

## Reprogramming Stars #4: A Reprogramming Approach for Parkinson's Disease— An Interview with Dr. Malin Parmar

Malin Parmar<sup>1</sup> and Carlos-Filipe Pereira<sup>2</sup>

**Introduction by Dr. Carlos-Filipe Pereira  
(Editor-in-Chief, *CELLULAR REPROGRAMMING*)**

**Dr. Pereira:** Good afternoon. My name is Filipe Pereira, Associate Professor at Lund University and Editor-in-Chief of *Cellular Reprogramming*. I am very happy to bring you a new episode of *Reprogramming Stars*, our flagship series capturing the findings, projects, and ideas of the leaders in cellular reprogramming. Today we have Dr. Malin Parmar, professor at Lund University and group leader at the Lund Stem Cell Center, Sweden. Malin performed her bachelor and master studies in Canada and did her PhD in developmental biology at the Medical Faculty of Lund University in Sweden. She joined Dr. Meng Lis laboratory as a postdoc at the Institute for Stem Cell Research, University of Edinburgh. During this time, she investigated molecular mechanisms underlying the generation of dopamine neurons from stem cells.

In 2007, she started her own group and since then had a stellar career at Lund University, making pioneering contributions to the field of translational stem cell biology and cellular reprogramming. In cellular reprogramming, her laboratory has made field-defining contributions showing the direct conversion of functional dopaminergic neurons *in vitro* and *in vivo*. Malin has been extremely successful and received funding and awards from prestigious institutions including a starting grant and a consolidator grant from the European Research Council, a Robertson investigator grant from the New York Stem Cell Foundation, and she also participated in several EU networks. Dr. Parmar, thank you so much for joining me today. It is a pleasure to have you featured as a reprogramming star.

**Dr. Parmar:** Yes, thanks, Filipe. It's great to talk to you today.



**Dr. Malin Parmar**

She also develops technologies for direct conversion of human fibroblasts into functional and subtype-specific neurons *in vitro*, and the conversion of endogenous glia into neurons *in vivo*. Her ultimate aim is to develop these cells and technologies for use in brain repair, with focus on Parkinson's disease.

**Dr. Pereira:** So, your laboratory combines long-term expertise in stem cell biology and regenerative neurobiology, with both *in vitro* and *in vivo* reprogramming. I wonder whether you could tell us a little bit more how your journey started in cell reprogramming.

**Dr. Parmar:** My interest, which I developed during my undergraduate really, and continued during my PhD, was developmental biology. I have always been fascinated how cells know what to become when you go from an undifferentiated cell to create all these different cell types of the body. My PhD was in developmental biology and I studied development of the forebrain. At that time, it was just when we started to learn how to culture neural stem cells from the brain outside the brain. This technical advance opened many interesting questions about what happened to the

**REPROGRAMMING STAR:**  
**Dr. Malin Parmar** is a professor in cellular neuroscience at Lund University and an NYSCF-Robertson investigator. The Parmar laboratory studies cell fate specification in the developing brain and in human neural progenitor cells using cell-based models of neuronal differentiation. Her current focus is to learn how to direct and efficiently drive controlled differentiation of human stem cells into subtype-specific neurons.

<sup>1</sup>Developmental and Regenerative Neurobiology, Department of Experimental Medical Science, Wallenberg Neuroscience Center, Lund University, Lund, Sweden.

<sup>2</sup>Molecular Medicine and Gene Therapy, Lund Stem Cell Centre, Wallenberg Centre for Molecular Medicine, Lund University, Lund, Sweden.

cells once removed from their environment and how fate specification and differentiation are controlled in the culture dish, instead of inside the brain. These fundamental questions are what subsequently led me into my interest in stem cells and my postdoc in Edinburgh at the Institute for Stem Cell Research where, at that point, they were one of few places in the world that were experts on mouse embryonic stem cells and had started, also, to culture human embryonic stem cells.

