CellPress

# Magdalena Götz

In an interview with *Neuron*, Magdalena Götz highlights the responsibility of scientists to educate the public about the process of scientific discovery and how ideas evolve. She also describes how her current research on neuronal reprogramming is influenced by her earlier findings that radial glial cells give rise to neurons.

Magdalena Götz grew up in Heidelberg, Germany, home of both EMBL and a famous castle, and studied biology at the University of Zürich and the University of Tübingen. After a successful postdoctoral fellowship at the NIMR in London, she came to Munich to start her own lab at the Max-Planck Institute of Neurobiology. She was then appointed director of the Institute of Stem Cell Research at the Helmholtz Center Munich and Chair of Physiological Genomics at the Biomedical Center of the Ludwig-Maximilians-University. Her passion is to understand how the brain develops and neurons are generated. She then takes the concepts learned from development and applies them to regeneration in the adult brain, such as after brain injury or in neurodegenerative disease. She and her team first implemented direct neuronal reprogramming from glial cells *in vitro* and also after injury in the living brain. This work was inspired by her discovery that radial glial cells generate not only glia but also neurons during development, acting as neural stem cells. This finding prompted her to compare these neural stem cells, in the adult and developing brain, to more differentiated glia and their reactive counterparts in the adult brain to further improve conversion of the latter into fully functional and adequately connected neurons.

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### *Neuron* is marking its 30th anniversary this year. Which *Neuron* papers have struck you as truly elegant or inspired, and why?

One of the publications that impressed me most was from the Arlotta lab, showing that cortical pyramidal neurons influence positioning of interneurons (Neuron *69*, 763–779; February, 2011). It was not only elegantly done but was the start of a series of work now showing that specific types of neurons also influence astrocytes and various other cell types in their vicinity. This work thus opened up the concept that pyramidal neurons assemble their correct environment within a layer by recruiting other neuronal components and diversifying the glial cells in a layer-specific manner. This entails the concept of master neurons regulating the rest of the circuitry, similarly to the idea that master transcription factors kick off an entire cascade of specification mechanisms.

### What future direction in neuroscience are you most excited about?

That we are moving toward an era when we no longer manipulate one gene at a time, but instead, thanks to epigenome editing, can now target many genes at the same time or differentially control entire gene networks. This is particularly exciting for questions of fate specification or using our knowledge about fate for changing it toward a desired phenotype. We can think of many ways this can be used—not only to turn a certain cell type into another but also to turn sick cells into healthy cells or aged cells into young cells. Changing cell states by (epi) genomic tools will be a huge development and very exciting.

### How would you like to see neuroscience evolve over the next 30 years?

Toward real interdisciplinarity. We have been talking about this for ages, but little has happened so far. I think we need a new generation of neuroscientists that are simply trained in all these fields—philosophy, psychology, and systems approaches to molecular biology. This has been established, for instance, during the last decade in the Graduate School of Systemic Neurosciences (GSN) in Munich, and I am optimistic that such education will allow much broader interdisciplinary research in the future.

### Which aspect of science, your field or in general, would you wish the general public knew more about?

I think it would be most important if the public better understood how science works. In most cases, we communicate specific findings, but we should strive to communicate how we arrived at certain conclusions, and that these conclusions may change at some point, because science moves on. In this regard it is also very important to communicate the importance of multiple approaches, because one technique may always miss an aspect. This would also add so much to the public understanding of sometimes contradicting findings (for example, recent conflicting reports on adult neurogenesis in the dentate gyrus). Because media (and sometimes scientists) always communicate new findings as "knowledge" and "truth," the public is then confused if those findings turn out to be different or "wrong." Instead we should communicate that this is the normal way in which science works. An appreciation for the multitude of techniques and approaches needed would also support a

better understanding of the need for animal research. Even if we had wonderful "organoids-on-chips," we'd still need other approaches that look at the entire system, including environmental exposure, an intact immune system, etc. Therefore, I am very much convinced that the most important aspect of science is to communicate how it works. Of course, this is best done not at an abstract level but by illustrating with one's own pitfalls and breakthrough discoveries that change the way we think about concepts and previous dogmas.

