Text: Louise Hagbard, Ph.D. **Photo:** Wille Nyyssönen

STEM CELL INNOVATORS

HELI SKOTTMAN

"Both RPE cells and LESCs have a high clinical potential for eye diseases and our long-term aim is to bring these cells towards clinical practice."

HELI SKOTTMAN, Ph.D.

PROFESSOR AT TAMPERE UNIVERSITY, FINLAND

ABOUT: **Prof. Skottman is Professor in Faculty of Medicine and Health Technology at Tampere University and has over 16 years of experience on establishing, culturing and differentiation of human pluripotent stem cells (hPSC). The main research aim for her group is to develop novel stem cell-based tools for the corneal and retinal repair through cell transplantation and ophthalmic *in vitro* tissue models.**

Prof. Skottman joined Tampere University, Finland in 2005 after a postdoctoral position at Karolinska Institutet in Sweden and University of Turku in Finland. Prof. Skottman holds a Ph.D. in molecular animal biotechnology from the University of Eastern Finland. She is also schooled in Bio business at Turku School of Economics in Finland. Prof. Skottman has devoted herself to eye research, targeting clinical applications for retinal and corneal diseases, developing hPSC based tools for disease modeling, drug discovery and cell transplantation. She is a member of the editorial board in Scientific Reports and she has over 100 peer reviewed scientific publications in the areas of biotechnology and human stem cell research. In 2019, the Scandinavian Society for Biomaterials honored her with the research award for her contribution to the field of biomaterial science.

Photo: Wille Nyyssönen

Photo: Jukka Lehtiniemi

TAMPERE UNIVERSITY

The Tampere University is a Finnish university that was established in beginning of 2019 as a merge between the University of Tampere and Tampere University of Technology. The new foundation-based university also has close ties with Tampere University of Applied Sciences.

↑ Human pluripotent stem cell derived corneal limbal stem cells on biomaterial carrier coated with Biolamin 521. Photo: Wille Nyyssönen

Tell me a little about your background. How did you get into stem cell research field?

"It started in the beginning of 2003 when I joined Professor Outi Hovatta's lab at Karolinska Institutet in Sweden. She had a Postdoc position for deriving new embryonic stem cell lines and optimization of the culture conditions. So, she took me in and that's how it started. After one year, I received Academy of Finland postdoctoral fellowship funding and I came back to Finland with the opportunity to continue the project with Professors Riitta Lahesmaa and Outi Hovatta at University of Turku. In the beginning of 2005, Outi got a visiting professorship at Tampere University and she took me with her. She didn't want to leave the position at the Karolinska Institute so we made a deal that I would be the one who would set up the lab and start the derivation of embryonic stem cell lines here in Tampere."

"I think it was a bit easier to get funding for the stem cell research because this was a new and innovative research field. However, the governmental research funding is limited here in Finland, so we have to fight for funding with other fields of medical and clinical research, including cancer research. So it's always a struggle. The research funding we have received has in part come from

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↑The Skottman team. Photo: Jukka Lehtiniemi

Academy of Finland but we also have been able to get support from Business Finland and foundations, including Sigrid Juselius Foundation."

How did you decide to start with eye research?

"The first couple of years in Tampere, we focused on deriving embryonic stem cell lines and we put a lot of efforts to develop our culture conditions to get defined and feeder-free systems. It was not until 2008, when I hired my first postdoctoral researcher, that we could focus more on the ophthalmology field."

"I think the idea came from discussions I had with Professor Hannu Uusitalo, Chief ophthalmologist here in Tampere. He said, 'Why don't you differentiate RPE cells from the pluripotent stem cells?' It was a really interesting topic and there was only one paper available, by Klimanskaya, that showed that it was possible to differentiate retinal pigment epithelial (RPE) cells from embryonic stem cells. Of course, we didn't have any preliminary research data so we were not able to apply for research funding for that project. We were lucky to find private donations, which is very unusual to get in Finland, and once we could demonstrate that, okay, it's possible to get RPE, then we were able to get funding from Academy of Finland."

"We continued the RPE work for several years and it was much about molecular and functional characterization and animal studies. We had a lot of collaborative projects with biomaterial engineers, doing a lot of biomaterial studies because we wanted to transplant RPE cell sheets and needed biomaterials for that. That was when I hired the first Ph.D. student who had an engineering background because that was knowledge that I did not have. Then we further continued the bioengineering track, with focus on cornea. The biomaterial solutions for cornea are a bit special because they have to be totally transparent. At the same time, we went into the bio-printing field, because we wanted to do 3D structures. However, we did not have these cool 3D bioprinters in Tampere. Those we had were more for material engineering. I was lucky that we could go to Professor Chikovitch's lab in Hanover in Germany to learn laser-assisted bio-printing. My postdoc has put huge efforts into getting this first paper out for the cornea printing. We are now continuing that work here in Tampere, not with laser-assisted printing but with the use of an extrusion printing system."

