Co-funded by the
Erasmus+ Programme
of the European Union

Meet a *Sci*-Star:

Smadar Ben-Tabou de-Leon

Smadar Ben-Tabou de-Leon is an associate professor in the Marine Biology department at the University of Haifa, Israel. Her main goals in research are looking at how development is regulated, principally by transcriptional Gene Regulatory Networks (GRNs) that regulate cell fate decisions, and the interplay with the cellular machinery that execute the developmental program. Smadar is a converted physicist by training and DigitalMarine interviewed her to ask about GRNs, her experience with renowned researcher Eric Davidson, changing fields, and her outreach work.

You were primarily trained as a physicist; why did you choose to make the transition to developmental biology?

Sometimes, what you really like to study is not what you really like to research, they can be completely different worlds. When I was a kid, I was fascinated by the physics that I saw around me, and I wanted to understand why everything moved the way it moved, the mechanics, how light works, and the physical phenomena around me. I enjoyed my Bachelor's degree in Physics and even my Master's, but when I was studying theoretical physics of condensed matter I realized that I wanted to study something that would inspire me more like when I was younger. And then I became pregnant, which was the first time I was really struck by the fact that "oh my goodness, a single cell is dividing and becoming so many different cell types!" Developmental biology suddenly became personal and I wanted to read all about it, even though it never interested me before. I started reading and thinking about biology constantly. I made the transition through a postdoc in applied physics before deciding that I want to do the real thing: study biology as a biologist. It was really the miracle of life that helped me find my love of learning again and helped me change domains.

That's a big transition – did you have to go back to school and get another degree?

That's a great question, in fact I didn't! I relied on

textbooks, so I read a lot and trained myself. When I came to Eric's lab, it had a whole atmosphere of doing biology and talking about biology, and that also taught me a lot. Like I said, there's such a big difference between studying and researching something, and I really liked researching biology - physics not so much. I decided to become a biologist after my 1st postdoctoral position in physics, which is very, very late when you think about it. But it didn't even feel like a choice to make for me, it was what I had to do, and it was definitely worth it.

Why and how did you select Eric Davidson's laboratory for your postdoc position? Why did he choose you?

Once I decided that biology was the thing for me I started looking for a postdoc in labs where the head was a physicist who had made a similar transition. By chance, another physicist that had transitioned to biology came and gave a talk at our physics seminar, and after her talk I came to her and told her I was keen to make the transition. She told me "you know, there is this guy, Eric Davidson, and he has this model of regulation of biological systems, you have to check it out and see if you can work with him." I said ok and started reading Eric's papers... and I didn't understand a thing! It was like a foreign language – blastula, gastrula, all these developmental stages – but the network itself was something much more understandable, like an electrical circuit. I wrote to many people back then and he was one of the only ones to answer, and he was willing to interview me even though I had no background in biology. Even though I was afraid to jump into the water, he was the only one to offer me a position. Later he told me he looks for the "intelligent spark" in people: he didn't care that much about the person's background, but he really cared about the potential. I guess he saw something in me and that's why he invited me to join his lab.

Group photo - the Davidson Lab, California, 2006

How was working with Eric Davidson and what was the scientific atmosphere like in his lab?

Working with Eric was always very stimulating, and he was really one to push you to your intellectual limits, which is something I really appreciated about him. I told Eric that I truly became a scientist in his lab, because no one before had pushed me as hard as he did: you couldn't come to him unprepared, you had to think about everything and really understand what you were doing to be able to communicate with him. He was always a step ahead of you and had such a broad vision of what he was doing and such a

strong personality. This also affected the atmosphere in the lab because Eric was kind of terrifying, but the lab was amazing. It was such a friendly place, his lab was at CalTech in southern California, and I arrived in 2004 right after the GRN paper was published and right before the genome project was published in 2006. It was such a great period: everyone was doing cutting-edge research and really revealing the secrets of life – what an atmosphere! We were all friends and living and breathing GRNs, and many of us were international scholars so we became each other's second family – celebrating holidays, birthdays, and new kids together – and we've stayed close since. I don't think this could have happened without Eric nurturing this environment and it was really one of the happiest places I've ever known. He pushed all of us in a really good way, and I've tried to create the same kind of atmosphere in my lab, because it was so inspiring to work there.

