[00:00:00.130] - Alexandra Magold
Good morning, Science. My name is Alexandra Magold. And a while back I had the pleasure of talking to one of my all time idols, Britta Engelhardt. Professor Engelhardt works on what you could easily call the biological final frontier, the blood brain barrier. The BBB had been overlooked for a long time, but pioneers of intra vital microscopy such as her have literally illuminated this critical intersection of the brain, the immune system and the entire rest of human Biology. Her work has shed new light on neurodegenerative diseases, the roles immune cells play for disease progression and opened up new avenues for treatments and maybe even cures in the future.

[00:00:37.690] - Britta Engelhardt
My favorite project is in principle cell migration into the central nervous system. But then it's not true, that it's a favorite because almost all our projects are related to how immune cells cross brain barriers, but different brain barriers in order to access the central nervous system. So this is really something that has ignited my interest many years ago. And there is one barrier after the other that we're tackling and coming from different directions. In the beginning we only looked at the blood vessels and therefore at the endothelial, blood brain barrier. But then eventually the choroid plexus as a structure deep inside the central nervous system, poking its extensions into the ventricles came into the discussion because the blood vessels there have no blood brain barrier. So into the stroma, the cells can migrate. And then the big question was can the cells reach a totally different barrier which is epithelial cells? So this is something we're looking at. And now more recently, I mean, people are discussing the meningeal layers, really the outer layer, the Dura mater that's connected with the bone outside of the central nervous system. And a lot of colleagues that just say, oh yeah, the cells come from the Dura mater into the brain and then it's us saying, no, there are barriers, barriers, barriers.

[00:01:59.450] - Britta Engelhardt
How can immune cells cross these barriers? Not meaning that they cannot, but I think people never think about that, there is a cellular barrier and it's there to protect. So it's not just the gate that's open, but on the other hand, immune cells are very clever, they know how to migrate. So in principle, I mean, it's one step after the other which is the next barrier, as I said, in order to establish methods and methodology, techniques in the lab, how to investigate that. So this is fueling me since over 20 years.

[00:02:32.640] - Alexandra Magold
Yes. And like I showed in the interview, you and your team have provided unbelievable images that really changed how we actually look at those different spaces that were basically invisible to the human eye before.

[00:02:47.990] - Britta Engelhardt
Exactly.

[00:02:49.250] - Alexandra Magold
And I saw that there are actually really strong implications for diseases out there, such as multiple sclerosis.

[00:02:59.150] - Britta Engelhardt
That interest brings along that eventually you come with a very easy or simple question and you look at one structure. So as I said in the beginning, blood brain barrier so the focus is on how can I have a model maybe in vitro first for this blood brain barrier and then to establish flow condition or microfluidics this is in the meanwhile, a lot of laboratories have very good methodology but then the translation from there into the in Vivo situation, that's not so easy and for the central nervous system, what we realize a lot is people coming from the trafficking field being very knowledgeable, they then translate findings and say well, if we now look in the brain or in the spinal cord, they then, for instance, interpret if you see something, a cell migrating into the tissue and I will just add something to that in a moment then you make a conclusion and the conclusion is always based again on your methods and I mean, what has advanced the field a lot is two photon intravital microscopy and I was saying this boring but very true sentence "You only see what you have labeled or what you have stained for!" and the human brain is a very interesting organ because we always make assumptions, we make conclusions and then if we see something, we say the cell does this and this and what in the brain

makes it so difficult now in the spinal cord is that if the cell extravacates across the first barrier, the blood brain barrier, it's not yet in the tissue parenechyma and it is totally different from all other organs where once the cell has crossed the vascular wall, it's in the tissue and can do in the tissue whatever it's supposed to do but somehow in the brain and the spinal cord there is this anteroom or I always play around in the lab with our model of the Castle and I always say I'm telling this as long as until everybody considers this, that you have a protected tissue like the Castle inside with two walls around and the outer wall the blood brain barrier that can be breached also maybe the outer barrier going into the cerebrospinal fluid drain spaces so this means going into the ventricular spaces, sub arachnoid perivascular spaces but then the glia limitans is another barrier and that's very often overlooked and it has actually been Joan Abbott with colleagues she went back and looked at very primitive vertebrates so these are these funny I always have to look up how these fish are called but they are already vertebrates and they have still the blood brain barrier at the Glia level so the Glia limitans, so to speak, is the old blood brain barrier indiscriminate vertebrates and these vertebrates still live until today and that's the nice thing.

[00:05:52.220] - Britta Engelhardt
So there are still examples of these guys swimming around somewhere in deep oceans but she has in her study found that the barrier moved in evolution in the development of the vertebrates twice or at least twice or even three times to the endothelial cells, so this gives an advantage in evolution. So when she discovered that back then, we said, oh, maybe this was in combination with the development in evolution of the adaptive immune system, would have been a very nice theory. Not true. Not correlating. So we thought when the recombination of the T-cell B-cell receptor, when that was a principle in evolution occurred, that this might have been a co evolutionary process of some sort so, that you have a room for adaptive immunity without killing the neurons. But that's not the case. So there must have been another driving force to give this an evolutionary advantage in the vertebrate evolution. But now you have this, you have these areas around and of course, this is super exciting to study now in Vivo with developing novel reporter mice. And that's what we had discussed before, having now a label and can say, this is the roof and this is the floor of the subarachnoid space, and that will then really allow us [to see] where is the cell doing what?

