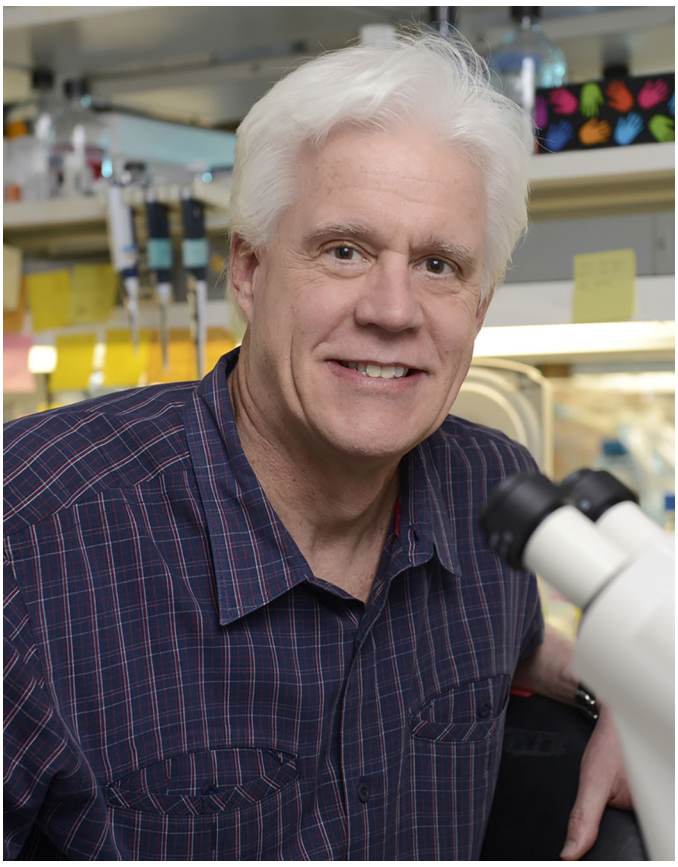
© 2020. Published by The Company of Biologists Ltd | Development (2020) 147, dev188854. doi:10.1242/dev.188854

INTERVIEW

An interview with Eric Olson

Alex Eve*,‡

Eric Olson is Professor and Chair of Molecular Biology at the University of Texas Southwestern Medical Center, USA, where he holds the Robert A. Welch Distinguished Chair in Science, the Annie and Willie Nelson Professorship in Stem Cell Research and the Pogue Distinguished Chair in Research in Cardiac Birth Defects. In 1999, he was elected to the US National Academy of Sciences and, in 2001, to the Institute of Medicine of the National Academy. He has received several awards, including the American Heart Association Research Achievement Award in 2008 and the Eugene Braunwald Academic Mentorship award in 2016. He has a lifelong interest in muscle development and disease, with a particular interest in Duchenne muscular dystrophy. In this interview, conducted at the Society for Developmental Biology's 2019 meeting in Boston, Massachusetts, USA, he discusses his experiences in academia and industry, as well as reflecting on the people and opportunities that contributed to his career.



Let's start at the beginning: when did you first become interested in science?

I was always interested in science. Even in grade school, I would go to the library after class and gravitate towards the science books, and read about space exploration and nature. So, I never doubted that I would pursue a career in science, but I didn't know at that stage what form it would take.

You pursued that interest by attending Wake Forest University. What contributed to your decision to go there?

Yes, I grew up in North Carolina next to the Wake Forest campus. It's a very good liberal arts school. I was interested in getting a liberal arts education, which would expose me to diverse areas, not only science but language and philosophy. I majored in both chemistry and biology because I wasn't sure in which specific direction of science I wanted to go. I decided to cover my bases and major in both.

I stayed there for my PhD work and, at that time, I thought about what I might ultimately want to do. I thought I would want to pursue a career in research, probably on a university campus. I was interested in muscle because it's the largest tissue in the body, controls all activities of life and is the source of many of mankind's most devastating diseases. I thought if I could establish a knowledge of muscle, I could ultimately apply it someday to try to understand muscle disease – one of the biggest challenges for medicine. That was in the early days before molecular biology, so no genes had been cloned and no transcription factors had been discovered at that point. I started to study muscle membranes and it turned out, interestingly, that almost 40 years later my lab discovered two key muscle membrane proteins, named Myomaker and Myomixer, that control myoblast fusion and muscle formation. I always had a feeling in the back of my mind that the biology of muscle membranes would come back later on. I've been back to Wake Forest many times to receive various alumni awards and to teach students, so I am still closely connected. It played a big role in my career development and I have a great debt of gratitude to that university.

