Sandro Da Mesquita: “What really motivates me is understanding the mechanisms and the potential clinical benefits”

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Mayo Clinic College of Medicine and Science in Jacksonville

Sandro Da Mesquita, is an assistant professor of neuroscience at the Mayo Clinic College of Medicine and Science in Jacksonville, Florida. Dr Da Mesquita's research focusses on the pathophysiology of brain ageing and neurological disorders, with a special interest in the role of the recently characterized meningeal lymphatic system. His main objectives are to advance the basic knowledge of disease mechanisms involving meningeal lymphatics and to develop novel bench-to-bedside therapeutic strategies that would prevent age-associated neurodegeneration, and the cognitive decline associated with age, particularly in the context of Alzheimer's. Dr. Da Mesquita participated in the CNIC Conference 2024: Cardiovascular Risk Factors and Brain Health.

- **What is important in this scenario where we know more about the association between dementia and vascular factors?**

What I am looking for at these conferences are new concepts in the field that I can later take to my lab and enrich, so to speak, my research programme at Mayo Clinic. I feel that I study a very particular type of vasculature that drains the brain, and I am already part of a highly specialized niche of research that is in constant development. And although I carry out experiments that are not always completely aligned with the rest of the research in the cardiovascular and neurovascular field, I always try to attend this type of meeting to learn about what is out there and then apply it to my own research at Mayo Clinic. The study of the lymphatic system is still at a very early stage, particularly in comparison to blood vasculature and circulation, which is why I always try to meet experts to understand what affects blood circulation and then transfer it, so to speak, to lymphatic vasculature and function.

- **Your research revealed crucial information about the lymphatic system…**

I don't want to attribute credit for the discovery to myself, also because… although I contributed to a greater understanding of the lymphatic vasculature that drains the central nervous system, I don't think that even the group where I did my postdoctoral research, led by Jonathan Kipnis at the University of Virginia and now at the University of Washington in Saint Louis, would want to take credit for having discovered the lymphatic system. When you go centuries back in history, there were already observations that the system was there, but the observations went ignored for centuries because they didn't have the right techniques to completely understand it. However, now, with the technology and the right experimental approach, the work of his group and the one I was part of helped to rediscover it. In the last decade, we have attempted to fully understand it. It is not a completely new type of vasculature; it is similar to the lymphatic vasculature we have in peripheral tissues, but now we know that it also extends to the central nervous system. Given the nature of the tissue, the lymphatics that drain the brain are a little different, and now our work is to continue research into how they work, how they change during ageing and in the context of disease, and how we can intervene to develop better therapeutic strategies, for instance.

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- **Do you have any clues about how to intervene, prevent or promote the mechanisms??**

We are at a very early stage. In my laboratory we use a lot of animal models, but any model has its

limitations. We are researching some potential molecules that could help improve lymphatic drainage of the brain, such as therapies based on vascular endothelial growth factor C (VEGF-C). But again, we know that molecule works in the peripheral lymphatic system and is also important for the lymphatics that drain the brain. Nonetheless, we are also discovering that there are many differences: not everything that works for a lymphatic vessel that drains the skin or the intestines works for one that drains the brain, which also changes a lot during ageing. Ageing leads to a degeneration of these lymphatics and finally, to a better lymphatic drainage to cervical lymph nodes. This does not happen in peripheral lymphatics; an old person may have good drainage of peripheral lymphatics, but this does not seem to be the case for brain lymphatics. We still don't understand why this happens, which is why I think attempting to understand it using different models would be a great step, whether that is small mammals or more complex in vitro models, before we can really move on to better therapeutic strategies.

- **When you started your career, did you have translational medicine in mind?**

Absolutely. Working at the Mayo Clinic really means you deepen your understanding of the importance of translational research. But to be honest, what really motivates me is understanding the mechanisms and the potential clinical benefit. I'm fascinated when, sometimes by chance, someone discovers that a medicine or a compound has a particular effect on the heart, even without understanding how. I understand the great importance of finding therapies and getting clinical benefits but understanding the "why" also drives me. I think that both aspects are extremely important. At times, in basic research using animal models, many things work well in mice, but not all of them translate to clinical results. That's why the translation of these findings is crucial and it's important to combine the best of both worlds. Animal models should always be used in combination with analysis of human tissue to see if our observations are the same.

- **It would be interesting to see that in human tissues…**

Exactly. It's important to keep open communications between basic research and clinical practice and foster translational research. Mayo Clinic is one of the best places in the world to put this into practice.

- **Are you thinking of any collaborations with CNIC researchers?**

Potentially, yes. I've met many new people and learned a lot. I've always been really interested in barriers in the brain, like the blood-brain barrier, and different niches and places where blood communicates with the brain environment. I am currently studying a different type of vasculature, lymphatics, which are also very important. Coming to this conference has allowed me to revisit all of my early interests and learn a lot. There are researchers here who really are leaders in the field, and it is gratifying to interact with them, learn from them and, potentially, begin new collaborations. I believe that a subject we should explore in the future is communication between the lymphatic system and the cardiovascular system. Anatomically, they always seem to go hand in hand; where you find a blood vessel you generally find a lymphatic vessel nearby. I think there is a dialogue between them that we need to understand better and maybe we could collaborate in this area

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