So I got excellent training in stem cell biology there and when I returned to Lund, I started to work with human stem cells and that led me into translational projects and to ask the question: how can you create cell types to repair damage in the brain? Also, around that time was when induced pluripotent stem (iPS) cell reprogramming was first published. And of course, working with regeneration of the brain, it is super important that the cell type that you make, whether it is from a stem cell or whether it is from different types of reprogramming, is as authentic, and functions as close as possible to the cells in the brain. So reprogramming was really a step toward generating new cells for brain repair using methods that can be better or simpler than stem cell differentiation.

**Dr. Pereira:** Now the neural reprogramming field is well established, but this was not the case a few years ago, right? It emerged very quickly and there are now many different groups working in this field. How did you first get interested in direct neural reprogramming?

**Dr. Parmar:** I was really inspired by the study published by Marius Wernig and his team in 2010 (Vierbuchen et al., 2010), where they show that mouse fibroblasts could be directly converted to neurons, without passing through the pluripotent or iPS cell stage. I found that fascinating, and from a translational or regenerative biology scenario, it was a fantastic opportunity that opened up. So as soon as I read that article, I thought this is it! And we started to ask, can you directly convert human fibroblasts into functional neurons? And what does it take to make them into dopamine neurons?

**Dr. Pereira:** The discovery by Shinya Yamanaka during your postdoc and the possibility to use the combinatorial overexpression approach to generate neurons were the key events that brought you to develop this field further.

**Dr. Parmar:** Yes. I think I was more inspired by the direct conversion, initially, because the stem cell field was still at an early stage. You have to remember what it was back in 2010. So, then it felt impossible with iPS cells. Now, 12 years later, I am super interested in iPS cells for brain repair. It has been a really dynamic field and very interesting to be working in it as it all kind of unravels.

**Dr. Pereira:** In your point of view, what is the main advantage of direct cellular reprogramming?

**Dr. Parmar:** Direct conversion allowed us to generate neurons for transplantation or repair *in vitro* (Pfisterer et al., 2011). But for the first time, it also opened up the possibility

to create neurons directly inside the brain that opened up a new strategy for repair that is not based on transplantation.

**Dr. Pereira:** You have been developing this idea, to use this molecular circuitry underlying cellular identity, to replenish neurons *in vivo*. Not too long ago, you published multiple articles in this field, including “*Generation of Induced Neurons via Direct Conversion in Vivo*” (Torper et al., 2013) and the “*In Vivo Reprogramming of Striatal NG2 Glia into Functional Neurons That Integrate into Local Host Circuitry*” (Torper et al., 2015). It will be interesting to hear more about these articles. What were your main findings?

**Dr. Parmar:** If you start on a positive note, the main findings from the first study were that we could show that it is possible to reprogram neurons directly inside the brain. So, we could use different types of glia, and then convert them into functional neurons *in vivo*. With the second study, we looked beyond just the formation of the cells themselves and studied how they functionally mature and integrate with local circuitry and the cells that are already in the brain. And this is of course a prerequisite for an effective brain repair. Another finding was that the factors, the fate-specifying factors used *in vitro* were not sufficient to direct the formation of dopamine neurons *in vivo*.

**Dr. Pereira:** That is very interesting. Do you know the reason why? Why did it not work in the *in vivo* setting?

**Dr. Parmar:** No, I do not think we fully understand yet why this is. It could be, of course, that the starting cell is slightly different because the cell *in vitro* is not the same as a cell *in vivo*. It could also be that the levels of expression of the conversion factors are extremely important. You may not reach the perfect levels *in vivo*. It could also be that the environment of the brain itself is not permissive, to the same extent, for forming dopamine neurons as *in vitro*. So, you might need to use other factors to override the environmental cues *in vivo*.

**Dr. Pereira:** I think those are very plausible explanations. For the audience, it is important to mention that in this field it has been challenging to define the starting cell type and how a cell changes *in vivo*. This has been a challenge way before the discoveries of direct conversion. So Malin, in these articles, you had to develop technology that allows you to know that you are actually starting from glia, right?