HIGHLIGHTED PUBLICATIONS

Xeno- and feeder-free differentiation of human pluripotent stem cells to two distinct ocular epithelial cell types using simple modifications of one method.
Hongisto H.
Stem Cell Res Ther. 2017, doi: 10.1186/s13287-017-0738-4

Methods for efficient and scalable, directed differentiation of high-quality retinal pigmented epithelial (RPE) cells and corneal limbal epithelial stem cells (LESCs). The two clinically relevant cell types are generated with simple inductive modification of the same basal method, followed by adherent culture, passaging, and cryobanking.

Efficient and Scalable Directed Differentiation of Clinically Compatible Corneal Limbal Epithelial Stem Cells from Human Pluripotent Stem Cells.
Hongisto H. Et al.
J Vis Exp., 2018, doi: 10.3791/58279.

This protocol provides a reproducible and efficient method for generating hPSC-derived Corneal limbal epithelial stem under xeno- and feeder cell-free conditions.

Human stem cell based corneal tissue mimicking structures using laser-assisted 3D bioprinting and functional bioinks.
Sorkio A. et al.
Biomaterials, 2018, doi: 10.1016/j.biomaterials.2018.04.034.

This is the first study to demonstrate the feasibility of 3D laser-assisted bioprinting for corneal applications using human stem cells and successful fabrication of layered 3D bioprinted tissues mimicking the structure of the native corneal tissue.

"Which culture substrate you use is very important. We are working with eye specific epithelial cells which are highly dependent on the extracellular matrix they grow on. The matrix is totally modifying the cellular functionality and properties."

Tell me more about the translational work that you do. Are you aiming for clinical applications?

"Yeah, both for retina and for cornea. With RPE, we are depending a lot on our collaborators abroad, especially Dr. Boris Stanzel in Germany. I also have a small affiliation in Singapore with the Singapore Eye Research Institute, and when Dr. Stanzel was there, we conducted preliminary safety and efficacy studies where we transplanted a combination of RPEs and a biomaterial scaffolds in a primate model. We haven't published that yet but we hope that we will submit the manuscript in spring this year. Dr. Stanzel is now back in Germany and we are now trying to get funding to start clinical trials in Germany. We also have an efficient protocol to generate corneal limbal epithelial cells (LESCs) which we would like to use in clinical applications, so we are in discussions with regulatory agencies around that as well. Both these cell types have a high clinical potential and our long-term aim is to bring these cells towards clinical practice."

How important is it for you to work with more defined culture systems?

"It's very important. We are working with epithelial cells, both RPE and corneal limbal cells, which are highly dependent on the extracellular matrix they grow on. The matrix is totally modifying the cellular functionality and properties. So, it's really important. We became very interested in BioLamina's products because of their biological and defined properties."

"My research aim has always been clinically-oriented, so I have always strived to develop defined culture environments so that the method can be more easily taken to clinical applications. In the beginning, in Outi's lab, we started early to develop our own defined and serum-free culture medias because there weren't any commercially available at that time. We started to use knockout serum replacement, which everyone is using today. We also used human foreskin fibroblasts as feeder cells to culture our hES cells on. That was quite new because most other stem cell researchers were using the mouse feeder cells.

What do you think about regenerative medicine with pluripotent stem cells? Will it be as big as we hope it will be?

"I don't know. I'm a bit skeptic that we will be able to do this in a cost-effective way. Are pluripotent stem cell-based treatments only going to be available for people who will be able to pay for it? That concerns me a bit, the financial aspect, how the governments are going to be able to put this in clinical practices and so on. Still, I think that there's a lot of potential for this field."

You've been working mainly with human embryonic stem cells, do you also work with iPS cells?

"Yes, we are producing iPS cells as well, but mainly for disease modeling. We have a lot more variability between our iPS cell clones so we are using embryonic stem cells for our more clinical-oriented work. We have a couple of very good human ES cell lines that differentiate nicely to those cell types we are studying. Anyway, I'm sure iPS cells are going to be used in clinical practice, also in the ophthalmology field, even though there are some additional risks related to these cells. For the diseases we are aiming for, like macular degeneration and limbal stem cell deficiency, there are heavy immunoreaction effects so there we will definitely need to use HLA-classified cell lines, and that will be easier to do with the iPS cells."

In the process of developing good differentiation protocols, what has been the biggest obstacles?

