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CELL SCIENTISTS TO WATCH

Cell scientists to watch – Gloria Brar and Elçin Ünal

Gloria Brar did her undergraduate studies in molecular and cell biology at UC Berkeley, USA and received her PhD from the Massachusetts Institute of Technology (MIT), Cambridge, USA, studying the control mechanisms of chromosome segregation in meiosis under the supervision of Angelika Amon. For her postdoctoral work, Gloria joined the laboratory of Jonathan Weissman at the University of San Francisco, USA, as an American Cancer Society Fellow to address gene regulation and translation in meiosis using high-throughput methods. She was named as a '40 under 40' scientist by Cell Press in 2014, a NIH Director's New Innovator in 2015 and a Pew Scholar in Biomedical Sciences in 2016. Elçin Ünal studied molecular biology and genetics at Bilkent University, Ankara, Turkey, followed by a PhD at Johns Hopkins University and Carnegie Institution for Science, Baltimore, USA, in the laboratory of Doug Koshland on the regulation of the cohesin complex during the DNA double-strand break response. She then moved to the MIT and the Amon laboratory to work on meiotic chromosome segregation and the link between gametogenesis and aging as a Jane Coffin Childs Postdoctoral Fellow. Elçin has been named as a 2014 Pew Scholar, a 2015 Damon Runyon Cancer Foundation Rachleff Innovator, and a 2016 NIH Director's New Innovator. Elçin and Gloria started their team laboratories in 2014 at UC Berkeley, where Elçin is an Assistant Professor of Genetics, Genomics and Development and Gloria an Assistant Professor of Cell and Developmental Biology. Since starting at Berkeley, Elçin and Gloria have run a team lab, with shared group meetings, laboratory and office space. Their lab also hosts a dog called Mochi, who belongs to one of Elçin's students.

Elçin Ünal (left) and Gloria Brar

What inspired you to become a scientist?

Elçin Ünal (EÜ): I am the only scientist and member with a PhD in my family; my dad is an engineer and my mom is a teacher. I've always liked nature and animals, but my interest for a career in genetics came from an incredible high school biology teacher, Mustafa Hoca, who was very caring and inspirational. In Turkey, at the time, you took a standardized test to determine your career path. My top two wishes for my major were molecular biology and genetics, and then medicine. Little did I know at the time that, I would have been a terrible doctor, especially because I can't handle blood very well [laughs].

Gloria Brar (GB): You could have ended up becoming a doctor, just based on a standardized test you took as a teenager?

EÜ: Yes, you wrote down what you want to major in before you even get to college. It may not have been a very systematic choice to put genetics first, but this was the result of my teacher showing me that you can have a career in this field. In order to get some research experience, I applied to labs in the US. I got lucky, had fantastic people to help me along the way and it has been a great journey ever since.

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How did your journey begin, Gloria?

GB: It was a little bit different in my case. Both my parents are scientists – they actually met in a fly genetics class at UC Riverside. My parents were very open to whatever I wanted to do, and for a long time I thought I wanted to do something related to art, although I'm not nearly talented enough to do that.

EÜ: No – she's great, she paints amazingly well!

GB: You are being very nice! What was really key for me was that I realized early on that science and research was an actual career. Many people assume that you have to be some sort of unrelatable super genius, or a severely maladjusted introvert type to go this route. But both of my parents are normal people who really loved their jobs and I would go to the lab with them on weekends. I thought it was fun – I drew stuff on whiteboards, I played with parafilm, and my mom paid me a little bit to rack pipette tips. In addition, when I started taking biology classes I realized I also had a deeper interest in biology. The key then was – similar to Elçin – that I had people who were willing to take a chance on me and invested time in teaching me things, which makes such a big difference.

What questions are your lab trying to answer just now?