**Dr. Parmar:** Well, I think that is part of the problem, that it is much harder to study cells inside the brain than outside the brain. We took advantage of methodologies that we used to study stem cells after transplantation. And by doing that, we could do functional studies, electrophysiology, and integration analysis. One benefit when you start *in vitro* and transplant the cells and study them though is that the cells have physically been separated from the brain at some point. This means that already *in vitro*, you can induce transcription factors, or labels, or activatable calcium channels to endow the cells with certain properties that you need for subsequent analysis, and then transplant them in the brain. This way you

know you have targeted the correct cells. A complicating factor is that once you do the conversion inside the brain, you have many technical difficulties with targeting the starting cell type and to do this precisely and exactly.

**Dr. Pereira: In your studies, you took advantage of drivers selectively active in glia, right? So, you would know the transcription factors to induce neural conversion would only be expressed in the brain, in glial cells. To what extent do you think that driver is specific to that cell type, or does it capture a broader group of cells at different stages of differentiation?**

**Dr. Parmar:** Yes. I mean, this is at the core of the problem, really! These Cre driver lines are usually not as specific as you think. And that combined with whether we use viral factors to deliver the transgenes, meaning that you only need a very very small amount of Cre to get recombination expression in other cell types. So, it is extremely important to always carry the experiments with appropriate and extensive controls. But even so, it is not the perfect system. And there is no perfect system that exists today. Now, there are increased opportunities to perform lineage tracing, fate mapping, and single-cell sequencing at different stages. That would bring you at least one step closer to studying the *in vivo* reprogramming process, mapping the fate change that occurs when you go from a glial to neuron *in vivo* and confirm glia to neuron conversion.

**Dr. Pereira: I also saw you published a nice review on the topic in Current Opinion in Genetics and Development in June (Parmar et al., 2021). Can you tell us, what are the main opportunities and challenges in utilizing *in vivo* reprogramming for Parkinson's disease (PD)?**

**Dr. Parmar:** If we start with the review that we just published, my colleagues and I took a critical read through the articles on *in vivo* conversion for PD that have published to date, including our own (Parmar et al., 2021). And unfortunately, the literature to date is full of discrepancies and findings from one group that does not match the findings from another group. And this is likely a combination of the conversion systems used, going back to the problem with the Cre drivers of viral delivery, for example, lack of controls, combined with a difficulty in studying cell conversion process, cell phenotype, and cell function *in vivo*.

So to date there is no convincing recipe or protocol for generating dopamine neurons from endogenous glia in the brain. I am sure that will be developed over time though. And when it is achieved, the next major challenge is to bring *in vivo* conversion a little bit closer to the translational questions. We know that human neurons mature and function quite differently than mouse neurons, but when you do conversion in transgenic mice, the resident glia in the mouse brain of course converts into mouse neurons. So, then there is going to be a big gap in the field. Once the basic biology and mechanisms from mouse studies are well understood, how do we take these findings and drive them toward therapies in patients?

**Dr. Pereira: Indeed. Even so, do you think that the *in vivo* approach has advantages in the way that you are**

**converting a cell that is already within the environment, and maybe easier to connect than introducing a cell that has been developed or generated *in vitro*?**

**Dr. Parmar:** Maybe, but not necessarily so.... I think it is all in the cell phenotype, the stage of maturation of that cell. Because we know if we start with human embryonic stem cells and transplant them into the brain, they can reconstruct the dopaminergic circuitry, for example. So, it is about having the right cell, in the right stage, at the right time. I think you can achieve this both through transplantation and *in vivo* conversion. But *in vivo* conversion has many appealing advantages when it comes to speed, simplicity, and cost, for example.