After receiving your doctorate, you then moved to Washington University in St. Louis. What drew you to go there and what was your research focus?

Luis Glaser was a distinguished biochemist there. He wasn't a molecular biologist but I was interested in work he had done on cell-cell interactions. I just wanted to go to a new environment – and it was a much bigger, more intense environment than I was used to – but I knew I had leave the comfort of Wake Forest and North Carolina. At Washington University in St. Louis, I studied another problem in muscle biology: how the acetylcholine receptor gets assembled in the muscle membrane. I forged a close collaboration with John Merlie, a great role model and muscle biologist. That was at the dawn of molecular biology and no one in the Glaser laboratory

*Reviews Editor, Development

‡Author for correspondence (alex.eve@biologists.com)

A.E., 0000-0003-3577-4324

Development (2020) 147, dev188854. doi:10.1242/dev.188854

was doing any molecular biology, but I wanted to learn it. So I purchased the cloning manual, which became the bible for molecular biology. I taught myself the fundamentals of how to do DNA cloning, hybridisation, etc. It was a big challenge because no one was doing that kind of work there, so I just kind of had to figure it out and wing it.

After that, I applied for some faculty positions. I got a position at the MD Anderson Cancer Center in Houston. When I went there, I decided to try to move into the realm of the molecular biology of muscle development and gene regulation. I was really fortunate at that time; I attracted a group of amazing students and postdocs who bet their careers on coming to work with an unknown guy, in a small lab in Texas. Together, we discovered many of the transcription factors and mechanisms of muscle development. It was a very exciting period in my career, both because it was the early days of molecular biology and the muscle field was really becoming the centrepiece for understanding how cell fates are specified, and how genes can be turned on and turned off. We were right in the middle of that.

In 1995, you founded the Department of Molecular Biology at The University of Texas Southwestern Medical Center (UTSW). What did you set out to create with this new department?

I rose to chair of Biochemistry and Molecular Biology at MD Anderson and I was chair there for several years – I enjoyed that position – but I wanted to do something new. I wanted to create something completely from scratch and I was offered an opportunity at UTSW to launch a new Department of Molecular Biology. I thought that was a great challenge and we moved there with my team – my whole group moved with me – and started the department. It's been great! Now the department is mature it has 18 faculty members: senior, junior and mid-career people. I wanted to create an environment that would be interactive, supportive, fun and collegial – collegiality is a big thing for me. I like to celebrate the success of everyone. I wanted to provide an environment where the only limit people would have would be their imagination: I would provide the resources and the infrastructure. It's been one of the most rewarding things I've had the privilege of doing.

What did you learn from this experience?

There are a lot of ways to lead, or to build an organisation. I see myself as a facilitator or an enabler, to create the environment that lets people rise to their highest level and flourish. I'm not a top-down, dictatorial leader; I'm more leading from behind and allowing people to find their success. Everyone has their own leadership style, but that's what I learned and I think that's reflected in the people in my lab and our department. We enjoy being around each other: we celebrate and we have very open interactions in a supportive environment.

I see myself as a facilitator or an enabler, to create the environment that lets people rise to their highest level and flourish.

You have also been involved with a number of biotech companies during your career. What were the biggest challenges in industry and how does the environment compare with academia?

I never set out to start a company, I just wanted to do science and follow where it led. The work we were doing to understand developmental mechanisms in muscle and heart was leading towards understanding muscle diseases – it seemed like there was a path in that direction. I didn't know anything about business or company building or therapeutic development but I felt, I'm just going to do this! What do I have to lose? What do I have to fear? Even if it doesn't work, it's a positive because I get to learn something from it. So, together with two friends, Mike Bristow and Leslie Leinwand, we started a company, which was called Myogen, and some key people from my lab went there to help establish the science that grew out of my lab.

Biotech and academia are extremely different. Academia is all about pursuing ideas at the outer envelope of knowledge and is a little bit of organised chaos: there are students and postdocs who often don't know what they're doing, and you've got to just let them explore and make mistakes. Biotech is completely different: you're working against the clock, and you're working against the money in the bank that you're spending down. You've got be focussed and you've got to have a plan, so I really learned a lot about that from Myogen.

I wanted to do it again if the opportunity arose. At that time our work had moved into the biology of microRNAs in heart and skeletal muscle development and disease. I thought this would be a good time to start a company to translate this work, so I started miRagen Therapeutics. Again, the key people from my lab that made the discoveries went to the company as pioneers to set it up. That company grew and expanded and it's been great! It has multiple clinical trials now for various microRNA drugs – which is extremely gratifying.

