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SPOTLIGHT

An interview with Mike Levine

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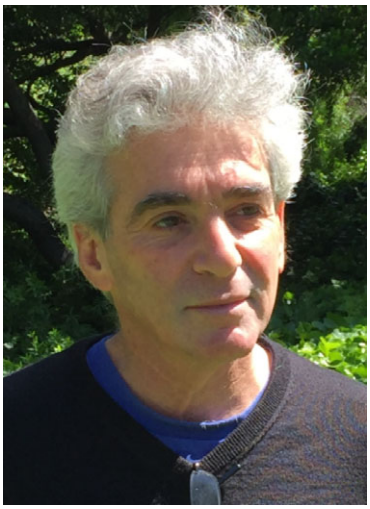
Mike Levine, director of the Lewis-Sigler Institute for Integrative Genomics at Princeton University, is a developmental biologist who has dedicated his career to understanding how gene expression is regulated during development. Some of his most significant research, such as the co-discovery of the homeobox genes and his work on *even skipped stripe 2*, was performed in *Drosophila*, but he has since branched out to *Ciona intestinalis*, which he is using as a model to understand how vertebrate features have evolved. We had a lively chat with Mike at this year's Society for Developmental Biology (SDB) meeting, where he was awarded the Edwin Grant Conklin Medal.



Here at the SDB meeting you will be awarded the Conklin Medal by the society. What does it mean to you to receive this prize?

It is a really special honour for me, for a number of reasons. First, the list of people who got it before me is pretty awesome, so I am very proud to be among them. People like John Gurdon, Nicole LeDouarin, and some of my friends and peers like Richard Harland, Cliff Tabin, Marianne Bronner… The other reason why this award is special for me is because Conklin did his lineage-tracing studies in sea squirts, and half my lab has worked on this model system for 20 years. To my knowledge, I am only the second sea squirt guy to get the Conklin Medal, after my good friend Nori(yuki) Satoh. For those of us who work on the same material that Conklin himself studied, this is a very special honour. He was always one of my scientific heroes.

You were SDB president a few years ago. What do you think is the role of the society?

A field of study is only as good as its smartest young people. I think it is important for the society to reach out to the young, talented stem cell, computational and genomics researchers and say: 'Hey, this is a really cool field of study'. We have one advantage over most other fields: we work on intrinsically beautiful material. What is more beautiful than a developing embryo? I remember when I was an undergraduate seeing for the first time movies of developing chick and frog embryos and I was just mesmerised. I just thought: 'Oh man, that is what I want to study'. And it is not only visual, it is a highly integrated science. It really pulls together so many different disciplines. We have a lot to offer to the next generations of discoverers, and the SDB needs to reel these young men and women in.

How did you first become interested in biology? I understand that you considered becoming a medical doctor...

I always had an interest in the life sciences, and enjoyed going to my backyard to dissect bugs with my little microscope. I came from a blue-collar family, so if you were good at biology, which I was, it was only logical that you should become a doctor and make some money. For a modest Jewish family, being a doctor is a big escalation in status. I tried to be a good boy and even took the medical school admissions test and went to a couple of interviews, but it really was not for me. I have always been a hypochondriac, so I can't even imagine how many times I would have tested my own urine and blood for whatever disease I was learning about! So I had this 'going to medical school' thing hanging over me during my undergraduate studies, but I was lucky to discover the wonderful world of biological research.

It was really hard in Berkeley to find a lab where you can do research as an undergraduate. Fortunately, I had an amazing stroke of luck to get to work in Allan Wilson's lab. He and Mary-Claire King had proposed that regulatory DNAs were really important in evolution and in distinguishing chimps and humans, and this definitely infiltrated my thinking.

During your scientific career you have examined how gene regulation is controlled. What excites you about this topic and why did you choose *Drosophila* as a model?

I love gene regulation. I love the process of transcription so much that I regard RNA as an unfortunate by-product of an otherwise elegant process! I think part of it is that when I was an undergraduate I must have learned about the *lac* operon in three different classes: genetics, molecular biology and protein biochemistry. It is an inherently beautiful mechanism. Who would have thought that a bacterium exposed to sugar would deploy this elaborate and elegant transcriptional response? The developmental biology classes by Fred Wilt also really stayed with me. So I had a strong sense that gene regulation was a cool process from my undergraduate studies. This was reinforced by my undergraduate research in Allan Wilson's lab. There they were talking about regulatory DNA, but instead of bacteria they were looking at animal cells.