**Dr. Pereira: Exactly, bypassing the patient-specific cell generation, right?**

**Dr. Parmar:** Right. In the future it could also become a noninvasive method. Right now, we inject the viruses into the brain for conversion, but there are many developments in the gene therapy field with systemic delivery and better vectors. So, *in vivo* conversion could in the future also offer a non-invasive method to create new neurons in a damaged brain.

**Dr. Pereira: When we think about possible applications, how important is the definition of the starting cell type? Is it important to define a starting cell type, or can several cell types be converted into the cell that is needed, that is, dopaminergic neurons?**

**Dr. Parmar:** For end result, that is, therapeutic effect in the patient brains, it does not necessarily matter. But in the experimental models, we need to ensure that what we study is *in vivo* conversion of glia to neurons and not labeling of already existing endogenous neurons, for example. This is why there has to be so stringent studies at the stage that the field is today.

**Dr. Pereira: I completely agree. You also work with *in vitro* reprogramming and the conversion of fibroblasts into neurons. And here, you have been approaching this from the molecular mechanistic point of view reporting the role of several small molecules, RE-1-silencing transcription factor (REST) complex and micro-RNAs in the reprogramming process. Can you tell us a bit more about the research in this field and how you can keep these two approaches, basic science and translational science; both are very high level?**

**Dr. Parmar:** To me they are not separate, rather a continuum of the same studies. And I think this is absolutely necessary to develop good therapies in the future. You need to have this strong experimental basic science. You need to understand in very fine detail how things work. And then you need to refine that, or develop that, into therapies. And when you do that, you cannot lose the scientific component of your therapy. So, to work at the very mechanistic level of cell fate conversion will be extremely important for developing new therapies in the future. So first, it was shown that you can convert human fibroblasts to dopamine neurons (Pfisterer et al., 2011). We, and others in the field, then had a lot of difficulty translating this to converting adult fibroblasts into same type of neurons.

And if you are going to go for personalized therapies, in neurodegenerative diseases, you need to be able to convert fibroblasts from aged individuals.

And this is where many of the studies we talk about here are how is the conversion process different from an adult fibroblast, compared with an embryonic fibroblast? And what molecular mechanisms are in play, which we can then mediate to achieve conversion, also, of adult fibroblasts? I am fully convinced that it is possible to make neurons of the same quality, but we need to understand more about what drives the cell fate conversion, what drives fate specification, and also what drives the maturation of converted cells.

**Dr. Pereira:** So, how is the protocol now? What are the components of the best protocol to generate neurons you have in your hands right now? Does it include transcription factors and micro-RNAs, inhibition of *REST*, or a combination of both?

**Dr. Parmar:** It is a combination of both and we have studies that we are about to publish, which shows you can also refine the dopamine identity by adding additional transcription factors. So, although *REST* inhibition, or micro-RNA modulation, is important for achieving neural conversion (Drouin-Ouellet et al., 2017), the skin fibroblasts have no regional identity. So, today we still need to direct this, or control this, by transcription factors. And I think you always need to direct and control it, but in the future, extrinsic factors, small molecules, and environmental signals could be used.

**Dr. Pereira:** So then, do you see that some of these micro-RNAs, or transcription factors, are also important to extinguish the identity of the fibroblasts? Or you feel it is more on the specification of the dopaminergic neuronal identity?

**Dr. Parmar:** Well, I think the factors we use to convert fibroblasts to neurons are based on inducing a neural fate. But I think that while you do that, the cells themselves also suppress the other cell fates. And if we understand more about this process, you could potentially also obtain a neuron by suppressing all other cell fates. But we do not know enough about this today, which is why we need very detailed studies and that many laboratories do; working on the very basic mechanisms and molecular aspects of understanding the reprogramming process itself is extremely important.

**Dr. Pereira:** Exactly. So how are the transcription factors mediating the conversions; which chromatin regions are they binding? Are they cooperating, or sequentially activating neural identity? I think that is very important for us to be able to generate optimal cells.

