e:Med junior research alliance LeukoSyStem

Interview with Simon Haas

Single-cell multi-omics leukemia researcher; e:Med alliance leader; BIH, Charité and MDC in Berlin; DKFZ and HI-STEM in Heidelberg

Simon Haas researches like he jogs: he constantly explores new directions. He was one of the first scientists in the world to examine hematopoiesis using novel single-cell technologies – and in doing so he turned conventional knowledge about blood formation on its head. Where a method is lacking, he develops it: most recently spatial single-cell multi-omics to detect leukemia stem cells and target them with therapies.

gesundhyte.de: *You are leading the* **junior research alliance LeukoSyStem** *within e:Med, a major funding scheme for systems medicine set up by the German Federal Ministry of Education and Research (BMBF). This is not the first project you have led, so what is LeukoSyStem aiming to do?*

Dr. Simon Haas: Our main aim with the alliance is to better understand leukemias (blood cancers) by focusing on stem cells and using **single-cell methods to identify new therapeutic avenues**. Leukemias are typically treated with traditional chemotherapy. But that's a bit like using a bulldozer. Although it effectively fights cancer cells, it also damages healthy cells and this leads to severe side effects. Moreover, chemotherapy frequently leaves behind cancer cells, and these are often so-called cancer stem cells. They are only a part of the tumor, but these few cells can completely regenerate the entire tumor mass. It is precisely these cancer stem cells that often provide the reservoir for relapse after successful therapy.

So we're aiming to develop therapeutic approaches that specifically kill leukemia cells and especially leukemia stem cells, but leave healthy cells untouched. These therapies should have fewer side effects and at the same time prevent relapse, which is the main cause of death in most forms of leukemias. To accomplish this, we are using so-called single-cell technologies. We obtain a wealth of information from individual cells, which enable us to understand in particular which cell is healthy and which is diseased. In this way, we can specifically identify target structures on the cancer cells and render these cells harmless while keeping healthy cells alive.

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gesundhyte.de: *That sounds plausible and very effective. What methods are you using to pursue this? Did you develop them yourself?*

The single-cell field is a relatively new research direction that has emerged only in the last few years. LeukoSyStem's members have been involved in the field since its inception and have developed many of the methods themselves. These include a spectrum of methods, from molecular experimentation to data analytics to medicine.

gesundhyte.de: *Your publications give the impression of an extraordinary goal-oriented journey. Has that been the case, or has each answer you found opened up a hundred new questions from which to choose?*

Simon Haas is developing single-cell multi-omics in order to detect leukemia stem cells – and target them with therapies.
(Source: © Felix Petermann, MDC)

Of course, it's a combination of both: Ideally you have a goal in mind, but you've also got new results coming in daily so you make adjustments according to what they say. You see what's possible with a new, specific method and you do things that weren't possible before. **Science really does thrive on unexpected results.** It's quite wonderful to follow them and perhaps arrive at findings that are even more exciting than those we expected from the initial research question.

gesundhyte.de: *What about the discovery that the microenvironment is so important? Did that come as a surprise, or were you expecting it?*

We've known that the cellular environment plays a key role in cancers for a while now. The immune system in particular is constantly working to fight the cancer. We've developed methods that allow us to examine this microenvironment in more detail. Initially, this was to help us **understand the healthy stem cell system. But now we're also using it to better understand leukemias.**

gesundhyte.de: *What are those methods and why do they work so well?*

Single-cell methods allow us to deconstruct tissue into its individual cells and see which components make up the healthy tissue and which make up the cancerous tissue. Our consortium has developed a variety of **single-cell multi-omics methods** that allow us to gather different types of information from individual cells at the same time. So for instance, we can simultaneously detect the activity of thousands of genes, DNA damage (such as mutations), and cell surface molecules in individual cells. This is particularly promising because many targeted therapies are directed toward cell surface structures. We're now using the methods we developed to identify very specific molecular targets so that we can accurately attack and eliminate cancer cells.

However, one limitation of the single-cell method is that we lose the spatial information. We understand the individual cells that form a tissue's scaffolding, but we can no longer see where they're located spatially. Traditionally, scientists are using microscopes to see how the cells are arranged spatially in a piece of tissue, but one can only examine a few parameters at a time like that. That's why we and other researchers have spent the past few years developing **"spatial omics."** These are methods that allow us to visualize thousands of pieces of spatially resolved molecular information. The idea is to join these two worlds – spatial omics and single-cell omics methods – so that we can better understand how an organ or tumor is constructed and organized.