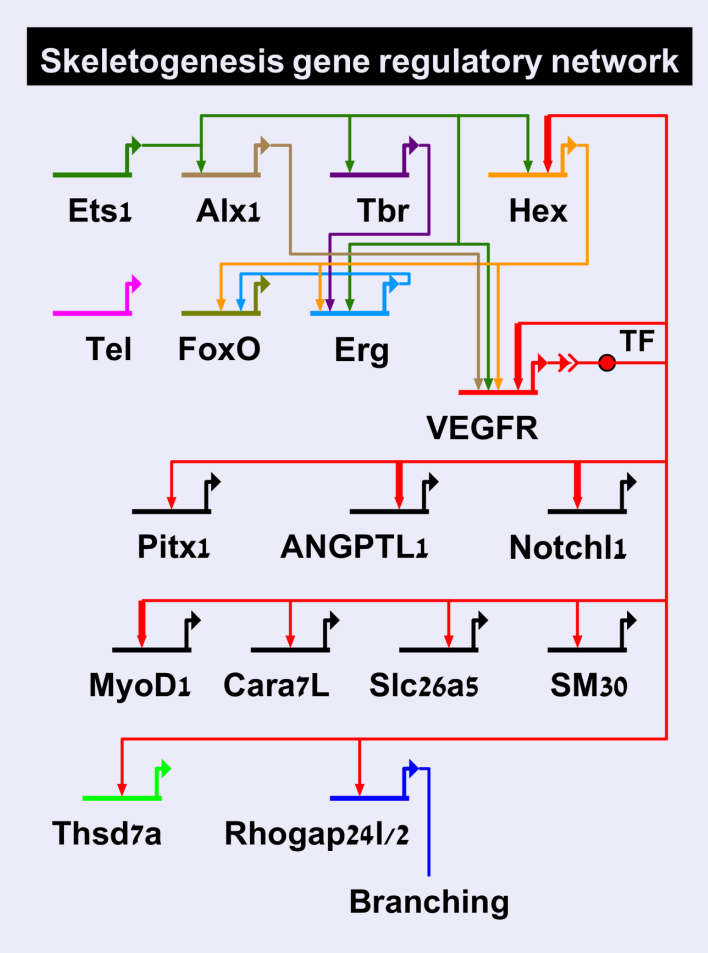
Let's talk about your field of study - why is analyzing developmental GRNs important for understanding developmental biology and evolution?

Gene regulatory networks are basically the mechanism that drives cell fate decisions, and this is the beginning of every developmental process since cells need to become different from each other and express specific genes. If you think about it, all the cells have the same genome, the same DNA, but for some reason, some of the cells start expressing a specific set while others express other ones, which makes them very different from each other. GRNs are the code that underlie these decisions. This cell differentiation is the beginning of organs and morphogenesis and the final body plan. This genomic code is already present in the egg, but is only brought to life during development, and its execution gives rise to different cell types. I think it's one of the most interesting and most basic processes in developmental biology. It's extremely important to understand this process of how cells decide to express one set of genes and not another, and how they communicate among one another to fine-tune this decision.

From an evolutionary perspective, we know that a sea urchin egg will give rise to a sea urchin, and a human egg will give rise to a human, and we know that something in these two eggs encodes the differences. If we understand the GRNs that underlie these different cell fates and different developmental processes, if we understand the changes in the regulatory code through evolution, we will be able to get insight into the genomic changes that brought about the biodiversity that we see today.

What was Eric's contribution to this field? How did he affect your perception of developmental biology?

