

A conversation with Rudolf Jaenisch

Ushma S. Neill

J Clin Invest. 2015;125(9):3305-3307. <https://doi.org/10.1172/JCI82629>.

Conversations with Giants in Medicine

Rudolf Jaenisch of the Whitehead Institute at MIT is a remarkable scientist at the center of the study of epigenetics. Jaenisch (Figure 1) created the very first transgenic mice and did the first experiment showing that therapeutic cloning could correct a genetic defect. He also conducted the first proof of principle experiments with induced pluripotent stem (iPS) cells to correct sickle cell anemia and Parkinson disease in rodents. Hear more of his stories about his first scientific experiments, how to effectively mentor trainees, and his views on the ethics of stem cell use on the JCI website at <http://www.jci.org/videos/cgms> JCI: What were you like as a kid? Jaenisch: I grew up in Germany, and my parents and my grandparents were medical doctors. I was also interested in medicine. My father was not so sure it was the right thing for me, but he consented and so I went to medical school. I liked part of it, but I didn't like the more clinical part, as it was overcrowded and one couldn't get into the lectures. The alternative I came up with was to do an experimental thesis at the Max Planck Institute in Munich on phage replication. It was an interesting time (the 1960s) because it was really the beginning of molecular biology. Bacteria and phages were really the workhorses [...]

Find the latest version:

<https://jci.me/82629/pdf>



A conversation with Rudolf Jaenisch

Rudolf Jaenisch of the Whitehead Institute at MIT is a remarkable scientist at the center of the study of epigenetics. Jaenisch (Figure 1) created the very first transgenic mice and did the first experiment showing that therapeutic cloning could correct a genetic defect. He also conducted the first proof of principle experiments with induced pluripotent stem (iPS) cells to correct sickle cell anemia and Parkinson disease in rodents. Hear more of his stories about his first scientific experiments, how to effectively mentor trainees, and his views on the ethics of stem cell use on the *JCI* website at <http://www.jci.org/videos/cgms>.

JCI: What were you like as a kid?

Jaenisch: I grew up in Germany, and my parents and my grandparents were medical doctors. I was also interested in medicine. My father was not so sure it was the right thing for me, but he consented and so I went to medical school. I liked part of it, but I didn't like the more clinical part, as it was overcrowded and one couldn't get into the lectures.

The alternative I came up with was to do an experimental thesis at the Max Planck Institute in Munich on phage replication. It was an interesting time (the 1960s) because it was really the beginning of molecular biology. Bacteria and phages were really the workhorses of understanding how RNA and DNA work, replicate, and are transcribed.

JCI: Did you finish your clinical training?

Jaenisch: I finished everything, but I had to promise I would never practice. I decided I wanted to go into science, and almost every one of my friends went to the United States because that's where science occurred; I managed to get a postdoctoral fellowship in a laboratory at Princeton.

JCI: Why choose to do a postdoc with Arnold Levine, who was just starting his lab?

Jaenisch: I was totally naive, had no idea where to go. I met someone who was working on phages and had just returned from Los Angeles. I asked him to suggest someone and he said, "Yes, my bay mate Arnold Levine in Los Angeles just set up

his own laboratory at Princeton, working on animal viruses." I wrote to him and was amazed that Arnie wrote back saying, "Yes, I accept you and here is a grant proposal that you can submit, I have it lying around. I don't know how it would work, you can submit it to the NIH for support." Immediately everything was effortlessly arranged, and I became his first postdoc.

He worked with a small tumor virus, SV40. It has the same size DNA as a phage I'd worked with, so that was very familiar, but it made tumors. Arnie had chosen to work with this virus to probe into DNA replication and gene expression in mammalian cells. I thought it was a valid approach and got hooked into it and worked on replication.

JCI: One of the things that puzzled you was SV40's viral tropism: infected mice got sarcoma, but not liver cancer or brain cancer or other organ cancers.

Jaenisch: It was a very naive question. If you inject SV40 into the skin, does it only infect skin cells or alternatively could it infect all sorts of other cell types? Or was there something in the liver or the brain that, even if infected by the virus, couldn't express and induce a tumor? That was a naive question, but I wondered how to study that. I had no idea until I read this very influential paper from a prominent developmental geneticist, Beatrice Mintz.