**Dr. Parmar:** Yes, and optimal cells and conversion processes are the most important when you do *in vivo* conversion. Because as long as you work *in vitro*, you have the fallback option of sorting out the cells you want, or selecting or taking away cells that you do not want. So, in a way you can accept the imperfection in that process, because we can

clean up the final cell product in the end. Although I am not saying that is ideal, it is possible. But once you move into *in vivo* conversion, all those fallback options disappear, and you need to have full control of all aspects of the process. And to gain that, you need to understand the process itself.

**Dr. Pereira:** Switching to your translational efforts now: the development of pluripotent stem cell-derived dopaminergic of neurons as a therapy for PD. It has been quite exciting to follow how you are approaching the clinic, and we are looking forward to hearing about the stage of the development and plans for clinical trials.

**Dr. Parmar:** This is an exciting time in this project. Developing a stem cell-based therapy for PD was my goal when I started my laboratory many years ago. And we have been working on it every day since then. That work has taken us through experimental studies of cell fate identity and specification, to cell function and cell maturation. In the last couple of years, me and my team have really dug into advanced therapy medicinal products development, good manufacturing practices (GMP), clinical trial design, safety and efficacy studies, which have been, in many ways, a fantastic journey, although, at times, a little bit overwhelming. But we are now at the stage where we have produced a large number of cells that are now stored in the freezer at the GMP manufacturing facility, waiting to be used in our first clinical trial. These cells have undergone safety and efficacy testing, and we are now in the final stage of getting regulatory approval, with the plan to initiate the first patient studies at the beginning of next year, so, it's really been a journey over the years. But after the first clinical trial, our achievements are not completed. The next step is to develop a therapy with global compliance available to all patients in need. And for that we collaborate with industry.

For my continued research, I am now very much focused on developing better cell therapies and patient-specific treatments based on reprogramming. I think the field is at a very exciting stage, where the first clinical trials using stem cells are underway. But at the same time, there is an enormous amount of potential and development, to develop the therapies for the future that starts on the more experimental side (Parmar et al., 2020).

**Dr. Pereira:** For the audience to understand a bit more about the disease, how are these patients going to be followed after transplantation? How do you measure safety and efficacy?

**Dr. Parmar:** Cell therapy in PD is based on the idea that transplantation of new dopamine neurons lost to the disease can restore many functions in patients. In Lund where I am based, cell therapy in PD was actually pioneered in the late 80s and early 90s, using fetal brain tissue. From those studies, we know that cell therapy can work, and we know a lot of what to expect when moving into trials based on stem cells. For example, we know that the effect of cell therapy takes many months to years to reach full effect, as the functional maturation of the cells is slow once they are inside the brain. Among the earliest effects that you can measure in the

patients are by brain imaging such as magnetic resonance and positron emission tomography. Also, the amount of Levodopa (L-DOPA) equivalents that the patients are taking is a good proxy, as when the cell transplant starts to become functional, the need for medication should decrease.

**Dr. Pereira: Lund has a long history in this field. Can you tell us a little bit more how it all started, and how your efforts are synergizing with the rest of the environment in Lund?**

**Dr. Parmar:** Yes. I think Lund is the perfect place for me to be based. It has the history of cell therapy for PD, so the environment has a very strong history and value translational research. I am based in the neuroscience environment, although I am not a neuroscientist myself. It allows me to use and develop excellent animal models and transplantation models that are extremely important for my studies. At the same time, Lund has also, in recent years, built up a fantastic stem cell environment and I have a dual affiliation with the Lund Stem Cell Center. At the Lund Stem Cell Center, I am exposed to colleagues with expertise in cell reprogramming, molecular biology, and single cell sequencing. So, I am happily placed in the middle of all this, which allows me to tap into the history in the field, and the long Lund experience, and merging that with the much newer environment focusing on stem cells and reprogramming.

