Dr. Matteoli: We're here with Professor Per Brandtzaeg for the interview of the Society for Mucosal Immunology. Professor Brandtzaeg was the first European president of the international Society for Mucosal Immunology. He's been trained as a microbiologist and immunologist at the medical center at the University of Alabama at Birmingham and he earned his PHD in immunology from the University of Oslo. Professor Brandtzaeg's research examined mainly the biology and pathology of the mucosal immune system including the study of mucosal diseases associated with chronic inflammation, allergy, and immunodeficiency. His main study has been concerning the role of IgA in the mucosal immune system.

Professor Brandtzaeg was the president of the International Society for Mucosal Immunology from '95 to '97 and has been awarded with the distinguished scientific achievement award by the International Society for Mucosal Immunology in 2009. Today he is with us for answering a few of our questions that will later be posted on the Society for Mucosal Immunology website.

Welcome Professor Per Brandtzaeg.

Dr. Brandtzaeg: Thank you very much. I'm looking forward to your questions.

Dr. Matteoli: Okay. I will start shortly. You contributed intensely to the scientific advance of mucosal immunology field. Could you share with us the moment when you felt that you felt your work would have changed it?

Dr. Brandtzaeg: Well of course, the great time, the greatest time in my career was in 1974 when I, found there were actually seven models. Everybody knew that there was a particular antibody out there on the surface of the mucus membranes which of course, is IgA now. There were seven models. Everybody was starting to find out how does it get out there to the surface. Then in '74, came this paper by Singer and Nicolson on the fluid mosaic model of the cell membrane. It was not a ball, it was actually a sea, where molecules are floating around. The idea struck me that perhaps all these other molecules suggested were wrong and that the, what we call the secretory component, this epithelial piece, which we knew were associated with the antibody out there on the surface, perhaps that is a receptor, actually. I started working on that and published it in 1974.

My greatest moment was that it seemed to be true, actually. I worked for 10 years to actually convince everybody that this was the right model. Then it was published in Nature in 1984. It took 10 years really to convince people that this is actually the model. These 10 years were actually the greatest period of my scientific achievements I think. It's now the textbook model, and everybody cites it without giving a reference.

Dr. Matteoli: It's now widely accepted as being the model of IgA secretion. I know you are still pretty much involved in laboratory work and supervising projects. Having made such a long-lasting career in the field of mucosal immunology, what still excites you about your own research?

Dr. Brandtzaeg: Well, what is exciting is that the interest for IgA was quite big then in the beginning. The first international symposium in '73 in Birmingham, Alabama was called the IgA Symposium. The society was not formalized until some years later at a business meeting in Europe with Jiri Mestecky as the first president. At that time, we didn't know much about the bacteria out there - what we called the microbiota - because it was all based on cultivation. Then in 2006, we got this molecular study which showed that there are an enormous number of bacteria which we didn't know of. I think there reckoned about 1000 different species and perhaps individually 70 or something like that. Anyway, it's part of our body. Don't forget that we started as a tube. I mean, millions of years before we had the bacteria around and they found this tube, which we now call the gut, as a nice place to live and get nutrition and so on.

We developed this symbiotic relationship to the bacteria. Some call us now a super organ, the bacteria are actually perhaps a – let's say 100 times - greater genome than in the microbiome - than in the human genome. Perhaps that's, we don't forget about bacteria, as perhaps they are more important than ourselves. That's exciting, how IgA is interfering in this relationship. Because this membrane, the epithelium, which is dividing us from the outer world is only 0.05mm. It needs support and IgA is - secretory IgA is - a very important support for this barrier.

The interest has now been blooming since this molecular study came and we know that there is a huge amount of bacteria out there. The problem is how can we tolerate this? How can we get tolerance to this bacteria and everything in that tube?

Dr. Matteoli: I understand. I have another question for you. In 2013 in an overview published in Frontiers in Immunology entitled "Secretory IgA: Designed for Anti-Microbial Defense", you wrote that, "The great efforts that are currently invested in developing known mucosal vaccine and the adjuvants will hopefully announce the possibility to exploit the secretory IgA system in mankind's fight against infectious disease and there we will improve in global health." What do you think we are still missing to develop successful oral vaccine?

Dr. Brandtzaeg: The problem is that, many, many, demonstrate a huge number of models in animals - in mice - for vaccine induction through the mucus membranes. They're mostly based on very simple molecules and then adjuvants. So adjuvants are playing a part in this. I think we missed something in the way we see and handle and modulate the microbiota - or commensals as we say – it's different from how we handle an infectious agent. I think we need to focus

more on the pathogenic factors or the pathogenic bacteria, the exogenous pathogenic bacteria.

Dr. Matteoli: So what will you suggest - to use the strategy of a pathogenic bacteria to develop oral vaccine?

Dr. Brandtzaeg: You know that the bacteria and the pathogens use many strategies to break a barrier. For example, the secretions and the exosome. We have to identify these things and it's a long way to go I think, but that you have to hit the right thing. I think we missed all these things by focusing on all these animals models, single models. Because there is no adjuvant which I see yet that can be accepted in humans before we post vaccines. You need to hit the right target. I think that's what has been missing - focusing too much on animal models with adjuvants and so on.

I'm optimistic. If we can identify these barrier-breaking pathogenic factors we can make vaccines against them.

Dr. Matteoli: Thank you.

