportunity to have my work spotlighted and a real honour to be chosen this year.

TC: Give listeners an insight into what your research involves.

ML: I'm working on a new model system that we've developed for studying human brain development in a dish. We've been able to generate brain tissue from human embryonic stem cells or we've reprogrammed induced pluripotent stem cells to develop into brain tissues that we can use to model brain development and neurological disease.

TC: What led you into this research?

ML: I've been interested for as long as I can remember in the human brain: how it's special and how it develops. We've started to reach a point in neurobiology where we need some kind of model system where we can look at human-specific processes of brain development. That is what got me interested in going *in vitro* to try to develop some kind of system where we could start to do that.

TC: You've turned pluripotent stem cells into miniature brains. How did you do that?

ML: We give them a few signals to try to make them become neural first. Then we give them the right environment to allow them to develop on their own using their own endogenous signals, to develop into the different brain regions that they would normally develop into *in vivo*.

TC: What did you see as the cells began to grow?

ML: Initially you end up with a white clump of cells. We didn't know what we were looking at. One organoid in particular showed a dark area of pigment [an organoid is a structure that resembles an organ]. It was a round, circular shape that looked just like eye tissue. When I cut it open I realised that is exactly what it was. It was retinal pigmented epithelium of the developing retina. That was really striking. Once we started staining for different regions not only did we see retina but we saw dorsal cerebral cortex, which is the most extensive part of the human brain. We also saw regions like the hippocampus, which is important for learning and memory, and the choroid plexus, which gives rise to cerebrospinal fluid. We could even see tissues of the ventral forebrain and the midbrain-hindbrain boundary, which is a very important boundary in early brain development.

TC: In a normal brain, there is a lot of interplay between these regions. Did you notice that in your tissue?

ML: One of the most striking aspects is that when you have an organoid that has different regions within the same brain tissue, these

regions can actually interact with each other. It is well known that there are neurons produced in the ventral forebrain that migrate into the dorsal forebrain. When we have organoids that contain both ventral and dorsal regions, that's exactly what we can see. So even over millimetres of distance, these cells automatically know where to go. They know to go from the ventral region to the dorsal region and they don't require any exogenous factors to do that.

TC: **Did these regions contain neurons?**

ML: Yes. In general, the organoids have a large number of neurons. We have looked at the neurons of the dorsal cerebral cortex, which seem to be functional. They can fire; we see spontaneous calcium surges; they can put out axons; and they can even perform axon guidance together in a way that looks a lot like axon bundling that you would see *in vivo* [axon guidance is the name given to the mechanism in which neurons send axons to a specific target cell]. They even know where to send their axons without any exogenous factors.

TC: **So this miniature brain is acting as a developing brain would at the very early stages?**

ML: Yes. It's important to emphasize it is at the very early stages. We're not modelling events any later than the first trimester but it seems to model those early stages very accurately. One very important difference is that although the different brain regions can interact with each other, like you would see *in vivo*, they are not organised in a stereotypic manner. We don't have any axes. There's no ventral-dorsal or anterior-posterior axis. It's as if you took apart an airplane and put it back together in a random fashion, with one wing on top and the engine at the back and the cockpit in the middle. These different regions are disorganized. That plane would never fly. Our organoids probably can't think and they're not functional, but we can study each of those brain regions individually.

TC: **This is really special as it's the first 3D model of the brain demonstrated in all its complexity.**

ML: Yes. The special aspect is that we have these brain regions within single organoids. It is important to point out that previously other researchers have used pluripotent stem cells or neural stem cells to generate brain regions but these have been isolated brain regions, for example the dorsal cerebral cortex or certain neurons of the cerebellum. But the idea that you could actually generate these regions together within one tissue — that's new. It is also very important because we find that when we have these different regions together and they interact, we get much more complex tissues that develop much further. If instead you drive them towards particular brain identities, they don't take on that complexity. So it seems like these different regions need to interact with each other.

Left to right: Wilhelm Plüster, Martin Lohse, Madeline Lancaster, Dieter Häussinger, Maria Leptin, Reinhard Jahn, Mathias Wenisch, Axel Jahns. Image courtesy of EMBL PhotoLab.

TC: **You used the miniature brains to look into a particular brain disorder. Tell us about that.**

ML: We were interested in seeing whether the organoids could be useful to learn something about biology or disease. So we turned to a disorder called microcephaly, where the brain size is much smaller than it should be. Microcephaly is not very well modelled in rodents, probably because there are aspects of brain development that are unique to humans that can't be modelled in rodents. So the test was to take cells from a patient, generate induced pluripotent stem cells, allow them to form organoids and then look at their development and see if they could recapitulate this disorder.

TC: **What did you notice?**

ML: The first thing we noticed was that tissues [we developed from the microcephaly patient's cells] were much smaller than the control [tissues]. This fits what we would expect from the patient because the patient had a much smaller brain [than normal]. The fact we could see that smaller size in the organoids suggests the organoids could be a good model to look at the disorder. When we looked more closely at the tissues we found the reason [that the tissues from the microcephaly patient's cells] were smaller is because the neural stem cells were differentiating to give rise to neurons too soon — at the expense of the neural stem cells. So the patient has fewer neural stem cells, which gives rise to fewer neurons.

TC: **What avenues will this open for microcephaly diagnosis?**

ML: Having learned what we've learned now about microcephaly pathogenesis, we can hopefully understand more about what's happening in patients. If we know that there's a defect in survival of the neural stem cells or in their self-renewal then maybe we can promote them to self-renew.

TC: **Can your organoids help research into other brain disorders?**

ML: That is an avenue we are interested in moving down, particularly neuro-developmental disorders. As I mentioned, the organoids only really model early stages of development. We would like to improve that and see if they can develop further. If we can, then we can start to look at other types of neuro-developmental disorders with morphological defects, for example lissencephaly [a rare condition], where the brain is smooth [and lacks the typical surface folds]. We are also interested in more common disorders, like autism or schizophrenia, where it is thought that there's a developmental aspect. Maybe we can now model brain disorders in the organoids.