**Dr. Pereira: I also wonder whether you could tell us a little bit more about your current reprogramming projects?**

**Dr. Parmar:** Actually, many of the studies I do today are centered around developing next-generation cell therapies for PD. Most of them involve reprogramming at one or several steps as we are very actively working on making better dopamine neurons through reprogrammed stem cells, as well as *in vitro* and *in vivo* conversions. In the stem cell study, we are looking at the cell fate transition stages and trying to identify how we can make better neurons for transplantation. And for *in vivo* conversion, we have set up new and exciting translational *in vivo* chimeric models to target human glia in the rat brain, and follow the conversion of glia into neurons.

Many of the reprogramming studies are aiming toward autologous grafting, or personalized therapies, which opens up the question: will these cells be affected by the disease process? In the stem cell trial we do now, we have healthy donor cells into the diseased patient brain. But what happens when you put patients' cells into a diseased environment? So we are studying a lot about how if the disease pathologies will develop in the reprogrammed patient neurons. And if so, how do you intervene with that process? So, at the end of the day, how can we treat patients with healthy versions of their own cells?

**Dr. Pereira: Does the pathology take a long time to be revealed?**

**Dr. Parmar:** Postmortem analysis of the transplant patients from the 80s and 90s analyzed up to 24 years after grafting revealed that a small proportion of the grafted neurons were actually affected by the disease. These were observations made when cells from healthy donors were used. So what

happens if you use the patient's own cells? This is challenging to study in animal models as the pathology takes decades to develop. To enable this, we have developed an animal model (published last year) that is the first xenograft model wherein one we can study this in a relatively short timeframe. And we are hoping that this model will let us distinguish what patient groups are more prone to develop the pathology in their cells than others. And also, then to work out strategies for how you mediate this to finally make neurons that are resistant to developing pathology. These would also have to be employed for *in vivo* conversion as these also start from the patient's own cells.

**Dr. Pereira: Regarding the *in vivo* experiments you have described, the idea is to have human cells into rat brains, right? This is a very innovative approach! Are you expecting to see major differences in the process when you compare it with mouse cells undergoing reprogramming inside the mouse brain?**

**Dr. Parmar:** I think that there will be differences because human cells mature so slowly. And I think that in the mouse brain, the developmental process is so short that it is often overlapping program that controls the specification and the maturation. In contrast, during the generation of human cells *in vitro* we observe that specification and maturation are more separate processes. So, I would predict that this is also the case for *in vivo* conversion: that although the first steps in the conversion where you make a subtype-specific neuron is fairly similar, there might be additional factors needed to push the human cells into functional stage.

**Dr. Pereira: Fantastic. It will be very interesting to follow this line of research! You have mentioned already some of your specific challenges in both *in vitro* and *in vivo* reprogramming, but I wonder whether you could name our top current challenges in understanding cellular reprogramming?**

**Dr. Parmar:** The key challenge for us, I think, is to understand how this process happens *in vivo*. And in many ways, that is a technical problem, because it is hard to study this conversion process *in vivo*. If you want to do it by single-cell sequencing, it is really hard to isolate the cells from the brain for sequencing. It is a little bit of a black box still what happens inside the brain. And because there are so many publications in the field that are contradictory, it is extremely important to develop methodology that allows for these types of studies. I think it is essential to do it, but today it may be technically too complex to achieve the level of insight into the reprogramming process *in vivo*. I think it is also important, of course, to study the process *in vitro*. But there, I think, the field has the tools to perform those studies. Especially, of course, because a bigger field with reprogramming is disease modeling or drug screening.

**Dr. Pereira: Yes. And I guess that collaboration will be important for all of us in the field, to reach consensus and to settle on protocols of generating cells and move forward. But can you describe your collaborative team efforts, both on the basic understanding of the process and also for the translation efforts?**

**Dr. Parmar:** Yes, I think collaboration is essential for everything. For experimental or mechanistic studies, you need to collaborate both in terms of technical expertise, and also across different cell types. I am a specialist on dopamine neurons. But, of course, there is a lot to learn from how other types of neurons are generated. And it does not stop there. There is also a lot to learn from the conversion processes or the reprogramming processes for hepatocytes, cardiomyocytes, or to any type of cell. I think it is only together as a field of reprogramming, we will get to the key questions and fully understand the process of conversion. When it comes to the translational studies, there are many areas of expertise that are needed. And their collaborations need to be within academia but also with industry, regulatory authorities, and the health care sector. Everything I do is in collaboration with others, I hate working alone! I love working in big EU projects or big projects group where we have one major common goal, and everyone contributes to this with their respective expertise.

