Q & A with Eric Wieschaus

An interview with CMM correspondent Daniel Gorelick

In February I sat down with Nobel Laureate and Howard Hughes Investigator Eric Wieschaus, an unassuming Princeton professor who, along with Christiane Nusslein-Volhard, performed the first systematic saturation mutagenesis screen in Drosophila. For those of you that don't remember Fundamentals of Genetics class, Professor Wieschaus discovered many of the genes that regulate embryonic development. The Lord of the Flies spoke passionately about everything from the ten day Nobel party in Sweden to his thoughts on working in Europe. His youthful ebulliance and insouciant humility engaged me for some time. What follows is an excerpt from our interview.

Q: You started graduate school saying "after three years of washing fly bottles [as an undergraduate] at Notre Dame, I never wanted to see another fly, much less work on flies for my thesis." In an interview after winning the Nobel Prize, you said you plan to devote your entire career to studying fruit-flies and all they offer to genetics and that "you can't beat flies."

That's true. I probably said both those things. I guess your question is how or what changed between entering graduate school and the Nobel Prize award. Ok. I think, what I—when I went to graduate school I didn't see myself as a geneticist, I saw myself as an embryologist. I saw myself as spending the rest of my life, or my scientific life, trying to understand how embryos develop. At the time people used chick embryos, frog embryos, sea urchin embryos because those embryos were easily available and because when you looked at them you could see these spectacular morphogenetic movements that happen in embryos. Even though everybody was aware that almost everything that a cell did depended on proteins and also depended on the genes that they made and everybody was in principle aware that it would be great to be able to apply genetics to understand embryonic development…it had never occurred to me that you would be able to do that with a traditional genetic organism like flies. I think at the time when I entered graduate school, and I've actually said this also on occasion, I didn't even know that flies had embryos. I don't know where I thought they came from but I—certainly it was not part of an undergraduate curriculum to study embryonic development. That's why I had no idea when I entered graduate school, that if you looked at the fly embryo, if you looked at the blastula stage, if you looked at gastrulation, seeing the same problems with it, the same visual impact, the same remarkable processes were still, were happening in a fly embryo just as much as they were happening in the sea urchin and the frog.

Q: So, you'd say you were studying flies as a means to an end, not as an end in itself.

Yeah, I think that's what anybody does in science, I think you study things—I mean everything that you do is a means to an end. I suppose the question is 'what is the end?' The end is probably to understand how things happen, how anything happens, how a cell moves, how an embryo develops…Most scientists are driven by the idea, or at least trick themselves into believing, that there's some generality behind what they do or what they're looking at. So you look at a fly embryo and you believe that if you understood

how a fly embryo developed you'd understand…something about how a human embryo developed or how any embryo developed. You'd understand something of more general importance…though the basis for the generality isn't always predictable. Meaning, if you really know something, if you've really done an experiment and it worked and you've learned something—that knowledge will inevitably have impacts in the generality beyond the specifics of the experiment that you did. But often you don't know, even when you've done the experiment, what that generality is, or what the impact is. I think it's very hard to plan your experiments to have a great generalizable impact. But I think that almost anything—to know anything with some level of certainty, to know anything with a scientific certainty, is almost enough to insure that it will have an impact beyond the specifics of what you know. So, that's true for flies and fly embryos as well.

Q: But when you were planning your 1980 mutant screen, you weren't thinking at all about how this will be generalized in a huge way? Did you know the significance—

Gosh, it's always hard to reconstruct in your mind how you do experiments, or what it is that you thought, particularly twenty years later, what it is that you thought when you were doing those experiments. It's safe to say that neither Janni Nusslein-Volhard or I anticipated the full impact of those experiments. Usually when you're doing experiments, though, you kind of know whether they're working or not. And you kind of—part of that working, part of that decision or criteria for working is that you know it's not, you're not just getting the data but that you can see that this is cool, that this is exciting, that you're learning things and thinking thoughts that you hadn't thought before, and that you could—that these are interesting enough that you could run out into the hall and tell somebody else about it and even if they weren't working in that field—but you imagine that if they were a reasonable scientist they would be excited about it as well. And so I think that certainly at the time when we were doing the experiments we didn't understand their full impact but we certainly knew that they were cool, and that they were working, and that it was exciting.

Q: You knew this was going to *Nature* or *Science*. I mean, this was big, right?

Not nescessarily when we did it. I mean that wasn't quite how we thought of it. You know, part of the issue of whether something goes to *Nature* or *Science* is the scale, and whether you can trim it into a scale that will fit into a *Nature* or *Science* format. So often you do experiments, you know that they're really important, even if you don't know where you're going to be able to publish them or how you're actually going to be able to publish them. I think it's a bad idea to approach the question of publishing too early…because it depends on so many contingencies outside and politics and just artistic aesthetic considerations…What is the way, the appropriate way, to package an experiment for a science editor, for the scientific community? In doing an experiment you realize that things have gelled into a pattern where there is a simple story, where you can write something for the general readers of *Nature* or *Science*. You have to have a relatively simple story, and those simple stories often gel out of a set of experiments that you have and—suddenly there it is, all gelled together and you see the story. You can't really predict where you can publish something. You can, though, predict sometimes that

something will have an impact, that it is great, and that it is central to the field even if you don't know that you're going to publish it in *Science* or *Nature*.