She used very early embryos from a black and a white mouse strain, aggregated them in a culture dish, and then transplanted the aggregates into a foster mother. The mice were now what's called chimeric. Instead of two parents, they had four parents. They were black and white with stripes. She did this experiment because she wanted to study a developmental issue on coat color, which I did not understand at all. But it just blew me away, that you could manipulate cells in a culture dish and make a mouse. I thought this was the coolest thing I'd seen.

I thought, if you could introduce the SV40 DNA into these early embryos, the virus would end up in the liver and the

brain because these early cells would, of course, contribute to all parts of the embryo. I thought this could solve my question, so I was all excited. I called her up and asked if I could visit her. She was very friendly, very gracious, and I suggested the experiment to her. She just had bought a microscope where one could do this experiment. Nobody had done injection of embryos with DNA before. But she was very skeptical. I mean, who was I? A totally naive phage guy, right? She called me back a week later and said she'd thought about it and I could do the experiment in her lab. And then Arnie came back from sabbatical in Europe, and I told him my plan. He told me I was nuts, but allowed me to do it.

Mintz showed me really everything I know about genetics, how you culture embryos and eventually how you make mice. I extracted SV40 DNA in Princeton, and I took it with me to Mintz's lab in Philadelphia and injected embryos and, marvelously, I got mice. I was really excited, but the mice were totally normal. Did the whole experiment work? Was there any SV40 information in these mice? Now, today, this is a trivial question, but then PCR or Southern blots had not been invented. I ended up taking cells from the ears of the mice and stained them for SV40 T antigen, which is a protein from the virus. I remember this very well. That evening, they were all positive, so I got really excited. I couldn't sleep. The next morning, I did the assay with control cells. And they were all positive too; it was a bad antibody. I was really stuck.

At that time, I got my first job at the Salk Institute, and this was really the greatest thing that could have happened to me. I got colleagues who really helped me along. Paul Berg had developed what's called nick translation, where you can radiolabel a piece of DNA. Using nick translation to analyze the DNA from the mice I had generated in Mintz's lab, I could see that the SV40 DNA had integrated into their brains, livers, kidneys, and everywhere. These were the first transgenic mice, though the name "transgenic" was not coined until 6 years later.



Figure 1. Rudolf Jaenisch on April 25, 2015. Image credit: Karen Guth.

But why were there no tumors? I didn't know about epigenetics (the term was not invented as yet) or how to study it. Two other young faculty came to the Salk from David Baltimore's laboratory. They brought with them an RNA tumor virus system, the Moloney leukemia virus. I thought using it would be helpful, since it would generate a phenotype (leukemia). Indeed, when I generated infected mice, some got leukemia, and they carried, like the SV40 mice, the viral DNA in their tissues, and they transmitted it through the germ line. I got hooked and wanted to understand epigenetics and development using these viral systems. If you think about development, it's all epigenetics.

I went from the Salk Institute to Hamburg, and there we found the answer to your original question about viral silencing. It was caused by DNA methylation. The virus gets immediately shut down by DNA methylation, which is a silencing mechanism in embryonic stem cells, and then embryos, but not in later stages.

JCI: You were surrounded by these brilliant minds at the Salk in an academic Shangri-la, so why would you leave that to go back to Germany?

Jaenisch: I got an offer to go to Hamburg, and I was very young. I almost felt obliged to go back. They offered me quite nice things, and Hamburg is an interesting city, but I was very depressed when I arrived there.

I stayed there for seven years, and we did some interesting things. We used the viruses as probes to probe into development because these viruses, when they integrate into the germ line, can mutate genes. This "insertional mutagenesis" allowed us to mutate genes and to isolate the mutated genes because the virus marked it. Only later, homologous recombination to target genes was invented.

David Baltimore had just founded the Whitehead Institute, and he offered me a job. That was very attractive for me, so I joined the Whitehead when it opened the doors in 1984. I had terrific students, one who knocked out DNA methyltransferase. This was a hugely informative mutation because it was the first time you could study epigenetics by genetic means. It got me really thinking about epigenetics and then came Dolly, the first cloned mammal, and a year later, the first cloned mouse.