GB: Although we work very closely together, our projects aren't entirely overlapping – we have some projects with a lot of complementarity and some that are a little bit different. We're interested in understanding how gene expression is temporally controlled; in particular, we examine meiotic differentiation in yeast, as a really cool system in which to study this, because you have a cell transforming itself into something totally different, mostly through a series of unidirectional transitions. We like to think of this as a model for cellular differentiation more broadly. We see that stress response pathways are internally induced as the yeast cells go through meiotic differentiation. So we think that in some cases, the conserved physiological role of these pathways might be to promote meiotic progression. The unfolded protein response has been studied in a lot of interesting and beautiful ways, but most of these studies depended on putting harsh drugs on cells. What we see

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Elçin and Gloria having fun at a painting night out in Berkeley.

in meiosis is that the cells turn on this pathway independent of any obvious changes in external conditions, and then they turn it off again. We'd like to know what's turning it on and off, and what this stress response pathway is doing to cells during meiosis. We're also interested in aspects of translational control – why are some mRNAs better translated than others, and how this might change with time. One project where Elçin and I have a lot of synergy, but are coming at it from complementary angles, deals with what we call long undecoded transcript isoform (LUTI) regulation, coined in a previous paper by Elçin. The idea here is that you have regulated toggling over time between two transcript isoforms that are expressed in a mutually exclusive way, and they have different translational capacity. Elçin's lab worked out in detail how this mechanism works and then we looked at it broadly through some large-scale datasets. Our group found that this is a common way that yeast cells regulate gene expression, in meiosis and elsewhere. Together with Elçin, we looked to see if this process is conserved and have now seen very strong evidence of this.

EÜ: As geneticists, we'd like to understand how the genome is decoded into function and what we have as our core tool is a dynamic gene expression atlas. We complement the genomic data with live-cell microscopy, where we examine a number of different processes over time in meiotic cells and try to see how they are coordinated with respect to one another, basically watching hundreds of cells carefully using different lenses – and examining what they are up to. From these types of integrated analyses, we try to understand how changes in gene expression could drive changes at the phenotypic level. By taking dynamic measurements for both types of data, we can infer causality. Even better, we can then directly test whether this is the case by clean and clever genetics – the beauty of using yeast. Gloria's gene expression atlas showed us that even a 'simple' system such as yeast gametogenesis does many things in a regulated manner and the revelation coming from my side was that it also causes cellular rejuvenation. We can now look at cellular state changes at the nuclear and cytoplasmic level and try to understand how gametes ensure their fitness through the meiotic differentiation program. For example, we have started to look at mitochondrial segregation and quality control, and how this is mechanistically regulated. Furthermore, we have recently discovered that meiotic cellular rejuvenation is linked to global nuclear remodeling; where the sequestration and elimination of age-induced cellular damage is coupled to the bulk exclusion of nuclear pore complexes. Interestingly, nuclear pore exclusion has also been observed in mammalian sperm – it's too much of a coincidence that these two things would have evolved separately. From that point of view, our work in yeast also serves as a discovery platform.

You're asking fundamental questions in yeast, but your labs also work side by side. Is this the model of success for you?

EÜ: We call it complementation. We have different ways of approaching science, but we respect each other a lot. It works incredibly well in science when people with similar interests but different ways of thinking come together for a bigger question that neither one can address on their own, and develop a team spirit and synergies. Research doesn't happen in a straight line and at steady pace – there are ups and downs, happy and sad parts, but it is good to go through a process together and also complement the deficiencies of one another. In addition, we definitely think differently, but because we respect one another and communicate a lot, it creates synergies. In our joint lab, we try to train the next generation of scientists to go after a question and not individual glory.

GB: There are really fundamental questions in yeast meiosis and gene regulation that haven't been answered. It's not that we're the only ones who have noticed this or asked these questions, but we're trying to go about them in a way that we think is interesting and maybe unique. It's been of huge added value that we have similar big picture interests, but come at them from really different perspectives. I think it is important for you as an individual scientist to find the best system to address your specific questions and also to look for synergies outside your own talents and knowledge base.

What has been the most influential work and who has inspired you in your field?

GB: There are a lot of people who have been influential in a lot of ways you don't even know because everything is built on what other people did, but I have been influenced in the most obvious ways by the people I have worked closely with. I'm biased, but I think they are two of the greatest scientists working now – Angelika Amon (David Koch Institute, MIT, Cambridge, USA) and Jonathan Weissman (UC San Francisco, USA). It was great to see that two people who had very different ways of thinking and going about things were both so amazing at this job. With both Angelika and Jonathan, I found their creativity really inspiring. They are both fearless in the way that they tackle problems and they are also both really nice, fun, and supportive people.

