

# Konrad Hochedlinger: A reprogramming revolutionary

In 1999, Konrad Hochedlinger squeezed into a packed lecture at the Institute of Molecular Pathology in Vienna to hear stem cell researcher Rudolf Jaenisch talk about nuclear transfer cloning techniques. Hochedlinger, a biology masters student, knew little about cloning, but he'd been intrigued by the technique ever since scientists cloned Dolly the sheep in 1996. "I was too shy" to talk to Jaenisch then, he says. But months later Hochedlinger stopped by Jaenisch's office at the Massachusetts Institute of Technology's Whitehead Institute for a chat. He ended up sticking with Jaenisch for six years.

Hochedlinger joined Jaenisch's lab at "a very fruitful and productive time," he says. He worked closely with fellow graduate student Kevin Eggan and postdoc William Rideout. The three published a slew of papers demonstrating how nuclear transfer triggers epigenetic reprogramming. "Konrad was pretty amazing in his diligence," says Rideout, now at AVEO Pharmaceuticals. "He was an eager learner and very enthusiastic about the work we were doing."

Hochedlinger's PhD project tested whether fully differentiated cells or just adult stem cells could give rise to cloned animals. "It was a very risky project because it was totally unclear whether it would work or not," Hochedlinger says. It failed for over a year, but eventually he managed to clone mice from the nuclei of B and T cells, proving that terminally differentiated cells can be reprogrammed.<sup>1</sup>

"I thought it wouldn't work," Jaenisch says. "But it's typical for [Hochedlinger] to pull through with complex experiments."

After graduating, Hochedlinger stayed on for a postdoc with Jaenisch. In 2004, he transformed melanoma cancer cells into normal embryonic stem cells using nuclear transfer. And in 2005, he activated the Oct4 gene in adult mouse cells, showing that this transcription factor prevented adult stem cells from differentiating.<sup>2</sup>

In 2006, Hochedlinger started his Harvard Medical School lab. Around the same time, Kyoto University's Shinya Yamanaka reported that mouse skin cells could be reset to behave like embryonic stem cells by adding just four transcription factors, including Oct4. Many researchers were skeptical, but "I knew right away that it was important," says Hochedlinger. "I had all the expertise and tools from my previous work" to create these induced pluripotent stem (iPS) cells. "Within a few months, we were not only able to reproduce the results but to improve the technology," he says.

The efficiency of the reprogramming was frustratingly low, Hochedlinger recalls. He tried to address this by switching the delivery vehicle from retroviruses, which integrate into the genome, to adenoviruses, which do not. The efficiency was still "dismal," Hochedlinger says, but he had successfully devised the first-ever protocol to generate iPS cells without viral integration, thereby bringing iPS cells one step closer to the clinic.<sup>3</sup>

Hochedlinger now finds himself working in one of the hottest fields in biology. "It's exciting on the one hand to be a part of it and to be a player, but it's also quite competitive," he says. Even so, "the fun outweighs the competitive aspect." —Elie Dolgin

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**Age:** 33

**Representative publications:**

1. K. Hochedlinger and R. Jaenisch, "Monoclonal mice generated by nuclear transfer from mature B and T donor cells," *Nature*, 415:1035-38, 2002. (Cited in 206 papers)
2. K. Hochedlinger et al., "Ectopic expression of Oct-4 blocks progenitor-cell differentiation and causes dysplasia in epithelial tissues," *Cell*, 121:465-77, 2005. (Cited in 111 papers)
3. M. Stadtfeld et al., "Induced pluripotent stem cells generated without viral integration," *Science*, 322:945-49, 2008. (Cited in 34 papers)