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I first became interested in flies because of a *Scientific American* article written in 1975 by the Swiss molecular geneticist Ernst Hadorn on transdetermination. He took wing imaginal discs out of larvae and cultured them in the stomachs of recipient flies, so they proliferated for longer than they normally would. He then grafted these discs back into a recipient larva that underwent metamorphosis, and found that sometimes the grafted tissue didn't become the original structure that it was slated for, but the whole thing transformed into a leg. I thought that was a really exciting discovery. Later on, I read about the homeotic mutants that Tom Kaufman and Ed Lewis were working on and figured: 'It has got to be gene regulation, and it has got to be in flies'.

As you mentioned earlier, part of your lab now works on *Ciona*. Why this organism?

I was co-director of the embryology course at Woods Hole for a few years, and this gave me the chance to get exposed to a lot of different systems in developmental biology. When I heard Richard Whittaker and Nori Satoh talk about *Ciona*, I immediately loved the system. I don't know if it triggered recollections about Conklin's work, which I had been taught about as an undergraduate, but I just liked the simplicity. Embryogenesis is amazingly complex, and I really don't think in 3D so well. But when I heard Whittaker and Satoh discuss *Ciona*, where the movements are not that complex, I thought: 'This is a system I can understand'.

Our fly studies have always been pretty abstract, studying gene regulation but never connecting it to morphogenesis. I always thought we should be able to link the two, but at least for me it seemed hopeless to try it in flies. There are so many cells, the processes are complex and occur very late in development. But I thought *Ciona* might be a good place to attempt this and complement our fly studies. The thinking was: 'Let us extend our studies from gene regulation in *Drosophila* to a model organism in which we can study gene regulation and the connection to cellular morphogenesis in development'.

Bob Zeller, who trained with Eric Davidson studying sea urchins but had done undergraduate work in sea squirts, came to my lab as a postdoc to set up this system. I thought we were nearing the end of the line with the flies, so the plan was to wind down and eventually just convert completely to sea squirts. But every time I think I am going to drop the flies, I just can't. I like sea squirts, don't get me wrong, but I am really a fly guy. I feel like Michael Corleone in *The Godfather III*: "Every time I try to get out, they keep pulling me back". The early fly embryo is the sweetest system in the world for looking at gene activity in development. The last 10 years have been dominated by fantastic new technologies, such as single-molecule live imaging, and these just work like a charm in the early fly embryo. So I can't leave it!

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You did your postdoc with Walter Gehring at the University of Basel. How did your time there influence your career?

Where do I begin in describing my 15 months in Basel? Culturally, it was a defining experience for me. I had never been a political person. But in Basel people would stay up drinking and discussing politics, and I learned that not everyone agreed with American policy. I had never realised how parochial my experience was until I went there, so it was really eye opening and gave me a broader perspective. There was also a special camaraderie that I had never experienced before. Ah, and Europe! I had never been to Europe before, and it is like a giant museum, with its cathedrals and art… It was truly a mind-blowing, defining experience.

As for the lab, it was a hot and cold experience. The hot part was that I met some of my best friends and collaborators, like Markus Noll, Erich Frei, Bill McGinnis and Ernst Hafen. Also on the good side, everything I have done with *Drosophila* for the ensuing 30 years was a direct consequence of my time in Basel working on gene expression in the fly embryo. Unfortunately, Walter and I just didn't get along, so I eventually had to leave. But as difficult as my personal relationship was with Walter, I would probably do it again, because I got an enormous amount from the experience, both culturally and scientifically.

What would you consider to be your most important discovery?

The work I did with McGinnis and Hafen on homeobox genes was pretty good, but I don't like to think I did my best stuff in those 15 months as a postdoc. I think that I am proudest of my work on *eve* stripe 2. The project was launched by a student named Dusan Stanojevic who was very mercurial, very high maintenance, but absolutely brilliant. When he started the project he said: "This is going to be the *lac* operon and the lambda switch of developmental biology!". At the time I thought he was cracked, but 25 years or so later I would say that there is something to it! Our work on *eve* stripe 2 was less a single discovery than a war of attrition. It took 3 to 4 years of really hard work, doing DNA binding assays, targeted mutagenesis and transgenesis, which were harder methods then than they are now. Some amazingly talented scientists, including Tim Hoey and Steve Small, worked through that problem.

Which scientific questions would you like to tackle in the future?

TA few years ago Delsuc et al. (2006) showed that the urochordates (which include sea squirts) and not the cephalochordates, as most text books still say, are the closest living sister group to the vertebrates. This paper has been extremely influential in our thinking because it means that if you are interested in understanding the evolutionary origin of some of the major vertebrate innovations, such as the neural crest, neurogenic placodes and second heart field, *Ciona* tadpoles are a good place to look. Of course *Ciona* doesn't have a neural crest, but it does have a cell type with some of the properties of neural crest. We also found that *Ciona* tadpoles have neurogenic proto-placodes, another feature of the vertebrate head.