EÜ: I would give almost exactly the same answer! Angelika was my postdoc advisor and Doug Koshland (UC Berkeley, USA) my graduate advisor – very different personalities and very different approaches to science, but this was highly instructive. I don't have any role models per se, but my mother has been incredibly inspirational and supportive. This, along with financial help from my dad, allowed me to be in places that just happen to be amazing places to do science. This set the trajectory, and I was lucky to end up with these great mentors, they are your scientific parents.

"It works incredibly well in science when people with similar interests but different ways of thinking come together for a bigger question that neither one can address on their own…"

Was the Amon lab the birthplace of the joint lab idea?

GB: Yes, it was! There was not a lot of time when we both worked in Angelika's lab, it was 8–9 months only…

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EÜ: But we had met before and we clicked.

GB: Yes, we did. We stayed in touch when I had gone out to the Weissman lab. We became really good friends and went on vacation together before we had any scientific collaboration, but then it became clear that there was great scientific synergy as well.

Did you sit down and plan this ahead of time? How difficult is a joint start into independence?

GB: Funnily enough, there was a very structured moment. I had gone out to Boston at some point, and Elçin and I met in a conference room where we drew our ideas on whiteboards. This was a year or two before we were on the job market. It wasn't clear if this was a realistic idea or a pipe dream almost until the moment we had the jobs. The way I often think about it is that if we could run a simulation of the way that whole year went down a hundred times, we would only get this outcome a small fraction of the time, because everything had to line up. It was a lot of luck.

EÜ: We also talked to our mentors.

GB: Yes, that's important! And they were very encouraging and hugely supportive, and that makes a big difference, but I don't think it's something that can be easily planned. Elçin is the more idealistic one and I am more practical. She had always believed that this could work and I was more sceptical. You hear about the statistics of getting a faculty job and you think 'how is this even going to work out for me alone?', and so to add this extra level of complexity seemed scary. What was surprising was that when we did start talking to people about it, they were positive and said something along the lines of 'I wish that I had done that'. In the end, there was no real strategy for how we did this and I don't want to give the impression that we knew exactly what we were doing! We didn't.

EÜ: We had the will to do it, but we got tremendously lucky!

What challenges did you face when starting your own lab that you didn't expect?

GB: Well, early on it didn't feel challenging. It was actually really fun! We have all these pictures of us standing next to piles of boxes as our lab equipment came in and it felt like Christmas! Many people say that the very beginning is the most challenging part. But because we were doing it together, I think we both found that period to just be really fun. You get to build things the way you want…

EÜ: And you get feedback from one another.

GB: Yes, and we were recruiting our first grad students and being able to do that together was just great. At the very beginning, it's busy and overwhelming and you sometimes don't know what you're doing. You're learning on the fly, but that was really a fun time, more than I have heard other people have had.

EÜ: And we got a great lab manager from the beginning!

GB: Absolutely. Karsten Weis (ETH, Zürich) was leaving Berkeley at the time and we were really sad that he left but we ended up recruiting his lab manager Christiane. To be able to start our lab with her was fantastic and it was a team of three people at the beginning, actually.

EÜ: And her last name is Brune, so it was meant to be that she'd be our joint lab manager! Another crucial aspect to our strong start was that two senior members of the Weis lab, Chris Mugler and Leon Chan, also decided not to move to Zürich. Since we had plenty of space, we offered them the opportunity to relocate to our lab in Barker Hall. They were very helpful in providing extra guidance and mentorship to our graduate students as well as providing valuable critique at our joint group meetings. Interestingly enough, Leon is now my partner (and Chris is now Gloria's partner) on a personal level, too!

How are the challenges that you're facing now different?

GB: There are phases in this job. At the beginning you recruit people, then you try to get projects going and then funding. Now it's definitely very different from how it was at the beginning. The new and fundamental challenge from my perspective is that growing projects is different from initiating projects. It's just a different skill set that we haven't needed previously because the projects were new when we started.