Have you seen a GRN before? Here is a network diagram, and it may look a bit scary because it's a lot to take in and is very complex, and this is Eric's work. Before Eric, people were drawing cartoons of proteins with arrows going in and out, but Eric wanted to make it more exact, wanted the diagrams to have a meaning. So the nodes correspond to genes and the arrows leaving the nodes are the proteins that these genes encode, and if the arrow goes from gene A to gene B that means that the transcription factor encoded by gene A regulates the expression of gene B. Eric formalized the visualization of gene regulatory networks, and creating this model was practically the invention of a new language. I feel that the visualization of science is really critical to our understanding because when you draw this kind of network, we then ask questions like "why is this gene activated so late in development and this gene activated earlier? Why is this gene activated in this cell and not in the other?" This means you're able to have an overview of and ask questions about the whole regulatory system of development, not just on one gene or another.



Example of a network diagram

This was Eric's major contribution, the formalization of the concept of gene regulatory networks: you write everything you know inside a model and try to see "is it enough? Does this explain what I see or am I missing information?" and that really shaped how I look at biology up until today.

Nowadays I'm studying the biological regulation of the calcite skeleton formation of the sea urchin larva and I'm mainly interested in the interactions between the gene regulatory networks and the cellular machinery that drives morphogenesis. I'm interested in the cytoskeleton remodeling proteins that transduce the regulatory code to generate organs and in the feedback between these proteins and the GRN. Even though it is a little different than studying transcriptional networks, I still use the same logical thinking and ask – what are the regulatory interactions between the factors I study and how they explain what I see? That is what Eric taught me, to look for the logic, to look for the links, to draw what I think is happening and to try to build a model to explain it, and if I'm missing something then that's a question mark (and there are always question marks!) Then you look at whether a link exists there or not, and drawing the model allows you to identify what you're missing and the causal relationships, which is quite like physics in the end! We also try to measure and quantify everything we can to make sure we really understand the phenomena we study, which is related to my physics background but is also just good practice in science.

What do you think are the main challenges in GRNs and developmental biology these days?

In the 2000s, Eric and other scientists did a lot of major work in deciphering GRNs that was critical to understanding the genetic basis of cell fate decisions. Yet, there is still a big gap between the activation of genes and proteins and the outcome, which is morphogenesis: cells moving and changing their shapes and building organs and shaping body plans. I think the challenge now is to fill this gap and understand how the networks are regulating these morphogenesis events, meaning the interaction between the network and the cellular machinery that executes the work. For me, this is the big challenge now, and this is what we are working on in the lab.

Why are sea urchins and echinoderms good models for such studies? What do you think is the future of these models in biology?

Sea urchins are a fantastic system for these specific questions because they are very small, transparent, and the fertilization is external, so observing the developmental stages under the microscope is easy. Obtaining eggs and sperm is quite easy - you can get thousands of embryos from a single spawning! You can down-regulate genes and observe the resulting morphological