In 2017, your lab developed a CRISPR/Cas9 therapy for treating muscular dystrophy in beagles. What is the story behind that work?

I started Myogen and miRagen with some other cofounders, but then I felt like I really knew how to do things and I wanted to see if I could do one by myself. But, you don't just start a company, you've got to have a really strong reason to do it. I'd had Duchenne muscular dystrophy (DMD) in the back of my mind for a long time and we had dabbled with it in the lab, but not in a serious way. DMD, which is caused by the absence of dystrophin, a muscle structural protein, is the most devastating of all muscle diseases. When gene-editing technology came to the fore, we started thinking about how we might apply this to something that we know about, and that is muscle disease. I started thinking, how could we turn this technology upside-down? Everybody was using CRISPR to knock out genes and I thought, what if we used CRISPR to turn on a dead gene – in DMD, the dystrophin gene is not functional – what if we snip out the mutation with CRISPR, could the gene be resurrected? It seemed like a good idea.

Around that time I met a young man in my neighbourhood named Ben. He has muscular dystrophy and he was a real inspiration for me and for my lab – he came to the lab – a very, very inspiring young man. We obtained some blood cells from him, converted them into cardiomyocytes through iPSC technology and we tested our single-cut CRISPR idea in his cells and, low and behold, it could restore dystrophin production in his own cells. One of the most inspiring moments of my career was when Ben came to the lab and we were looking through the microscope at his own heart cells beating, and they were making dystrophin protein that his body couldn't make. We call him our patient zero.

Then we started receiving emails from mothers from around the world telling us about their sons with DMD; telling us about their mutations, asking if they could be corrected, in principle, with CRISPR. We collected blood cells from patients, converted them to cardiomyocytes and tried to correct them. Using CRISPR, we

Development (2020) 147, dev188854. doi:10.1242/dev.188854

also recreated human mutations and tested them that way and it worked. Next, we made mice that had some of the most common mutations responsible for DMD and those mice had muscular dystrophy. We successfully corrected the disease in the mice with a single dose of adeno-associated virus (AAV) loaded with CRISPR and we published that work – it was an important paper.

I thought this had potential, but I wasn't ready to start a company because I was concerned it was too big of a problem – it may not work. If we could apply this to a large animal, and if it could work, it would give us some confidence that maybe this could be translated, even knowing all the challenges. So, we identified a certain pedigree of dogs, beagles, from the Royal Veterinary College in London. These dogs have the same type of mutation that is the most common mutation in boys with DMD, and the mutation we had just corrected in mice and in human cells. We engineered the virus, went to London and we treated the dogs. We initially started with intramuscular injection and that worked – it could restore dystrophin production. Then we did it systemically and restored dystrophin production throughout the whole body, including the diaphragm and the heart, and restored ambulation to these dogs. It was incredible. The day we saw that result, it brought tears to my eyes and all the other people, they just couldn't believe what they were seeing.

It wasn't even an option anymore not to start a company. I just felt this had to go forward. Even knowing all the challenges, as I had started other companies before, I knew by that point how to orchestrate this. I joined forces, initially, with a patient advocacy group called CureDuchenne and they raised money that enabled us to do the dog study and start the company called Exonics Therapeutics. When the dog study worked, we obtained a very large-fund investment to really take the company to the next level. Ultimately, Exonics was acquired by Vertex Pharmaceuticals, a fabulous company with the knowledge and wherewithal to move this technology forward in the most effective manner possible. My next goal is to take this all the way: first, make sure it's safe and then try and apply this technology to the boys that need it. I am determined to do this!

You've since investigated aspects of regeneration, therapy and disease. How do you think fundamental developmental biology contributes to these fields?

I am a developmental biologist at heart and I've tried to apply the principles of developmental biology to understand muscle and how it forms and functions. Developmental biology, at its heart (no pun intended), is understanding mechanisms: how genes interact, how they orchestrate complex mechanisms and behaviours, and how those processes go awry in diseases. So, yes, I think our efforts in developing new therapies for muscle diseases have been highly informed from our studies of muscle development and gene regulation.

And what are the remaining 'big questions' for the field as a whole?