**Dr. Pereira: For the clinical trial for regenerative therapy for PD, who are you collaborating with?**

**Dr. Parmar:** Well, it is a long, long list of people. Our own project has developed mostly within EU projects with both academic and industry collaborations. There is also one big group in Japan working on stem cell-based therapies for PD that is led by Jun Takahashi, and a big group in New York led by Lorenz Studer. And we, early on, recognized the need to collaborate to bring these studies all the way to patients. So, we formed what we call GForce-PD. It is a fantastic collaboration that has now been going on for many years.

In the early days, we guided each other in the refinement of cell identity, and it switched over to cell manufacturing and how we ensure safety of the cell products, and then in the latest years into design of the clinical trials. So that is a fantastic collaboration that I am part of! It is interesting that those two teams are our biggest competitors, but they are also our best collaborators. So it really takes something, I think, to achieve this. But we managed, and I think that is a fantastic way to work!

**Dr. Pereira: Oh, that is great to hear. Can you tell us about your ambitions and vision for the field? What is your personal take on how the reprogramming field will evolve in the next 10 years?**

**Dr. Parmar:** So my vision for the field is that we get a much deeper understanding of the molecular and cellular processes that take place in cell reprogramming. And that we learn to use the cells in biomedical applications or medical applications. For me, personally, I think that in 10 year's time, cell reprogramming has allowed me to develop even better and more refined strategies for repairing and regenerating the brain in PD.

**Dr. Pereira: Needless to say, you are a fantastic role model for many, many scientists. So, I was just wondering whether you have any advice you could give to younger scientists, or even the female scientists, who are starting their careers now and looking toward the future.**

**Dr. Parmar:** Well, for the young scientists in general, male or female, I think a good advice is to just go for it and enjoy what you are doing. I am in this because of my interest in development and my enjoyment of the job. I wish for the younger generation to not feel so much of the pressure that builds up around you. Instead, just enjoy the science, and try to trust that your career path will work itself out. I see too many young scientists working more on their career than working on their scientific problem. You do not have to be perfect when you start. And you do not need to know exactly where you are going in the end. Just do what you enjoy at the moment.

**Dr. Pereira: I completely agree. Focus on the question you are trying to solve. And if you put your energy there, you will find something that is interesting for you and everyone else. All the rest will get sorted out, right?**

**Dr. Parmar:** Exactly, learn to see the opportunities around you. Just do what you enjoy and interact. And if something exciting comes along, go for it.

**Dr. Pereira: I think that is a fantastic piece of advice to young scientists, enjoy the gratification of discovery, right?**

**Dr. Parmar:** Right. A good mentor of mine said once, "You never make it or break it with one thing." And I think this is very wise. If your one article gets rejected, that is not the end of your career. If your one article gets accepted, that does not fix your career for the future either. It is never one event but a series of successes and failures that lead you forward.

**Dr. Pereira: Do you have any example of an Eureka moment? These moments when brilliant ideas or reflections made you turn into the right direction.**

**Dr. Parmar:** Well, I do not know about Eureka moments. My work has always, sort of, slowly developed over a long time, it feels like. But there has been a few. I think the one Eureka moment was when we realized that we could make functional dopamine neurons by reprogramming of skin cells, or fibroblasts. The implications of that are enormous, to sit and watch those first cells that were made, and knowing what that could mean for the future. That was quite something!