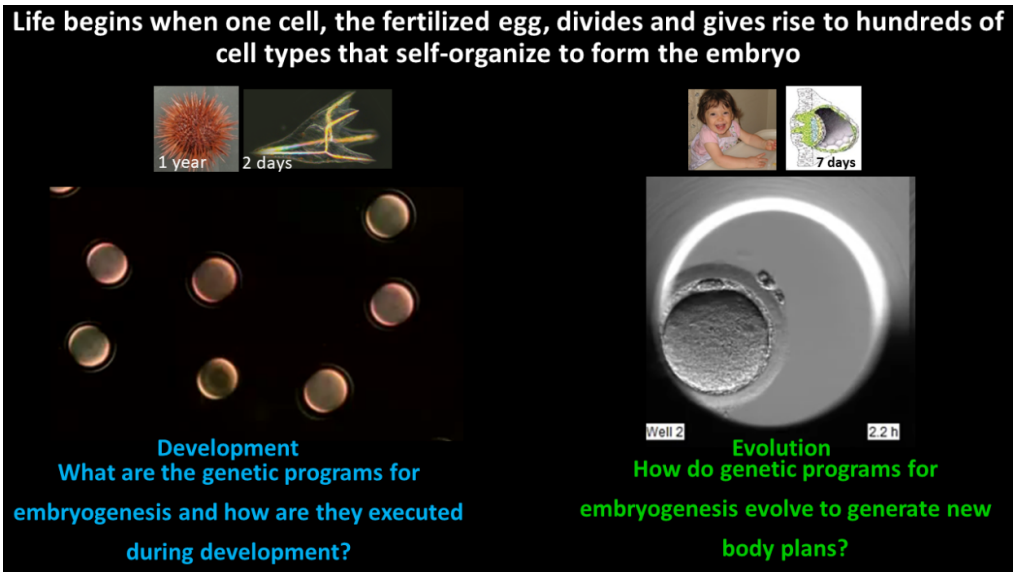
phenotypes and changes in gene expression and protein activities, and this allows us to study the links between genes, proteins, and morpho-genesis in a very effective way. This goes for echinoderms in general: there are different clades of echinoderms, and in almost every clade there is someone doing experiments like these, so we are able to compare them and learn about evolution. For example – some echinoderms, such as sea urchins and brittle stars, have a larval skeleton, and some echinoderms don't, like sea stars and sea cucumbers. As such, we can compare their GRNS and learn about the evolutionary gain and loss of this character. So to summarize, sea urchins and echinoderms in general are powerful models to study the regulation and evolution of developmental processes because of their experimental advantages and because of the studies making GRN comparisons possible.

I believe that the future of echinoderm research depends on the collaboration and support within the research community. Eric was a force of nature, but he also rubbed some people the wrong way and made some rifts. His loss left a huge void and I think we're still trying to move forward. With the people doing excellent work in the field and implementing new tools, I think the future holds a lot of potential, and collaboration will be the key for us taking full advantage of it.

When you speak to the public, how do you make them interested and inspired by GRNs?

I've been doing some outreach to schools with young teenagers and adults, and I try to base my talk on what they know, to relate to their experiences, their bodies, their development. They know that human babies develop from embryos, so I show them pictures of both human and sea urchin embryos so they can observe the similarities themselves. I want them to be amazed by what they see, so they'll want to learn more! When introducing concepts like "what is differential gene expression?" I make the links with their own bodies – they know that they have different cell types – muscles, bones, neurons, so I ask them: how did all these cell emerge from only one cell, the egg? I try to make them think about it and see the wonder in it. I explain to them that the genes in the DNA encode the proteins, and only a few of these proteins are cells specific, and I ask them: How do the cells know which genes to activate? Then I show one gene and the transcription factor that activates it, and I ask: How does the transcription factor knows to be expressed in this cell? This is the concept of gene regulatory networks that exist in all living things.

I think that when we build this understanding step by step we can explain quite sophisticated biological concepts and amaze the audience with the principle underlying natural phenomena. Once they understand the basic ideas, I show them images of our own research. The thing that always blow my audience's mind is that we can rescue the knock-down of sea urchin genes with human genes. This is the best demonstration that learning about sea urchins is really



Extract from a presentation for high school students in Haifa

learning about ourselves, which makes all these comparisons more relatable. I try to give them a glimpse of the natural phenomena that we study and of some of the building blocks of biological regulation, and most of all I try to make them curious about it. I also try to get across the importance of model systems and using them to understand human health better.

I enjoy talking to the public very much now, but it took me a long time to develop these scientific communication skills. When I started doing talks to the public in 2004 it was a disaster, and it took a lot of work and feedback from people to get better. I think this is part of our job as scientists, to reach out and educate the public. We're given money to do research and we should be giving back to the community in this way, sharing what we learn.

Do you have an advice for young researchers contemplating a career in cell, developmental, and marine biology?