I thought cloning was the greatest thing, especially if you're interested in epigenetics. I switched my lab's direction, introduced cloning into the lab. Many questions were raised — therapeutic potential, can you use cloning for patient-specific stem cells? We showed you could, in rodents.

And then Yamanaka described iPS cells, with four factors being sufficient to reprogram cells. The initial iPS cells were not really like normal ES cells, as they

could not make chimeras. He established the principle, but people didn't believe it initially; it was too simple. I believed him, and a year later our group and two others published on the same day that iPS cells were identical to ES cells. They could make mice; they could contribute to the germ line. This led to an explosion of the field, which is sort of still ongoing because of its enormous potential for studying human disease.

JCI: You've been very quick to pivot your lab, especially when it comes to new methods and technologies.

Jaenisch: We have always developed methods to ask a question. I'm not interested in developing methods for the sake of methods. The last one was a CRISPR technology that we adapted for working with mice. It is certainly in my interest to use this technology to ask a relevant question.

CRISPR technology is so efficient that we can introduce mutations into mice just by injecting the vectors into the zygote; before, we had to use homologous recombination in ES cells, a long and complicated procedure, which takes a year, sophisticated technology, and knowledge. Now, it's very simple. CRISPR has really simplified things and has revolutionized the way we can manipulate genes.

JCI: Should we use CRISPR in humans?

Jaenisch: We can ask the question first, "Why should we?" The argument you hear from those in favor is that you could eradicate a disease gene. I believe this is a weak argument. There is no way to determine at the zygote stage which embryos are normal and which have a mutant disease gene. If you want to correct a mutation, you can't genotype an embryo at the one-cell stage. Therefore, if you want to correct a dominant mutation such as in Huntington's disease, 50% of the time, using CRISPR on zygotes will mutate a normal healthy embryo, and this is totally unacceptable in my opinion. Instead, we should use preimplantation diagnosis to test whether a given embryo carries the mutant gene. Some people argue, "Well, don't do it at the zygote stage, but do it later through injectors." This also is not a good option, as one would only correct a gene in some cells of the embryo.

The only other use of human germ line manipulation is for enhancement — if you

want to add a gene, let's say, for growth. Adding a growth gene to a healthy embryo could generate, for example, taller individuals. But then the question is, should we do that? Is that something society wants to do? And this is not a scientific question. It's an ethical and moral question which needs to be debated.

One opinion is to ban all manipulation of human embryos, period, while others argue to do the research under certain precautions and clearly defined conditions, but impose a moratorium on any application at this point. I believe that banning everything is just not a feasible thing to do. We should not ban research. It is fundamentally different from limiting the application to affect a human being who can't be asked for its permission because it is manipulated at the embryo stage.

JCI: Stepping back from genetic manipulation to cell therapy and implantation of corrected cells — how close are we to actually being able to use cell therapy?

Jaenisch: We are close, but I would say it's not around the corner. There were quite a number of safety issues — we had to make iPS cells that were not genetically modified. We had to learn how to differentiate these cells for the right cell type; that works for some lineages, not for others.

JCI: When your students are mature enough to leave the lab, do you counsel them to take on high-risk, high-reward research, especially in the resource-poor environment, as we find ourselves in currently?

Jaenisch: I think this is a complex question. How do you find your niche where you can shine and where you get promoted because you're successful? How do you secure funding? This has changed enormously. When I went to Salk, I had this idea about transgenic mice, although the term hadn't been coined yet, and I wrote a grant to the NIH. Mike Bishop was the study-section chairman. They funded it immediately, but now, it would be triaged because there were no data to support the premise. Study sections are now risk averse.

Can you get the money for an exciting and risky project? Trainees are now facing a very different situation than I did. I would think the goal should not be to have a paper in *Nature*. The goal should be, "I'm really passionate about this. I want to solve this question," and go after it, taking risks.

JCI: If you couldn't be a scientist, what other vocation do you think could have kept you enthralled?

Jaenisch: Oh, that's an interesting question, which is hard to answer. I think I would want to address some of the issues that I feel very passionate about, like issues of protecting the environment. But I worry I would not be very good at this. I would be passionate, but probably totally ineffective. I like to build things out of wood, like a carpenter. It is a very satisfying thing: you design something; you start and you finish it. In science you do something. It never works. We don't finish it. That might be a nice alternative.

Ushma S. Neill