

Matthias Nahrendorf

Healing Insights

Karen Patterson

Born in Salzwedel, East Germany, Matthias Nahrendorf entered adulthood just as the Iron Curtain was lifting in Eastern Europe. He earned his medical degree and PhD in cardiovascular biology at Heidelberg University, and completed his residency plus fellowships in internal medicine and cardiovascular imaging at University of Wuerzburg.

In 2004, a postdoctoral position at Massachusetts General Hospital's Center for Molecular Imaging Research brought Nahrendorf to Boston. He is now a principal investigator at MGH's Center for Systems Biology and director of the hospital's Mouse Imaging Program.

Nahrendorf, 45, is pursuing a deeper understanding of the consequences of ischemic injury, especially regarding how monocytes/macrophages impact acute healing and scar development,¹⁻³ and how an imbalance in the process fuels prolonged inflammation and then heart failure. An associate professor of radiology at Harvard Medical School, Nahrendorf and his collaborators are also developing molecular imaging tools to noninvasively study regulators of heart failure biology and infarct healing processes.⁴⁻⁶ A long-term goal of the work is to devise new therapies for ischemic injury that reduce the action of inflammatory cells to what is necessary only to promote healthy healing, Nahrendorf says. If that could be achieved, "Ideally we wouldn't have heart failure anymore."

Describe Your Childhood.

I have one brother, he's younger, and my parents. It was a pretty sheltered childhood. I grew up in Magdeburg, and the (Berlin) Wall came down when I was 18. Army service was compulsory in East Germany. So I spent one year in the army and then Germany reunited, so I was free to go wherever I wanted.

What Did Your Parents Do?

My parents are both doctors. My dad is a cardiologist, my mom a pediatrician. I had a happy childhood.

Did Your Parents Influence Your Interest in Science and Medicine?

They were never telling me what to do. But I was obviously influenced by their jobs. They talked about patient care and what happened at work.

After the Wall came down, my dad built a private cardiology practice in Magdeburg, and I think he was hoping that perhaps one day I would take it over.

The interest in science actually started when I was finishing medical school. The supervisor of my thesis (George Ertl) was the chief of cardiology in Mannheim at Heidelberg University. He got me started in looking into cardiovascular research and imaging. He was pretty influential in getting me interested in pursuing

science and also gave me the freedom to do research while working in this hospital, which was a freedom not many people had. He also gave me my first appointment, so my internship, residency, and fellowship were under him.

How Did Your Training Take You to the United States?

There's a typical period (in Germany) where people in academic medicine go to do a postdoc in the US, and that's encouraged in order for them to come here and learn new things and broaden their horizons. I did this in 2004,

and I joined Ralph Weissleder's lab (at MGH). He is a radiologist, and he is known for being influential in molecular imaging.

In Germany, I had started working on cardiac imaging, primarily MRI. And I've always been fascinated with imaging. But molecular imaging is a different step because it involves looking at biological processes, not just the anatomy.

(Ralph) was the most important mentor for my career in addition to Peter Libby (previous chief of cardiovascular medicine at Brigham and Women's Hospital). Instead of going back (to Germany) as planned and resuming clinical work and part-time research, I decided to stay here and pursue science. I'm not seeing patients now. That was a decision that wasn't necessarily easy but I felt like science interested me so much that it was worth taking this risk.

Do You Regret That?

I don't. It was good to go through (medical) training because it gives me a clinical perspective in my research. But what I really value is the freedom that comes with being a scientist in the United States. I'm driving my research program, and I think it's a privilege that you can determine what you do. Clinical medicine is a very important and very demanding job, but compared to science, there's less freedom.

What Connected You and Peter Libby?

I'm interested in inflammation in the setting of ischemic heart disease, and Peter has been studying inflammation in arteriosclerosis for decades. I got to know him through collaboration when I



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was a fellow with Ralph. Ralph and Peter Libby had a large grant together.

One of most important things to happen to me was that at that time I met a fellow, (immunologist) Fil Swirski. We basically started on the same date (in 2004). He was hired by Peter Libby. He's a very close friend now and a very close collaborator with whom I have a lot of common projects and interests.

He's now also an associate professor here at the Center for Systems Biology. Now and then we have joint lab meetings, and I drink a lot of coffee with him, sometimes beer. We've published more than 70 papers together, and he was a big inspiration in me getting interested in inflammation as a research topic.