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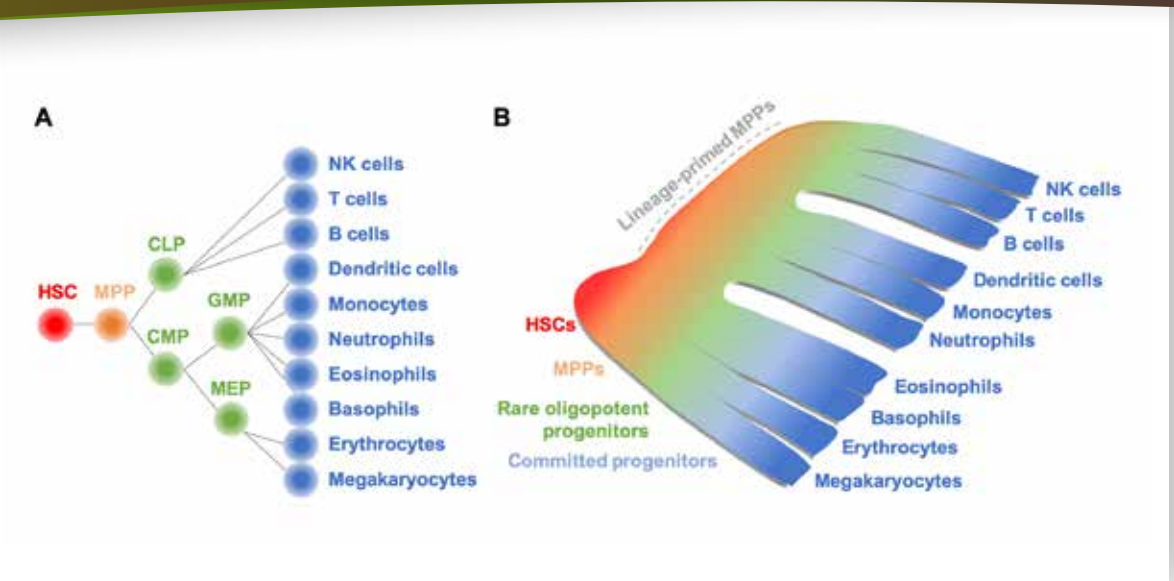

Figure 1: A) Classical model of blood formation (hematopoiesis), B) Revised model of blood formation.
(Source: https://www.sciencedirect.com/science/article/abs/pii/S0301472X20302678).

gesundhyte.de: *That's fascinating. Are these novel methods also helping you understand physiological processes better? Which methods do you think have the most potential?*

We recently showed how blood stem cells develop – these stem cells are responsible for creating new blood and immune cells throughout a person's life. This was the first time these rare cells had ever been characterized using single-cell multi-omics technologies. As well as giving us a detailed understanding of these important processes at a molecular and cellular level, it also provided a new model for hematopoiesis that is now recognized as the standard. Prior to this, the textbook knowledge of how blood and immune cells are formed in the bone marrow was that stem cells develop step-wise and then gradually branch out, like a tree. It turns out that it's not a step-by-step process at all. We demonstrated that a) the stem cells choose a blood cell line very early on, and b) this differentiation occurs in a continuous flow. This model has now essentially replaced the old one.

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The spatial omics methods that we developed also allowed us to examine at an extremely high resolution the bone marrow environment in which the blood stem cells exist. This led to the discovery of several new cell types that help the stem cells do their job.

I think single-cell multi-omics analyses that allow us to examine hundreds of surface markers have the greatest potential for the future. The methods could bring vast therapeutic benefits. We're currently working on a way to use them in a clinical setting.

gesundhyte.de: *That would be a really important step. Does Charité offer especially good conditions for this? You've only been in* ***Berlin*** *for about a year. What where the reasons for your choice?*

Berlin is really the place to be right now. There's so much going on – exciting research, new institutions. I'm associated with three institutions here: the BIH, which specializes in medical translation; Charité, one of the largest university hospitals in Europe; and the MDC, which is a leader in developing single-cell technologies. The joint focus area "Single Cell Approaches for Personalized Medicine," which was set up by Professor Angelika Eggert and Professor Nikolaus Rajewsky, gives the institutes a platform where they can develop single-cell methods together. At Charité, I'm part of the Department of Hematology, Oncology and Tumor Immunology. This means I can interact closely with the clinicians and we can integrate the new methods directly into clinical routines.