EÜ: Another thing is that you are getting busier and busier, I think. At the beginning, I felt 'oh this is a lot of stuff', but now it's even more! I need to pace myself because if I can't do things well it drags me down, so I try to maintain my balance. Also, you have to deal with the transitional nature of science. It's the best and worst part of the job that you meet a lot of people and share ideas but you also need to say goodbye because people are moving on.

"There's a lot of value in continuing to be a happy person."

What is the best science-related advice you ever received?

EÜ: Doug told me that as a group leader, you have to get the best out of your people and make them realize their potential. You need to give freedom, but at the same time, guidance. Every one of us has individual talents and strengths and weaknesses. As long as we are aware of them and are transparent and communicate, you get a functional relationship between a mentor and a mentee. One of the many things that Angelika taught me is 'be selective, don't go too fast, don't expand too quickly'. That was extremely valuable advice.

GB: She also said: 'the best way to do good science is to surround yourself with the best possible people'. And: 'there's no reason to feel intimidated by people' – she is fearless with asking questions and saying what she thinks. I believe it comes from her belief that there's really no point in doing this if you're going to only do and say things that you feel totally comfortable with. Then you're kind of not going to be doing anything original. She's well liked but doesn't base what she studies on what others think. She has very strong views that have led her to study things in really different ways than others. And she's been extremely successful doing that. Jonathan doesn't give a lot of advice verbally, but I did learn a lot from watching him. He works extremely well with other people; he's very collaborative and very thoughtful. I think that he looks at scientists as individuals who each have something to offer. His lab consists of a lot of different people with different interests who are all collaborative, which allows his group to productively study a remarkably broad range of things.

How do you achieve a work–life balance when you're trying to establish yourself as an independent investigator?

GB: We're doing this job because we love it. So if it's not fun at some point, it's a good idea to take a break, do something else for a bit, and figure out how to fix it. There's a lot of value in continuing to be a happy person. Also, I am a mom now and being able to have a family and do science is something that I feel strongly about. There are a lot of people, women especially, at the graduate and post doc level who believe that there's a choice to be made between the two – the job or the family, and you're not going to be able to do both, or do both well. And I'm not saying that I'm perfect at either one, but the key here is that this job offers so much flexibility that you can work at whatever hours you want, with some small, practical limitations. You can take a day off to go take care of your kid – you can decide how you restructure your time to make it work. The idea,

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at least for me, is to remember that you're really in control of your time, and that's both a blessing and a curse, right? You can stretch yourself out as much as you want, but if you're doing this job, you should really take advantage of that perk.

EÜ: I need to be disciplined not to over commit. I get super-excited and very involved in things and running experiments at the bench used to help me take my mind off things. Now I'm in my office and I have to take care not to get upset about scientific or worldly issues. So I try to keep a balance. It's a marathon and not a sprint. You want to enjoy it and listen to your body and brain. I do climbing and yoga, and I also have incredible support from family, friends and colleagues.

Could you tell us an interesting fact about yourself that people wouldn't know by looking at your CV?

EÜ: I mean, you're an artist! She's great at painting!

GB: No. Not really. I like art, but I'm not really good at it.

EÜ: She's very good. Apart from that, a lot of things are amazing about you, like your love of animals. You're not even afraid of rats like I am. When we traveled together, Gloria was able to hold pretty much any animal without being scared the slightest. Which surprises people to hear.

GB: That's another aspect of our complementarity. I'm pretty sensitive and Elçin is this force of nature – she's tough and idealistic and has big, amazing ideas. And she's an incredible cook!

EÜ: Unlike science, I often follow recipes very lightly when it comes to cooking. I find it to be liberating, adventurous and creative that way. Basically, I put my heart into cooking. It makes me happy, especially sharing the food I made with loved ones.

Elçin Ünal and Gloria Brar were interviewed by Manuel Breuer, Features & Reviews Editor at Journal of Cell Science. This piece has been edited and condensed with approval from the interviewees.