Describe the Dual Role of Macrophages That Your Lab Identified,² and What Led You to That Finding.

We got interested in these cells because in patients, the number of leukocytes that are circulating in blood correlates with cardiovascular mortality. It's pretty obvious that the cells have central roles for repair and defense against infection, but it was also obvious that they can do damage and that, for instance, had been studied by Peter Libby for quite a while, and others in the field. So we approached the heart and asked the question: What do monocytes and macrophages do in the heart after myocardial infarction but also in the steady state?

While we were studying these cells, it became clear that they were fairly short-lived. The life span of monocytes is measured in the order of days or hours, so it became clear that the supply of the cells must be important, and we began following the cells upstream to their source and looked at what happens in hematopoietic organs (the bone marrow and the spleen) in cardiovascular disease.⁷⁻¹⁰

What Led You To Look at the Spleen?

That was actually an idea of Fil's. In his work, he was studying monocytes in atherosclerosis, and he was looking for a source of monocytes, to isolate them and study them in mice. There are only a certain amount of monocytes in blood and you can get them from the bone marrow but there are many, many other cells. Then, at some point, he looked at the spleen and found a lot of monocytes in the spleen.

That's how we got interested in studying the spleen after myocardial infarction. One of the first papers showed that there's actually a ready-made reservoir of monocytes that can be released from the spleen after myocardial infarction,^{7,8} and that cell population then travels to the heart. Later, we found that the spleen can also make monocytes. It had been known previously that the spleen can be a site of hematopoiesis before birth, but it wasn't known to have any relevance to cardiovascular disease as a production site for leukocytes.

Once These Are Deployed From the Spleen, What Do They Do in the Heart?

What they do there is what they are supposed to do—they basically remove cells that died because there wasn't enough supply of oxygen, and in later stages there is a different set of macrophages that supports wound healing. That is a process that is fairly universal; it happens after other injuries also. If that healing process is well balanced, you get a stable scar. But if it is off-balance because there is too much inflammation, then wound healing is suboptimal and heart failure can develop because the scar gets very thin and stretched out.

If you have too many of these inflammatory leukocytes in the heart for too long a time, that will lead to heart failure.

How Did Your Subsequent Work Link That to Atherosclerosis⁹?

If you look at atherosclerosis, it's a chronic inflammation. If you look at myocardial infarction you could think of myocardial infarction as acute inflammation. So I was wondering (about) their interaction. And we were intrigued by a finding in patients: If you look at the patient, what's very frequent is that once they have one infarct, they are very likely to get a second infarct. So we asked the question: Is that because the disease had just progressed to a certain stage where you get complications all the time, or maybe the disease trajectory changed because of this acute inflammatory event, myocardial infarction? Does it make atherosclerosis worse?

We found that that's the case,^{9,10} that there's signaling via the sympathetic nervous system that increases production of white blood cells in the bone marrow after myocardial infarction and in the spleen after myocardial infarction, and these white blood cells not only go to the heart but also migrate to the vessel wall and can be recruited into other atherosclerotic plaques and make them more inflamed and more likely to cause subsequent ischemic events such as reinfarction or stroke.

How Has This Work Collectively Impacted Medicine's Understanding of How a Heart Attack Happens and Heals?

There are probably two aspects where this work has changed the view: One is that there are two phases of wound healing when it comes to monocytes and macrophages. There's an early inflammatory phase, and then there is a second, reparative phase. Both of these phases are necessary to get appropriate wound healing, and if any of these phases is lacking, or if inflammation persists too long and resolution of inflammation doesn't happen, then that's bad and it leads to heart failure.

The second aspect is that myocardial infarction is something that happens to the entire physiological system. It's not just happening in the heart, but you get changes everywhere. This includes remote organs such as the spleen and the bone marrow.

At This Point, Are There Clinical Implications?

We're thinking about neutralizing some of these signals to reduce inflammation in the infarct. There are a lot of considerations that have to go into this because what we're planning on doing is interfering with the immune system, and this immune system is very important for many aspects of defense, such as defense against infection. So one has to be smart and really be very careful.

There are some clinical trials going on that I'm not involved in and I didn't instigate, but the field is moving towards trying to find drug targets that will interfere with these pathways that we have discovered.

Where Does Your RNA Interference Work Fit In?

We were looking for ways to manipulate the monocyte/macrophage response in the setting of cardiovascular disease. We silenced certain genes that we thought are important for, for instance, migration of monocytes to sites of inflammation.