**What is your guiding philosophy for running your lab? Your personal philosophy?**

My main guiding principle for postdocs and students is to show and communicate how much fun science actually is and what an enormous privilege scientists have to be able to follow their curiosity. Another main issue that I try to communicate is that one should always be critical and creative. It is very important to never simply believe in or rely on the current state of "knowledge" but instead to always check its experimental evidence and always be open to surprising findings. I also try to communicate that being a scientist is the best job you can ever have—so diverse and changing over time, where you decide entirely yourself what you work on—almost like an artist, but with a little more security.

**What are the questions that inspire your lab?**

The lab is as excited as I am about the prospect to manipulate glial cells for repair, e.g., as a source for replacing neurons *in vivo* in the damaged brain. Even students or postdocs working on developmental processes see the bigger picture and realize that the most unexpected proteins we try to understand in their developmental function may become crucial for neural tissue repair. I am extremely privileged to work with such wonderful scientists who share the excitement and the bigger picture.

**Do you have a favorite anecdote from doing science that you'd like to share (perhaps a key discovery moment)?**

When I started my own lab, I continued to work on the observation that most dividing cells during neurogenesis are actually radial glial cells (Neuron *21*, 1031–1044; November, 1998), which I had made as a postdoc. I therefore suspected that the prevailing concept at the time, that these cells would just be guides for migrating neurons and/or only generate glia, might not be true. I set up FACS isolation of these cells and indeed found that radial glial cells generated neurons. I was super excited and passed on the project to the first postdoc in my lab, Paolo Malatesta. But when he isolated the radial glial cells, he did not see neurons generated, so we were really puzzled. Of course, poor Paolo was very nervous because he could not reproduce my findings. When I joined him at the FACS, however, it all resolved in a very interesting manner. Typical of our respective personalities, it turned out we had simply used different gating strategies—he isolated only the cells with highest GFP levels (driven by the human GFAP promoter), while I took all that were above the negative control. This not only gave us an answer but also provided the start for -projects isolating low and high GFP+ radial glial cells separately and examining their transcriptome. This showed us then that the highly GFP+ radial glial cells are the ones that generate transit-amplifying progenitors. The transcriptome analysis revealed a series of exciting genes as candidates for regulating the differences of these sets of radial glial cells, and we are still following up some of these candidate proteins today. This is typical in science—you constantly learn from solving problems, and they lead you down new unexpected avenues—a simply wonderful journey.

**What has been the highlight of your career?**

This question refers of course to "so far" — as I hope many highlights are still to come—but certainly one of several was when I saw some neurons emerging from cultured postnatal glia upon the expression of the transcription factor Pax6 back in 2002. I would never have believed that this conversion from a glial cell to a neuron could occur so easily, and it still amazes me today when we do this *in vivo* and relatively few factors are sufficient to turn a mature glia into a rather differentiated neuron. Now we know that transcription factors can convert even further distant cells into each other and even into pluripotent cells, which has been one of the real revolutions in recent times, making this area even more exciting.

**Who were your key early influences?**

My parents were certainly the first key influence here, as they early on nourished my curiosity for natural science and taught me that I should always go for what I really like—rather than "the most promising job." The next big influence was my first biology teacher at school. She not only presented stuff to learn by heart but was the only one who also made us think, took us out to nature, challenged us with inspiring questions—something very rare at that time in German schools, I am sad to say. Ever since, it was clear to me that I wanted to become a biologist. But of course, this was also not the last key influence. Studying in Tübingen and Zürich I had the privilege of being exposed to a broad range of great leaders and pioneers in their field, followed by wonderful PhD and postdoc supervisors who fostered my ideas and curiosity and provided the space to develop my own ideas and experiments. After a spell in a company, this freedom in academic science has become one of the highest values in my life.

**What's your favorite experiment?**

The experiment that gives surprising answers. This is the biggest joy in science, when something unexpected happens, and you can try to better understand this surprising answer. The other favorites are experiments that give an answer, whatever the outcome is.