The most important thing is to know yourself. It's hard to know what you're going to want to be in the future, so you need to pay attention to what you feel now, when you're doing things. Ask yourself "do I enjoy what I do? What parts of what I do are really exciting to me, when do I feel good about my work?", and listen to your own answers. Failures and everyday struggles are a part of life as a scientist. Scientists never feel like they're good enough and having self-doubt is normal, that's why we work so hard to make discoveries: we're not satisfied with what we already have in terms of knowledge.

So if you're sad when you fail, but you can dust yourself off and get back up and say to yourself "ok now I'll try and do it better" and you're still enthusiastic and happy to learn... if you're excited when the experiment goes well and you discover something, and you can't stop thinking about it in the morning and when going to bed... then you're probably in the right place! This was the "know yourself" part, now about the "trust yourself": Eric always said "follow your nose" and I think it is excellent advice. If you really want to understand something and you can't stop thinking about it – just follow your nose!

You can see Smadar's GRD lab website here: https://sites.google.com/marsci.haifa.ac.il/grd-lab/

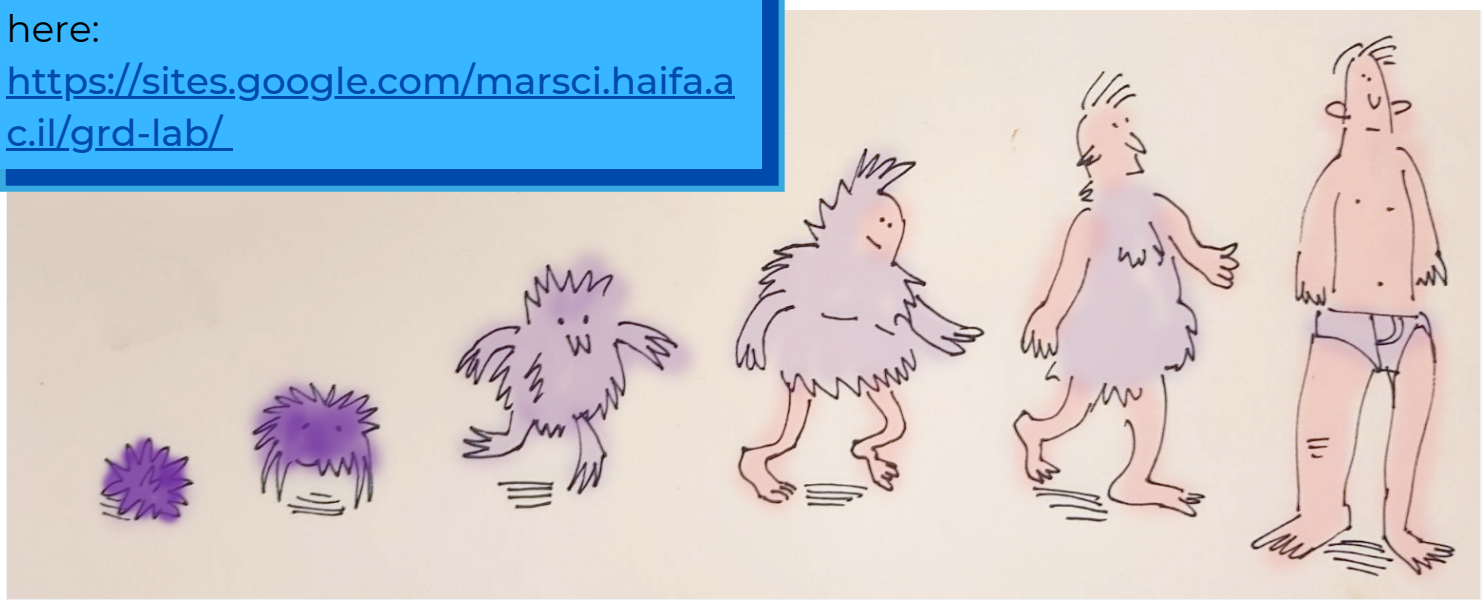


Illustration by Yarden Ben-Tabou de-Leon