On the fly side I am very excited about the use of single-molecule live imaging. One of the big benefits of my recent move to Princeton is the close proximity to two of my favourite young *Drosophila* collaborators: Thomas Gregor, a physicist who does live imaging in the fly embryo, and Stanislav Shvartsman, a chemical engineer studying signalling in fly eggs and embryos. Collaborating with these two labs is going to invigorate our studies. One line of research that I am most excited about is visualising enhancer-promoter communication directly. The human genome is just riddled with hundreds of thousands of enhancers. In other words, a typical gene in the human genome is regulated by up to 50 different enhancers. So all of a sudden you have to worry about trafficking: how do the right enhancers get to the right promoters at the right time? For all we know, this could be the rate-limiting determinant in the

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patterning of the *Drosophila* embryo. Thomas is devising strategies for directly visualising the interaction of remote enhancers with promoters in living embryos during key patterning events. That is very exciting.

You mentioned that you have moved to Princeton, where you are now the director of the Lewis-Sigler Institute for Integrative Genomics. What are you hoping to achieve in this new position?

The Lewis-Sigler is called a genomics institute but it really started as a systems biology institute, initially led by Shirley Tilghman and then David Botstein. Botstein was the first person I heard explain properly what systems biology is and the concept really turned me on. Systems biology is the systematic identification of every component of a complex process. You need the experimentalists to generate the big data, the computer scientists to handle the big datasets, and then quantitative biologists to model these datasets so that you can understand emerging properties of the process. I can know everything about a neuron in the neocortex but if I multiply that by a million I am not going to learn how consciousness works. You have to do something different. This is the philosophy of systems biology and I still believe in it. The Lewis-Sigler institute is like a scientific Noah's Ark: it has a couple of computer scientists, a couple of high-throughput biologists, a couple of physicists, a couple of engineers. It is just the right mix of talents for systems biology, so I see no need to deviate from Botstein and Tilghman's original vision. I just want to have some fun, and bring people together towards this enterprise of trying to learn the emerging properties of really complex processes, like the patterning of the fly embryo. I think there are wonderful challenges and opportunities, and with these new technologies we can take systems biology into the new millennium.

What is your approach to running a successful lab?

The alumni of my lab are an amazing group of people, and so many of them run their own labs now. I would love to take credit for it but, believe me, they came in pretty good! I have a reputation of being pretty demanding, a pretty tough boss. I have in me a bit of my Jewish uncle, who fought in World War II and had this warmth on the one hand and this tough 'you are not quite good enough' on the other hand. And I think I do a little bit of that in the lab.

I aim to keep my lab members excited about their project. I try to constantly look at the big picture and, if I have an idea, I try to give it to them when I am at my most enthusiastic. They might tell you that I am tough, but I hope they'll also tell you that I do love science. It's like with sports people getting towards the end of their careers: when you ask them what keeps them going they all say the same thing – they love the process. They like getting up in the morning, working out, training, they like the banter in the locker room. I really enjoy the process too. I like going in to the lab. I think whatever influence I have had in helping my lab members has been my enthusiasm for the process.

What is your advice for young scientists?

It is much harder now to find an identity for yourself in science. I was in the right place at the right time, I admit it. I got a great job when I was young and the field was wide open. It is much more crowded now. The whole 'follow your passion and everything will work out' may have been true 20-30 years ago, but it is not as true now. My hard-nosed advice to young scientists who want to continue being scientists (and you can do this in many capacities, it doesn't have to be as the PI of a lab) is to learn technology. Go to a graduate programme or do a postdoc where you have access to the cutting-edge technologies. When I was a postdoc in the Gehring lab, Ernst Hafen and I helped develop the first *in situ* hybridisation methods with fixed tissues and I think it was that method that really got me a job. When you know a good technology, people are interested in it, even if they are not interested in the specific process you are working on. You increase your value. Discovery depends on technology now more than it ever did. The old guys did the easy stuff: we pillaged the low-hanging fruit a long time ago. I do believe the best is yet to come, but it requires technology. I would advocate imaging or genomics, or, best of all, somewhere in between! I also relate what I heard from many people over the years, including James Watson: "Don't go straight up the middle in an established discipline. The action is at the cusps". I think that is also very good advice.

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What would people be surprised to find out about you?

There is the perception that I am a bit of an eccentric, and I think that even the people in my lab would be surprised to see how ordinary my private life really is. I am a family man, and I enjoy a tightknit relationship with my wife and two sons. We enjoy conventional suburban pleasures, such as going to the movies.

To hear Mike give his account of when he almost set one of his postdocs on fire have a listen to the audio file available online at
http://dev.biologists.org/lookup/suppl/doi:10.1242/dev.130609/-/DC1

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