Q&A for Upcoming ISEH Journal Club

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The New Investigators Committee is excited to announce the second ISEH Journal Club, which will run next week (24 - 28 April). We'll be discussing a recent paper in EMBO entitled *Osteopontin attenuates aging-associated phenotypes of hematopoietic stem cells* with the paper's first author, Novella Guidi. Starting 24 April, you can ask Novella any questions about the paper through the ISEH Facebook group. As before, to help introduce this paper and start the discussion, we conducted a Q&A with Novella. This recent publication came from her PhD research with Dr. Hartmut Geiger at the University of Ulm. Novella is currently a postdoctoral fellow with Dr. Valter Longo at the University of Southern California. **What was the motivation for studying hematopoietic stem cell aging?**

What motivates me and the laboratory about studying the aging of hematopoietic stem cell (HSC) is that aging at the stem cell level is one underlying cause of aging-associated immune-senescence as well as leukemia. In fact upon aging HSCs undergo changes in function and structure, including skewing to myeloid lineages, lower reconstitution potential and loss of protein polarity, which influences health span. What is highly exciting about studying HSC aging is that the functional decline of aged stem cells may be reversible and that rational interventions to achieve HSC rejuvenation can be developed by targeting HSC aging mechanisms, thereby allowing for a more healthy aging. **What are the key findings of your paper?**

The first important finding in the paper is that an aged-related decline of osteopontin (OPN) in the bone marrow niche microenvironment is able to extrinsically result in HSC aging, while so far mainly HSC intrinsic mechanisms have been considered to be the important driving force of the aging process. Secondly, exposure of aged HSCs to activated OPN fragments attenuated aging of old HSCs, resulting in increased engraftment, decreased HSC frequency, increased stem cell polarity and a restored balance of lymphoid and myeloid cells in blood. This nicely demonstrates how rescuing osteopontin levels in the niche supports a more youthful HSC function. **How do you think your story will impact the blood field? What do you see as the important next steps?**

I think our findings emphasize the importance and the contribution of the niche microenvironment in driving or exacerbating HSC phenotypes, and especially being considered when rejuvenation therapies are being established. Our study in fact points to exciting novel ways to improved immune system in old individuals and possibly reduction of oncogenic transformation upon aging, by therapeutically targeting the place where blood

stem cells reside. Interestingly, osteopontin levels are not only low in the bone marrow niche, but also in the peripheral blood upon aging therefore as a next step we are aiming to use osteopontin replacement therapy in mice to reverse the influence of an aging niche. Our findings cannot at this stage be directly extended to clinical treatment of human patients, but the data provide interesting leads that one day could benefit human health by boosting the immune system of elderly people. **Are there members of our ISEH community that contributed to the context for your paper? How did he/she contribute to your research question?**

Yes, there are few people of the ISEH community that contributed to my project development path. Most of all it was the work previously done by Dr. Susie Nilsson that inspired me in digging deeper into the osteopontin signaling pathway upon niche aging. In fact, she previously showed that OPN knock-out mice had an increased HSC pool size in vivo with markedly enhanced cycling, suggesting osteopontin as a key regulator of HSC quiescence. Moreover, work from Dr. Peggy Goodell showed how aged circulatory factors and the bone marrow cytokine RANTES are able to influence the HSC myeloid skewing phenotype and that heterochronic transplants of aged HSCs into young animal generate less myeloid cells. Altogether their data implied a critical role of a young and functional niche in supporting young and healthy HSCs and immune cell production, which directly inspired me to investigate the role of osteopontin in influencing HSC aging-related phenotypes. **Who would you particularly like to read your paper?**

If I have to think about someone I would particularly like to read my paper this person would be Dr. Paul Frenette. His excellent work on unraveling the nature and function of the HSC niche microenvironment has always fascinated me. He elegantly demonstrated, based on distinct genetic mouse model and advanced high resolution imaging, that the perivascular area of the sinusoidal blood vessels is the region in which HSC mostly resides, surrounded by important niche cell types that further regulate HSC function and maintenance. The endosteal niche is highly vascularized, implying that the cellular components of the niche that regulate HSC function are interconnected. During the past years' conferences, I got the chance to meet him a couple of times and I always loved discussing my data and findings with him. His critical point of view always inspired me to view, analyze and interpret my results critically. These conversations gave me the confidence that I was digging in the right direction. I would like him to read my paper because I am sure he would be highly critical by asking a lot of tricky questions, while he would have of course additional advice for the next steps in my research endeavor. Thank you to Novella Guidi for participating in our 2017 ISEH Journal Club. Please visit the ISEH Facebook group from 24 - 28 April to submit your questions and join the discussion.

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