"With the RPE cells, time is the limiting factor. It still takes a really long time to get mature RPE cells from pluripotent stem cells. The efficacy is fine, it just takes some time. You get the pigmentation quite easily and fast but to get really functional, polarized RPE cells, it takes several weeks, even months. Whatever project we use RPE for, it is always really long. So, I think that has been the bottleneck."

"When it comes to the limbal stem cells, the process is much faster. Within 30 days we are able to get a nice pure population of limbal stem cells. We are now in dis-

“Are pluripotent stem cell treatments only going to be available for people who will be able to pay for it?”

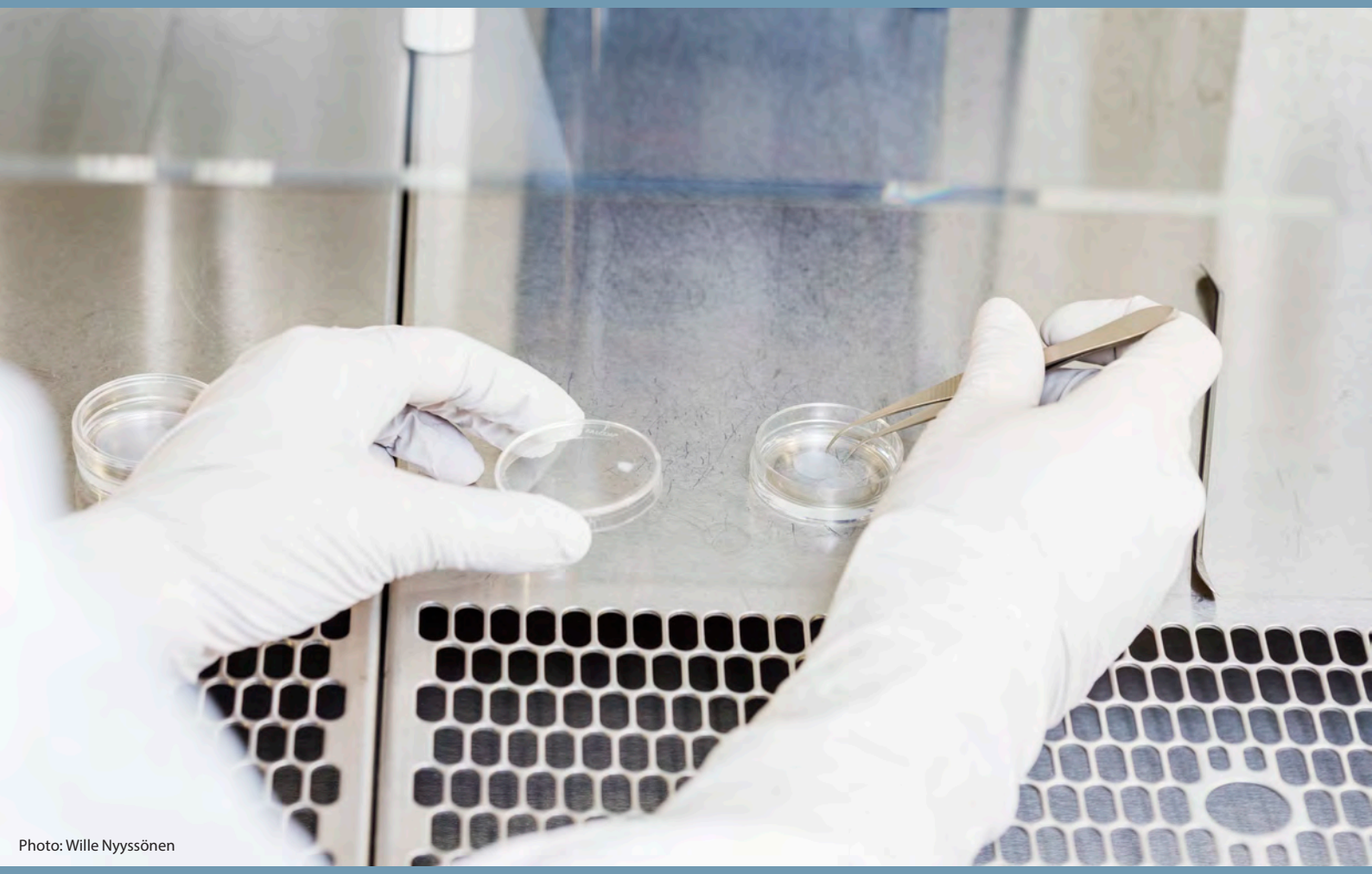


Photo: Wille Nyyssönen

“I’m proud of myself for being able to build teams and collaborations that has allowed me to put myself in situations where I don’t have to be an expert but where I get the opportunity to learn.”

cussions with regulatory agencies to get these cells into clinical applications. The issue there is safety. The differentiation process from undifferentiated pluripotent stem cells is very short and we are planning to transfer highly proliferative stem cells into the patients So, we have to pay even more focus on the characterization of the cell population, on the safety issues and on the quality control in our production to make sure that the end product does not contain pluripotent stem cells and is safe for the patients.”