Lots of questions! Beyond skeletal muscle, the heart is still a huge area of unmet medical need. As everyone knows, heart disease is the number one killer. We are working a lot on mechanisms of heart regeneration. A few years ago, we published an influential paper showing that the newborn mouse heart can regenerate whereas the adult heart cannot regenerate, so we're trying to uncover the mechanisms that drive neonatal regeneration and harness them for adult regeneration. That's a big challenge but it is a really interesting area of developmental biology that's right at the interface of medicine. One of my former postdocs, Deepak Srivastava, myself and some of his colleagues in San Francisco cofounded a biotech company called Tenaya Therapeutics, and they're working to use developmental transcription factors and other mechanisms to drive heart repair and regeneration. I think that's a really exciting area.

In 2016 you received the Eugene Braunwald Mentorship Award. Do you consider mentorship an important part of your role as a group leader?

Mentorship has been a huge part of my career. I immerse myself completely in the experience with my trainees and forge lifelong relationships with them. There have been more than a hundred students and postdocs from my group that have gone on to be really successful in science, so I find that to be very gratifying. It was an aspect of science that I didn't anticipate in the beginning, but it's one that I've found to be probably the most long-lasting aspect of my career.

What advice do you give to members in your lab? About science, careers or life in general?

I give them a lot of advice! I guess I would say: think big, don't fear failure, keep moving forward, enjoy science – it's a great privilege to do science. You hear a lot of senior scientists complaining about writing grants and those kind of things but, at the end of the day, it's an incredible honour to be able to do science, to have no boss, to explore your own instincts. There is a lot of public trust, the public are handing over money with the faith that we know what we're doing and will use it wisely to pursue important questions.

This year you have been awarded the Society for Developmental Biology's Edwin Grant Conklin Medal, which honours a society member who has performed distinguished and sustained research in developmental biology. What does this award mean to you?

To me, the award represents the combined efforts of the many trainees I was so fortunate to have in my lab and the body of work they created. The award also represents the seminal contributions of the previous recipients of the Conklin Medal, many of my heroes in developmental biology. I am honoured to have my name added to the bottom of the list.

To me, the award represents the combined efforts of the many trainees I was so fortunate to have in my lab and the body of work they created.

And what do you consider your own personal greatest achievement?

What gives me the greatest satisfaction is the body of work we've produced that spans three decades – I think it's a solid body of work that will stand the test of time – and the many people I have had the privilege to work together with as a team effort. It is extremely gratifying to be part of something bigger than oneself. It's not all about me, I'm just part of it, I just happen to be fortunate enough to enable a lot of stuff to happen.

You received the Annie and Willie Nelson Professorship in Stem Cell Research. Can you tell us how that came about?

One of my musical idols was Willie Nelson. He's a nonconformist, independent, freethinking, iconic musician – the most iconic Texan

Development (2020) 147, dev188854. doi:10.1242/dev.188854

for sure! I admired him from afar for a long time. But, I never thought I'd ever meet him.

I played various instruments throughout my life and always wanted to play in a rock band. It was a life fantasy! I was approaching 50 and thinking, well I'm not getting any younger – if I'm going to get in to a rock band, it looks like I'll have to start one. So, I identified some guys in my department and around campus that were really good musicians, and we had the same musical taste, so we started a band. I named it The Transactivators – not many non-scientists understand what that means, but most scientists get it. We have played all over Dallas and in many other cities, mostly rock and roll and a little country music.

One day, Willie Nelson's wife, Annie, brought their two young sons to UTSW for a medical check-up. The President's Office knew I was in a band and that I was interested in music, probably more so than anyone else around the school, so they asked whether I would have lunch with Annie and the kids – and I said 'heck yeah'! So, we had lunch and I told Annie about what we're doing in the lab and she got really interested – she's a very smart, engaging lady. She said, 'This is awesome. We're going to get Willie to do a benefit concert for your research.' So, he did a concert and raised some money – he's very interested in charitable causes, raising a lot of money for farms, all kinds of causes. Then, they created the Annie and Willie Nelson Professorship. I got to know Annie quite well. I have visited Annie and Willie at their ranch, and have gone backstage with him many times at concerts.

What was it like to meet him in person?

It was exhilarating the first time I met him. He travels around on a famous bus called the Honeysuckle Rose and I've spent some time with him on the bus. He's autographed the guitar that hangs outside my office. It's become kind of the 'touchstone' of my department – everyone likes to come and see it. It's just a unique set of experiences that connected us and reinforced this notion that you never know where this career can lead. Be open to new opportunities and keep following them, and sometimes good things happen.

Finally, is there anything Development readers would be surprised to find out about you?

Can anything top being in a rock band?!