**What is your view on big data-gathering collaborations as opposed to hypothesis-driven research by small groups?**

I very much believe in and truly appreciate diversity in life and likewise in science—we need different people, styles, cultures, ways of thinking to make life fun and great, and the same is the case for science. We need big data, we need people driving technology forward, and we need hypothesis-driven research. I think we live in a very rich scientific environment at the moment, which propels science forward—but only when we take advantage of all facets of science, rather than pouring all money on one heap.

**What do you think are the biggest problems/challenge science as a whole is facing today?**

The media and publication changes. These days everybody states something, deposits something, and it is inevitable that this will explode and is already exploding. So, we will have to come up with new filtering mechanisms to identify the reliable data.

**What is your view on the role of neuroscience for society?**

Neuroscience is among the most influential areas for society, as we see in the many fields emerging, such as "neuroeconomics," "neuroethics," "neurotheology," and the huge relevance neuroscience has for jurisdiction. It is amazing how many aspects and parts of society expect their answers nowadays from neuroscience—which implies huge responsibilities, most importantly the ones mentioned above, namely that we do not know the truth but can only ever communicate the state of the art of our knowledge and communicate to the public that this is "present knowledge" and may well change—apart from how limited it still is. In times of "no-lie-MRI" and false promises about what neuroscience could tell you, but actually cannot, all of us, including neuroscientists, should be aware of our limited insight when it comes to human behavior, consciousness, etc.

**Where do you see the strongest potential for progress and new breakthroughs in neuroscience?**

Obviously, the biggest gap in our knowledge is between our understanding of neurons and glia and their physiology and cell biology and the final outcome of the network. Only in very few cases do we understand how a neuronal network brings about a certain function, and almost never do we understand this for more complex functions—which is why we should not pretend that we do. Now we have the tools to not only to examine circuitry as it is and manipulate it but also to actually create new circuitry, by bringing into a network defined classes of neurons and probably soon also defining their connectivity. I coined this field "synthetic neurobiology" in 2010, when it was first shown that one could induce cortical pyramidal neurons in the striatum. Thus, manipulating neuronal networks by bringing in defined neuronal subtypes—i.e., synthesizing new circuits—may fuel insights into how circuits can work and do work.

**What advice do you find yourself giving to your students and postdocs?**

To always follow what you want to do, and never go for something just because you think it may be good for your career. If you are happy and like what you do, you will always be better than those who do something because they think they must.

Of course, I also praise the huge advantages that a job in academia has—you are your own boss, you work on your own questions, and your work always changes (from working mostly in the lab to other tasks later), but again, how it changes and how much space you give to the different tasks you have depends entirely on you. And if you have a family, you can to a very large extent choose your working hours very flexibly—because it does not matter when you do your experiments, when and where you read, and when and where you think about new experiments or analyze your data.

**How do you find inspiration?**

Hiking or biking in nature, or while swimming. I get the best ideas when there is time for free association. It is also great fun to think about new projects in the bathtub or at a lake …

**What question keeps you awake at night?**

Besides the many touched upon above, I think a lot about how a cell's identity is actually maintained. Now that we can reprogram cells so readily, it is fascinating to think about how a cell's identity is stabilized. We need to better understand when and how new stable states are achieved and the long-term mechanisms that stabilize such states. We used to think of DNA methylation and fixed chromatin marks as stabilizing fate, but we have learned that this is not the case—so what else is it?

**Did you encounter particular difficulties?**

I guess one challenge was when I first presented our data showing for the first time that radial glial cells generate neurons, at the Society of Neuroscience meeting in 1999. During the Q&A time, an influential person from the field commented that our findings could not be true, and if they were true, definitely not in primates. Only afterward, I heard how vivid the debate on the topic was behind the scenes, with many people saying that that neurogenesis from radial glia was not possible. But when other publications came out shortly after ours, reporting also that radial glial cells give rise to neurons, the field was quickly convinced. Fortunately, I could largely ignore this incident and get on with my research, and these people had little influence on my career in the end.

**What career paths did you consider other than scientist?**

None—I always wanted to be a scientist and have never ever considered anything else. Sometimes I envied my friends who were discussing different job options and whether to go into farming or science, because I've only ever had one option—I am truly glad it worked out.

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