How has your interaction with the regulatory agencies been?

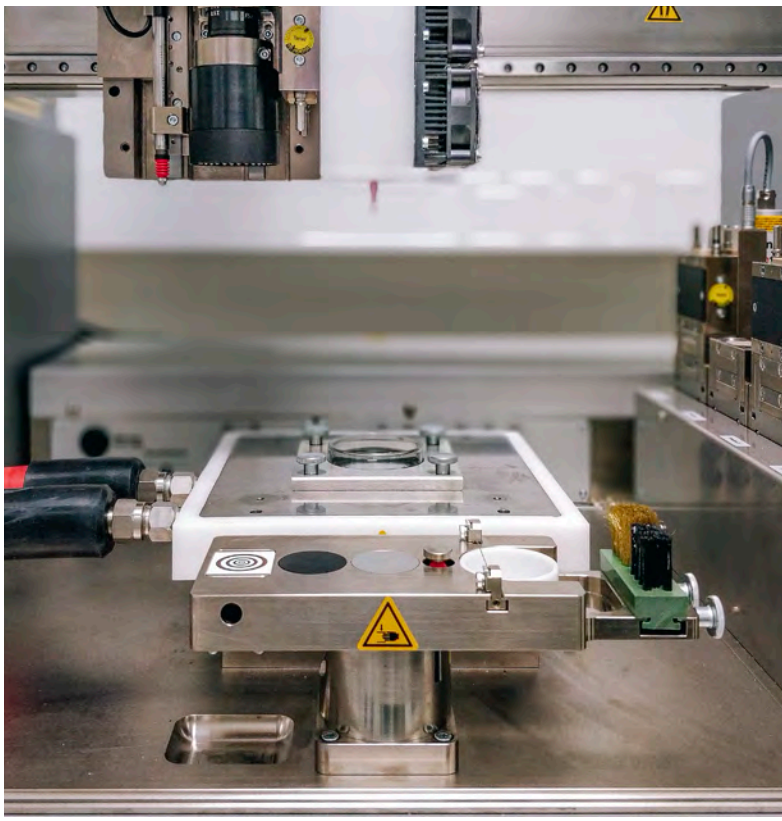
“I think it has been beneficial. The regulatory landscape for pluripotent stem cell derived products is still young and the clinical protocols need to be designed with tight synergy between the researchers and regulatory authorities. In my experience, regulatory authorities here in Finland are always willing to discuss and help. I think that it’s very useful.”

Is there something in your career that you are extra proud of?

“I’m proud of myself for being able to build teams and collaborations that has allowed me to put myself in situations where I don’t have to be an expert but where I get the opportunity to learn. I’ve always had that kind of drive to hire team members who know something which I don’t. It doesn’t make me feel small just because they know something better than I do. I enjoy working with them and I learn a lot at the same time. This has enabled me to move into research areas which I don’t know that much about, like ophthalmology and that has been very motivating. I didn’t know anything about the eye when I started but now, I have a much better understanding of the field.”

Who has been your biggest inspiration?

“Of course, I want to mention Outi Hovatta. She has had a big influence on my career. She was the one who brought me into this area. If I hadn’t been doing my postdoc in her lab, I don’t know if I would be working in the pluripotent stem cell research field at all. She has always been very research-oriented, a very dedicated person. She is a mother of four children, does a lot of sports and somehow, she has been able to do a great scientific career. In that sense, she has not been a good role model, because it not easy to keep up with her. Another powerful woman who has been kind of a role model for me is Professor Riita Suuronen. When I came to Tampere, she was Director of the newly established Regea, Institute for Regenerative Medicine, which she had been able to build up from scratch. So, a very inspiring person as well. I have always had these strong ladies as role models, here only two of them are mentioned.”



↑ The Skottman team is using 3D bioprinter for establishment of full-thickness cornea from human stem cells and functional bioinks. Photo: Anni Mörö

HELI SKOTTMAN ON FUNDING

? If you had a hundred million dollars, how would you use it?

! "I would like to continue working on developing stem cell therapies for diseases where we currently don't have a treatment. I also think this whole field of 3D bioprinting is very fascinating, to making more complicated tissues and structures by combining biomaterials and-cells. Stem cells are also very useful for studying human development and disease modeling, to get a better understanding of certain genetic disorders and to find potential drug targets. I think it's important to invest in all these areas because they all bring different things to the table."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