Alexander Meissner: Learning the reprogramming code

Meissner studies the epigenomics of pluripotent cells.

Cells keep a record of their developmental history by chemically modifying their histones and DNA to alter chromatin structure and control gene expression. Resetting these epigenetic marks is an essential step in reprogramming adult cells to produce embryonic stem (ES)–like cells able to develop into every tissue of the body.

Alex Meissner first became interested in epigenetics as a graduate student with Rudolf Jaenisch at the Whitehead Institute in Cambridge, MA, where he studied cellular reprogramming through nuclear transfer. To mitigate ethical concerns over the destruction of viable blastocysts, he devised an alternate nuclear transfer method that used blastocysts incapable of implantation and in utero development (1). When Shinya Yamanaka's group discovered that just four transcription factors were sufficient to convert somatic cells into induced pluripotent stem (iPS) cells, Meissner's work in the Jaenisch laboratory put him in a good position to improve the new technique (2, 3). Having adapted bisulfite sequencing methods to identify DNA methylation sites across the entire genome (4, 5) Meissner dissected some of the steps involved in reprogramming by measuring the epigenetic changes induced during the process (6). Increasing the efficiency and safety of iPS cell production is vital if these cells are to fulfill their therapeutic potential in regenerative medicine, but Meissner is also interested in epigenetic changes associated with normal development and diseases such as cancer.

In 2008, Meissner became a group leader at both Harvard University and the Broad Institute. In a recent interview, Meissner discussed the events that marked the development of his own career to date.

ENGINEERING BACKGROUND

How did you get interested in science?

I grew up in Germany and after high school I joined a biotechnology program at the Technical University in Berlin that was focused on engineering rather than basic science. I only had one genetics and maybe one biochemistry course, so I never really thought about biology research. But I did a lot of internships with some small biotech companies and started learning a little bit more biology.

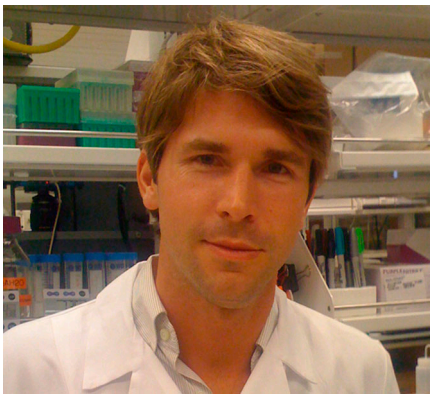
The big change came when I got an internship at the Dana-Farber Cancer Institute, where I started doing "proper" biology. During that time, I learned about Rudolf Jaenisch's work on nuclear transfer, which sounded much more interesting than the engineering training I'd had. I contacted him to see whether I could learn about nuclear transfer. That led to me joining his laboratory and not leaving for another eight years!

How did your first project in the Jaenisch laboratory come about?

During my first year, I spent a lot of time learning about nuclear transfer, so when we came up with an idea for alternate nuclear transfer, I was one of the few people who could actually do all of the experiments.

> "There's a crossroads between communicating to other scientists while being mindful of how the public perceives certain ideas."

It was mostly to show, as a proof of principle, that there are alternative ways to create pluripotent cells that don't involve using blastocysts capable of implantation. That's where my engineering background came in: I thought, well, if there's a problem, you can engineer a solution. In this case, we blocked the *cdx2* gene so that the blastocysts could never implant. That went well, although it's still a controversial approach, but we never meant to claim that it was the best way to do it. We just wanted to stimulate a discussion and get people to think about other possible solutions.



Alex Meissner

THE MAGIC TRANSFORMATION

Then Yamanaka published the first iPS cell paper. Did that come completely out of the blue?

There was an idea that something like that might work, because the nuclear transfer experiments and a few studies using cell fusion showed that you can reprogram a somatic cell. And whatever factors are present in oocytes are also present in ES cells, because if you fuse an ES cell to a somatic cell, it will also reprogram. So there must be a defined set of factors present, and by looking at these different cell types, you could already guess which factors might be involved.

In fact, I—along with several postdocs in the Jaenisch laboratory—had already made inducible vectors for Oct4 and had also guessed Sox2, but those two alone weren't sufficient to reprogram anything. So although the Yamanaka group's discovery of c-Myc and Klf4 was a surprise, the notion that you could put in a defined set of factors to reprogram cells was expected.

That being said, when Yamanaka first presented his result at a Keystone meeting in Whistler, there was a lot of skepticism in the audience. But Yamanaka was right and there were three papers shortly afterwards, including one from us in the Jaenisch group, that repeated the experiment and proved it. That happened so fast because half of the system was already present.