Dr. Brandtzaeg: That's a long way because it will have to be immunized for the pathogen you are working with.

Dr. Matteoli: Yes, so it needs to be pathogen specific and probably-

Dr. Brandtzaeg: Yeah exactly.

Dr. Matteoli: Okay. Thank you. In this, in the recent years we have seen exponential growth of interest for the mucosal surface and for the mechanism that are modulating - specially the morphological response of the mucosal source. What do you think is happening? Why this is the case?

Dr. Brandtzaeg: Well I think removing all of the false immunology has been actually quite parallel with the knowledge we have gained about the commensal bacteria. That there is such a huge number within the microbiome - perhaps 100x of the human genome. This is why some people like to call this an organ. We are a super-organism with bacteria as part of the organ, or organism. You can see that this interest [in this idea] has increased. I review a number of papers now from major journals focusing on IgA.

We have our own journal, the *Mucosal Immunology* journal. It's a great success which I, when I was the president I was not so very interested in having a special journal for mucosal immunology. I thought we should compete with the general immunologists in the major journals. But, I must admit that I was wrong. Because of course, the *Mucosal Immunology* journal has been a success. I must say that.

Still people have these big articles published in *Nature Immunity, Nature Immunology*, now there's a new journal which we call *Nature Microbiology*. Because of this interest in microbes and, I think, this relationship between them. What is a symbiont? Why is some of these bacteria seen in symbiosis? Why do they have dysbiosis? What is that? So many diseases are related to dysbiosis which means there is a change in the composition of commensals that a secondary or a primary phenomenon? We don't know. This supporting of IgA which we actually first saw in 1968 and it took 30 years before it was rediscovered! We also observed that some of the coated bacteria could continue to grow, so it's not always inhibiting the growth of the bacteria. There are a lot of things we don't know about this intricate relationship. How a symbiotic bacterium transforms into a pathogen - a pathogenic bacteria - we don't know.

Dr. Matteoli: For you, what are some of the primary unanswered questions that we will need to address in order to take advantage of the mucosal immune system? You think this interaction between the microbiota and the way that we tolerate or react to the microbiota this is one of the main points, I guess?

Dr. Brandtzaeg: I think this coating of IgA which we saw in 1968 for the first time, which is now a focus of interest in medicine. Why is some of this symbiotic bacteria going into, what do you call it, pathobiontic bacteria or pathobiont. What is dysbiosis? Why is it secondary or primary? These are things we don't know. People are starting to understand what is coating the IgA on the bacterium, on the commensal bacterium. How much does it have to do with tolerance? Why do we tolerate all these bacteria? What is the effect of breaking this tolerance? There are so many open questions which have developed along with the understanding of the microbiome.

Dr. Matteoli: Okay. Now, going back to the focus of the Society for Mucosal Immunology, what do you think the Society should do to promote scientific progress in our field?

Dr. Brandtzaeg: Well, as you know the wall in Berlin came down in '69 [sic] I think it was. A few years after the establishment, the former establishment, that the Society for Mucosal Immunology was replacing, the meeting in Buffalo. When I was president, I was very keen on opening up for all these new scientists that were sitting there, without resources, previously behind the Curtain. At the business meeting in Prague, we decided to reduce the fee from ten to five dollars for these new people. This is a small support because they cannot dream about the resources we have in the West. Still, I was very keen on making this more of an international society really. I was actually fighting to change the name to International Society for Mucosal Immunology. We had a general poll in the society and the majority of members at that time were Americans and they beat me (laughs). I had to accept it.

Dr. Matteoli: To convince many of them!

Dr. Brandtzaeg: Well a slight majority was for keeping the name. I don't think that was a disaster, but I still hope it's very important to work to have this as an international society. It has improved enormously because now we have representatives from Japan and from all these lands and also from-

Dr. Matteoli: From Australia.

Dr. Brandtzaeg: Yeah, yeah.

Dr. Matteoli: From New Zealand.

Per Brandtzaeg: And those which were behind the Curtain before. It's growing slowly into a really international society. I'm very happy to see that.

Dr. Matteoli: That's also thanks to your contribution and your support of this society. Now you know that the academic job market is getting increasingly competitive and it's really difficult to switch from post-doctoral position to an independent career. You need a great amount of support - showing to your institution that you are collecting grants, publishing in high impact journal. What will be your advice to a young member of the Society for Mucosal Immunology?

Per Brandtzaeg: That's a very good question actually. I think what I see as a failure for some of these young people is that they switch projects. I think that's very responsible [for their challenges]. I think it's very important to stay with a project you are working on. That depends of course on what sort of supervisor you have. You need to be very careful and choose -

Dr. Matteoli: The right mentor.

Per Brandtzaeg: Right. The right man or the right woman. I don't know. I think the supervisor will tell you something about the environment where you are going to work. You have to trust that the supervisor has given you the right advice. Don't switch. It's very important to stay on with what you are working with because that's the only way to get advance-

Dr. Matteoli: Proceed in-

Per Brandtzaeg: Yeah, to proceed is to be stubborn and say that this is what I am going to solve. I think that's the best advice I can give, because at the end you depend on having a degree and that is what you should show for you when you apply for a job. Well, it's very [general] advice of course, but that's what I can say.

Dr. Matteoli: Thanks. I thank you on behalf of the Society for Mucosal Immunology for your time and I look forward to meet you at the next society meeting. Thank you. Have a good day.