**Dr. Pereira: Yes, the first time you actually see the evidence confirming your hypothesis...**

**Dr. Parmar:** Yes.

**Dr. Pereira: Malin, thanks so much for the insight. I would like to finish this interview with two completely unrelated questions to learn more about yourself. I am wondering... if you were not a scientist, what would you be?**

**Dr. Parmar:** Well, I actually do not know what I would be, but I grew up in the countryside and I did not even know you could become a scientist. The one thing I have dreamed about doing was to be a travel agent because that was the

only way I could figure out that would let me leave my little corner of the world and see what is out there. But, luckily, I realized that there are more things in life, and there are other ways to see the world than being a travel agent. In my current position, I maintain the interest in the world, people, and different cultures though. So this is an interest that I had growing up that I maintained and now can cultivate also as a scientist. For example, through all my collaborations, my engagement with the International Society for Stem Cell Research and Science for Democracy. If I was not a scientist, I do not think I would have been a travel agent, but I think I would have been something that allowed me to navigate in the global environment.

**Dr. Pereira: Science is indeed a global venture. What would be the best piece of advice that you have ever been given?**

**Dr. Parmar:** I mean, up until today, it was probably, “You never make it or break it with one thing.” But today one of my postdocs came to the laboratory in a new T shirt with the print, “Fear is not an option.” So maybe that is going to be my new favorite advice to take with me, that fear is not an option.

**Dr. Pereira: Thank you so much Malin, for your time and insight. It has been great to talk to you and learn from you.**

**Dr. Parmar:** Thank you.

## References

- Drouin-Ouellet, J., Lau, S., Brattås, P.L., Rylander Ottosson, D., Pircs, K., Grassi, D.A., Collins, L.M., Vuono, R., Andersson Sjöland, A., Westergren-Thorsson, G., Graff, C., Minthon, L., Toresson, H., Barker, R.A., Jakobsson, J., and Parmar, M. (2017). REST suppression mediates neural conversion of adult human fibroblasts via microRNA-dependent and -independent pathways. *EMBO Mol. Med.* 9, 1117–1131.
- Parmar, M., Björklund, A., and Björklund, T. (2021). *In vivo* conversion of dopamine neurons in mouse models of Parkinson’s disease—a future approach for regenerative therapy? *Curr. Opin. Genet. Dev.* 70, 76–82.
- Parmar, M., Grealish, S., and Henchcliffe, C. (2020). The future of stem cell therapies for Parkinson disease. *Nat. Rev. Neurosci.* 21, 103–115.
- Pfisterer, U., Kirkeby, A., Torper, O., Wood, J., Nelander, J., Dufour, A., Björklund, A., Lindvall, O., Jakobsson, J., and Parmar, M. (2011). Direct conversion of human fibroblasts to dopaminergic neurons. *Proc. Natl Acad. Sci. U. S. A.* 108, 10343–10348.
- Torper, O., Pfisterer, U., Wolf, D.A., Pereira, M., Lau, S., Jakobsson, J., Björklund, A., Grealish, S., and Parmar, M. (2013). Generation of induced neurons via direct conversion *in vivo*. *Proc. Natl Acad. Sci. U. S. A.* 110, 7038–7043.
- Torper, O., Ottosson, D.R., Pereira, M., Lau, S., Cardoso, T., Grealish, S., and Parmar, M. (2015). *In vivo* reprogramming of striatal NG2 glia into functional neurons that integrate into local host circuitry. *Cell Reports* 12, 474–481.
- Vierbuchen, T., Ostermeier, A., Pang, Z.P., Kokubu, Y., Südhof, T.C., and Wernig, M. (2010). Direct conversion of fibroblasts to functional neurons by defined factors. *Nature* 463, 1035–1041.

Address correspondence to:

Malin Parmar  
 Developmental and Regenerative Neurobiology  
 Department of Experimental Medical Science  
 Wallenberg Neuroscience Center  
 Lund University  
 Lund 22184  
 Sweden

E-mail: malin.parmar@med.lu.se