[00:07:15.180] - Britta Engelhardt
And then also avoid misinterpretation of data. We say, well, this is now a disease causing cell. No, not necessarily. If this is in the subarachnoid space, this is not causing a disease, we cannot say that because it might be just a normal immunosurveilling cell. And that brings the next challenge, because now you want to go into animals that are healthy. And so now you go so far into very tedious image analysis because now you don't look at thousands of cells, right. So you have a situation where you have low numbers of cells, you follow them, you have to do meticulous analysis, follow individual cells for hours, and have, of course, a very high standard animal experimentation set up. I mean, we have here a surgery room that almost resembles the one, you know, at the Insel Spital for you, it's all the equipment. So it's very sophisticated to really do that. But it's absolutely fascinating because that's now just the ongoing project where we follow and can now say, yes, this cell crawls along the arachnoid barrier, this cell crawls above the pia, can it cross? Because at the end, this is not known, nobody has shown this before.

[00:08:26.720] - Britta Engelhardt
And this is what keeps you going in science, right?

[00:08:29.420] - Alexandra Magold
Yeah, absolutely. This is the frontier you're working at. Exactly. So from a more practical point of view, what part of your work you do so many things. This is what people need to know, like your lab spans the entire width of, I would say what's almost possible. So when do you feel in your element? What's your favorite part?

[00:08:50.810] - Britta Engelhardt
Actually, I feel now in my element in the meanwhile, not when this happened the first time, but when you start to understand that your working hypothesis is not right with your own experiments, when you design experiments where you can eventually see this was not a correct way of thinking, and then

to discuss this, because with me, of course, a whole group of colleagues, we have hypotheses it's usually not you by yourself , right? So the field believes like this. And then you start to do the experiments and you realize that doesn't fit. That doesn't fit. And then you think and then what is really a lot of fun if you have colleagues who are not dogmatic but open and really discuss, so that you can really get into this and they challenge me, I think it's like this. And then the other colleague goes or also the team says no, but I've seen that. And how does that fit? So having seen being in this privileged situation that we can always see something for the first time and then interpret and discuss together, this is something I can do 24 hours, no sleep necessary.

[00:10:05.670] - Alexandra Magold
Well, yeah, of course I get it. And unfortunately we have to compress things here in this podcast. But I really want people to look up your work because guys, it's unbelievable. There's stem cells. There are so many different things involved.

[00:10:21.950] - Alexandra Magold
But the one question that I really want to know and that I love asking is, if there were no limitations if a fairy came down and gave you all the means you needed money, people, whatever, what would be your favorite thing to do? What would be your dream project? What would you tackle?

[00:10:37.800] - Britta Engelhardt
I would have two approaches because we are in vivo and in vitro people. So mouse in Vivo models. And also more recently, as you said, stem cell derived brain barrier models.

[00:10:49.380] - Alexandra Magold
Unbelievable work, people look it up!

[00:10:52.350] - Britta Engelhardt
Both things are unbelievably expensive. So if there was no limits in order to understand how immune cells cross the junctional components in the blood brain barrier in vivo, I would just then make reporter mice for every single junctional molecule on the planet, which of course needs a lot of this would be really knock in. So you replace in principle, the endogenous molecule with reporter molecules so that you can visualize where these different junctional molecules are and then do your imaging. And then I don't have to explain this. Then of course, you have to cross these mice back into the barrier report. So this is unpayable for a normal scientist. And the other project is that we in the meanwhile think from our stem cell derived blood brain barrier models, we have established from healthy controls and MS [multiple sclerosis] patients that there is really an intrinsic component contributing to the barrier dysfunction in MS and that would require to make stem cell clones from many, many MS patients and many healthy controls, which again because you work with the synthetic media is something that costs you easily several millions if you do this in a whole project in order to get them to transcriptome analysis, let's say ATAC-seq analysis, methyl-seq in order to really get the whole omics picture and then be able to later on target and tackle individual molecules to understand if they are contributing to barrier dysfunction in MS.

[00:12:28.610] - Britta Engelhardt
So I have two dream projects.

[00:12:32.310] - Alexandra Magold
It's going to be switching on the lights and seeing what's going on and what's possible.

[00:12:37.290] - Britta Engelhardt
But at the end when you say that unlimited resources unlimited resources always to have an approach and I noticed a little bit back from my time when I was at the Max Planck society where there was basic research money around and we always call this the play money where you can really try something totally crazy and it flies or it doesn't but very often out of these crazy things and it can also be something you just knock out everything or you may report everything off and then you discover something which you're not discovering if you only have to focus always on this now, I have a million Swiss francs for the next five years, I have to do this so you have to focus you cannot play

that's a little bit the problem in recent years right now.

[00:13:25.850] - Alexandra Magold
Right? You cannot ask for something if you don't know it exists in the first place.

[00:13:32.250] - Alexandra Magold
Oh, my God, this was amazing. Thank you so, so much, Professor Engelhard. I really appreciate it.

[00:13:38.570] - Britta Engelhardt
You're very welcome.