It's amazing though: it's one of the most robust things that I've seen in my career. People might fail to repeat a published PCR protocol, but this magic transformation seems to be easy; everybody can do it.

Text and Interview by Ben Short
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Is there no longer interest in nuclear transfer?

There's minor interest; it's still a remarkable process. If you put a somatic nucleus into an oocyte, you can reprogram it within a day or two; it happens with very few cell divisions. With iPS cells, reprogramming takes one to three weeks, and cells divide quite a few times. It's not clear why this is so slow, so I think there might still be some use for nuclear transfer in studying the basic mechanism involved.

But there's certainly no therapeutic application for it in regenerative medicine. It involves the donation of oocytes, it's technically very challenging, and there doesn't seem to be a way of mass producing customized stem cells.

What is it like to work in a field that generates such public interest?

It's very interesting, but also complicated. It's one of the few things that actually makes it onto the front pages once in a while. That's a good thing, and most people can easily understand what a stem cell is, and why its potential is so interesting. So you can talk to them about it, which is fun, because if you work on a complicated protein network, or something like that, it's hard to explain to your friends or family what you're actually doing. Even if other scientists talk to me about a complex problem in their specific field, I might not be able to follow it completely. But pretty much everybody can follow what you're talking about with stem cells because, in a way, it's much simpler.

But the public perception is slightly different; there are a lot of false expectations. So, you can say that there's now a solution to nuclear transfer, and that's true scientifically, but it doesn't really change anything for the public yet. iPS cells are a great step forward too, in terms of basic science, but it doesn't really bring any stem cell therapies closer to the clinic at this point. There's a crossroads between communicating to other scientists while, at the same time, being mindful of how the public perceives certain ideas.

Meissner enjoys the extra benefits of scientific meetings: traveling and snowboarding.

MAPPING OUT THE FUTURE

When did you first get interested in epigenetics?

It started when we did the nuclear transfer experiments because the genomes don't always completely reprogram. One of my first thesis projects was to set up bisulfite sequencing—which nobody was doing in the laboratory—to monitor how successful reprogramming would reset DNA methylation.

> "The goal is to have complete chromatin and DNA methylation maps for every cell type in the human body."

There was a nice moment when I had a chat with Rudolf and Eric Lander and we decided to move the studies to a genomic scale, and I had several meetings with people at the Broad—in particular Andreas Gnirke—to discuss how to do this. Andi and I spent about two years working out the procedures and published a small paper in 2005, based on classical Sanger sequencing, that showed you could, in principle, measure DNA methylation genome-wide. We didn't actually do it though, because it was too expensive.

But then we used next-generation sequencing technologies to run a lot more samples on a genomic scale, and that was published last year in *Nature* as the culmination of almost five years of work. Now this has moved into the next phase where, together with Brad Bernstein, I'm directing the Epigenome Initiative of the Broad and one of the NIH's Reference Epigenome Mapping Centers. The goal is to have complete chromatin and DNA methylation maps for every cell type in the human body. Right now we want to produce a human embryonic stem cell epigenome, that's as comprehensive as possible so it can serve as a real reference.

What is your laboratory working on now?

There are a lot of projects that relate to the basic mechanisms of how epigenetic markers are established and maintained during normal development. On the reprogramming front, we're trying to understand the epigenome of stem cells and how it compares to other cell types. What changes when you go from A to B? Right now, this is confined mostly to iPS cells, but there's a more general interest in how you define the state of a cell.

In collaboration with groups at MIT and Memorial Sloan-Kettering, we're also applying this to cancer, which is one of the diseases where epigenetics play a major role. We want to know what changes in the epigenetic makeup of tumor cells.

What are the next challenges in the iPS cell field?

To be therapeutically useful, you ultimately need to make safe iPS cells, which means making them without any viral integrations. We don't play such a big role in that, but the other main question is how can you determine the quality of all these cells that you're generating? That's a much bigger challenge in human than in mouse, because researchers can make mouse chimeras and test for germline contribution. In humans, you have to resort to alternative approaches to define the quality of your cells. A lot of our basic work on stem cell biology and epigenetics relates to figuring out a way to quickly screen for the best ones. With a good reference map, you might identify spots where you really need to look for variation that will tell you whether your cells are reprogrammed or not.

When we have iPS cells that pose no health risk, we'll still have to figure out how to use them. How do you differentiate them back into target cell types? How do you genetically manipulate them to correct defects? These are challenges that existed before iPS cells so people will have to go back and do the same work that has been going on for the last 10 years with ES cells.

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