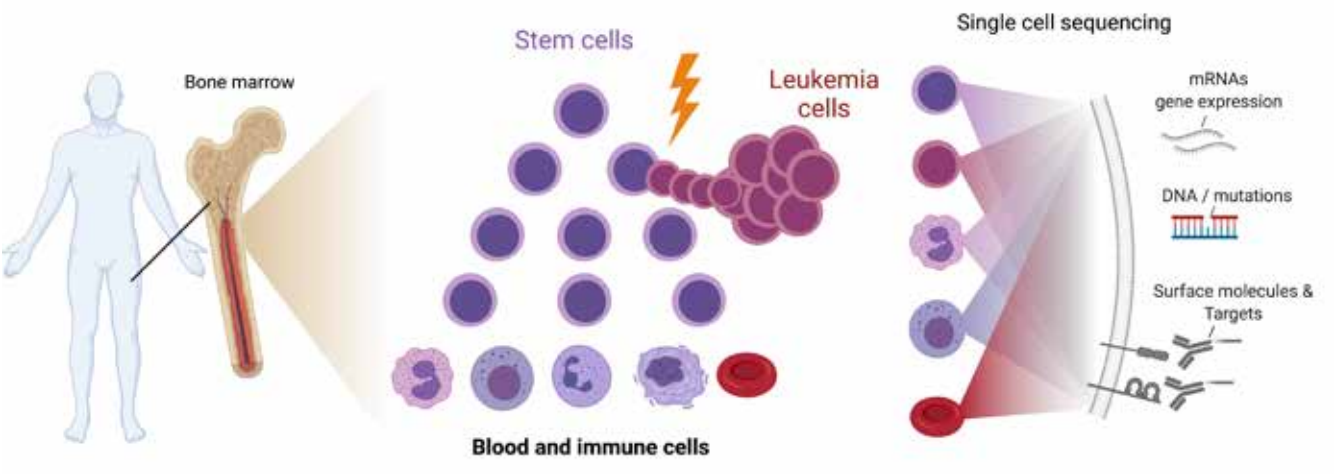

Figure 2: Single-cell sequencing enables the study of leukemias. Healthy hematopoietic stem cells in the bone marrow produce blood and immune cells. The cellular environment in the bone marrow (niche) is essential for hematopoiesis. Leukemias develop from hematopoietic stem cells or progenitor cells through the accumulation of DNA damage (e.g. mutations). Single-cell sequencing provides a detailed understanding of the molecular processes that occur during the transformation of healthy stem cells into leukemia cells. The interaction between leukemia cells and the cellular bone marrow environment can also be studied. (Source: © Simon Haas, Created with BioRender.com)

What I like most about Berlin is **the energy and the willingness to work together** – across different institutes in a really interdisciplinary way – to achieve something meaningful.

The **funding that the BMBF provided through e:Med** has helped get things in Berlin off to a good start. The **support for young scientists** is especially valuable as it carves out space for creative ideas. Systems medicine is going to be important in all areas of modern medicine and will play a significant part in improving medical care.

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gesundhyte.de: *You "grew up" in the scientific community in* ***Heidelberg.*** *Until recently, you were working at the German Cancer Research Center (DKFZ) and the Heidelberg Institute for Stem Cell Technology and Experimental Medicine (HI-STEM). How has that shaped you as a scientist?*

I've studied and done research in the UK, the USA and Germany. But the Heidelberg research scene definitely had the biggest influence on me. Heidelberg is an incredible research location, especially when it comes to biomedicine and cancer research – and that's primarily thanks to the DKFZ, the European Molecular Biology Laboratory, and the university hospital. I owe an enormous amount to this environment. Even when I was still a student, I was able to participate in research activities, such as the iGEM program for synthetic biology that Professor Roland Eils coordinated. I wrote my doctoral thesis under Dr. Marieke Essers at the DKFZ, and set up my first research group at HI-STEM under the leadership of Professor Andreas Trumpp. I actually still lead a research group there and am involved in a lot of collaborations with Heidelberg.

Simon Haas in his laboratory at BIMSB-MDC/BIH.
(Source: @ Thomas Rafalzyk, BIH)

gesundhyte.de: *Do you see your work being translated into clinical practice?*

Absolutely. It's not an easy road, but it's our goal. **We'll keep going until we get it right** – and that means sparing no effort and working in close collaboration with the Departments of Hematology and Oncology at Charité and the Heidelberg University Hospital. I'm very confident that we'll be able to use many aspects of basic research to achieve significantly better prognoses, diagnoses and therapies for patients. Right now, when a cancer patient comes to the hospital, they're examined using a battery of different diagnostic assays. With the single-cell multi-omics analyses, we're trying to develop diagnostic tests that combine everything into one test so that we can predict as accurately as possible which patient will respond best to which targeted therapy. That's still a long way off, but hopefully we'll get there soon.

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gesundhyte.de: *You are very creative and go-getting. What drives you in your daily work?*

I love breaking new ground and going down new paths. What's motivating about science is that you face new challenges every day and are always learning something new. You develop yourself along with your own research and discoveries. It's very gratifying to see **your work advance understanding in a field**. The scientist's profession may come with many obstacles, but it's a great advantage to be able to set your own research agenda.

gesundhyte.de: *Let's come back to your newly adopted city of Berlin. How do you perceive it, and what do you do when you have free time?*

I love Berlin. It's just incredibly diverse, it never stands still and there's always something new. Berlin's history is of course also particularly interesting, and it's very evident in many places. Outside of work, I exercise a lot. From my apartment in Mitte, it's easy to go jogging and explore Berlin in all directions. The COVID-19 pandemic has had us in its grip since I've been in Berlin, so I'm looking forward to being able to immerse myself in Berlin's cultural life more than is currently possible.

Dr. Silke Argo conducted the interview.

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https://www.bihealth.org/en/research/research-group/systems-hematology-stem-cells-precision-medicine