One prominent target there is CCR2,¹¹ which is the chemokine receptor that monocytes use to migrate to atherosclerotic plaque but also to the acute infarct. So what we did here is neutralize expression of this chemokine receptor, and that reduces the migration of the inflammatory monocytes to the heart.

What Do You Envision Happening in the Next 10 Years? How Might Healthy Healing of an Infarct Be Achieved?

I think that the goal is to understand mechanisms that govern the action of immune cells in that wound-healing process, and once we gain that insight, use it to design therapy to optimize the leukocyte response and to reduce the action of inflammatory cells to what is necessary to the wound-healing process.

Besides the Fact That You're Tinkering With the Immune System, Are There Other Challenges?

It's not a black-and-white drug target, so it's not a target you can hit as hard as possible and all will be good. You need a certain amount of macrophages to have appropriate wound healing, so you have to be subtle and probably monitor what you're doing quite carefully in order not to overdo it. It's clear that if you deplete macrophages, it's not good for the wound-healing process in addition to these defense mechanisms. You need macrophages to survive and heal the wound, so they're a complex target.

Are There Other Areas of Your Work That Seem Very Promising or Exciting?

One area that I'm very excited about is understanding better how the bone marrow behaves in cardiovascular disease¹² and the signals that lead to an increased or decreased production of immune cells. One area we're looking at is how the central nervous system may or may not be involved in it.

Are There Other Fruitful Collaborations to Mention?

There are a number of collaborators I work with including in neurology and also at MIT. We're working on the brain-hematopoiesis connection, also in the setting of stroke. And then with the MIT folks, it's basically the RNAi work where we're trying to deliver material to cells that are involved in these inflammatory processes.¹³

One other collaborator that I want to mention is my wife (Kamila). She is a scientist too. She works in cancer genetics, a completely different field. But she's very good in being a sounding board for all sorts of ideas, and she's also practically involved in some of the projects because she's very good with big data, so she helps me analyze big datasets.

How Did You Meet Her?

I met her at MGH at work. At that point (in 2008) she was working in the lab of a colleague of mine. She was here for three months or so, and then we kept in touch but really became a couple only two years later. We got married two years ago.

What Is Your Workday Like?

I usually come to work between 8 and 9, and in the morning I try to reserve time to read and write (papers and grant applications). I frequently have coffee with Fil at some point late in the morning, and then I have meetings with fellows to discuss projects and so forth. I go home around 6 or so if it's a normal day, and then try to go to the gym to blow off the steam.

Besides the Gym, What Do You Do for Recreation?

I like hiking. So I go to the White Mountains. I hang out sometimes at the ocean. I do like to exercise, as a balance to sitting in the office. I also read quite a bit, and (enjoy) meeting friends. I don't watch TV. I do screen movies—more the light fare, entertaining. After thinking all day, I enjoy being distracted.

How Do You Balance Work and Time With Your Wife?

It's very good that we both work in research because we both understand the mechanisms and what it takes. We can talk about issues and problems that come with it and help each other find solutions. We also understand each other well; it happens to me and to her that we wake up in the morning and the first thing we think about is a certain gene or a certain cell. We completely get it, that that's what happens if you're very excited about a certain project. It's very helpful to have that kind of insight in your partner.

Which of Your Personality Traits Do You Think Have Helped Propel Your Career?

I think I'm curious; I enjoy discovery. Also, I'm fairly persistent. So I'm well-organized and if I decide to pursue something, then I don't let go easily.

How Instrumental Has Plain Hard Work Been to Your Advancement?

It's very important because it's a hugely competitive field. If you look at acceptance rates in good journals and funding rates at the NIH (National Institutes of Health), it becomes clear that you have to work really hard.

But I think a lot of people do. It's almost a given. It's also important to take time to step back and think very hard. I definitely encourage my fellows to do that. That's something enormously important, to think about where to focus all the hard work, not just run and do.

Describe the Best Piece of Advice You Give to Young People About Science, or About Life.

I think it gets back to the point that I already mentioned, that it's very important to take time and think hard about what you want to do—don't just plunge into the next study or project, but really think hard about why you want to do this and why it's important. The other advice is to play it as a team sport. Science is so complex that it's hard to win it all by yourself. So if you can manage to surround yourself with top talent that has complementary expertise and people that you just can run with, it's extremely helpful. Teamwork can be really a huge catalyst.

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