Q: How much do you think your work did to pluck the fly from the stocks of genetic obscurity?

I think it is true that the success of those experiments, and their long range and unforeseen impact on areas as diverse as neurobiology or cell biology or the whole—their success in illustrating how you could use genetics, a combination of genetics and molecular biology and everything else it's possible to do in flies to study development, that success clearly pointed the way to say, 'well, if you can do that with embryonic development you ought to be able to do that with neurobiology, you ought to be able to do that with the cytoskeleton, you ought to be able to do that with just about anything, any biological problem.' And that's actually what I believe is the central contribution right now of flies to biology—is that it's an animal, a functional, living animal in which you can study genes in the context of their normal function. You can study processes, you can get a genetic handle on how processes work. It's a real animal, and that as we begin in this century to approach the more complex problems of life on earth it seems to me that we want a real animal, we want something…we want to study a process the way it actually is, the way it actually happens, the way it is actually regulated. You want to be able to understand the molecules, you want to be able to understand the biochemistry, but you want to understand those in the context of a real animal. And flies are a real animal and they're probably the favorite choice of a real animal right now…in part because those experiments demonstrated how easy it was to deal with flies, how easy it was to do those experiments with flies. I think that that's the thing. If it weren't easy…there's no reason to do these with flies. But because flies are so easy to do any of these things with, it makes them really attractive. If you want to go into the lab in the morning and discover something by the afternoon, it's hard to imagine how you can do that in any other animal. Oh, there are other animals you could do it, as well, but flies are really great in that respect.

Q: That's quite a fondness for flies.

Oh, well, not really. It's a fondness for success.

Q: So if you were eating dinner, and a fly was buzzing around, you'd have no qualms about killing it.

Oh absolutely not, no. I mean you have qualms about killing any animal, in reality. And you don't normally go off and kill animals that aren't buzzing, you know, that aren't really bothering you. It is true that sitting out at a picnic a *Drosophila* buzzing around wouldn't bother me as much as a housefly. I would probably want to kill that housefly more than I would want to kill that little *Drosophila*. But I don't think it's much affection for *Drosophila*, it's just that houseflies are so obnoxious.

Q: Now that the Drosophila genome is sequenced and targeted gene knockout is possible, is the conventional mutagenesis screen obsolete?

No. I think the big advantage of a conventional screen is you don't have to know anything to do it. You just—the whole idea is you randomly knockout—if you're interested in a process you randomly knock out genes and you see what's going to affect them. A targeted knockout screen means that you pick a gene based on what you think you know. And a lot of times we're smart enough to pick the right gene, and you knock it out, and we might learn something. But, it's not clear to me that for all things that are interesting in biology we know enough to pick the right genes.

Q: Let's talk about Europe. Do you think there's still a significant opportunity for young scientists in Europe, as compared to America?

Oh sure. The significant opportunity for scientists, for young scientists probably the most important thing, is to put yourself in the circumstances, in a laboratory where there are other smart people around who want to do great things. And where that is doesn't matter as much as the greatness of the things that you do. So the question is, would I advise a graduate student to go abroad? Would I advise an undergraduate to do their graduate work in Europe? Would I advise a graduate student to go to Europe for a post-doc? Sure. It's not necessary, but I think it's a myth that the job market—you know, people say that if you're a grad student and you do a post-doc in Europe you'll never get a job coming back to the States. You'll get a job in the States, or anyplace, depending on what you do. And you're not going to get a job in the States unless you do something really exciting and whether you do that in the States or in Europe, people know about it. I think it's not worth it to go to Europe, and go to a lab that you don't believe is a great lab. I don't believe it's worth it to you to go to Europe because you want the European experience. I think if you go to Europe because there's a great lab and you want to work there, you will end up with having the European experience. And that's great. But, there's no disadvantage that I can see in doing a post-doc abroad.

Q: The Nobel Prize—was that just a fantastic experience?

Yes. The thing that I didn't know about it, what was really great, I mean they give you some money, you split it with the other people, the United States government takes half of it in taxes, it's the only government that does that—

Q: A full half.

Full half, 52% in my case. The United States, New Jersey taxes, the whole works. It's considered taxable income so you don't really end up with that much. It's still money, but it's not that much. It's not the money. It's actually not the fame. You're already kind of famous, you already have a little bit of respect in the world by the time you get there—it doesn't come that much out of the blue…But what is really great is that you go to Stockholm in December and it's, for 10 ten days, it's just like continuous parties. And you wear these fancy clothes that you would never wear except if your children were

getting married, and…you have your family there. I had my folks there…You understand, also, that when you're in Sweden it's kind of far North, and the sun comes up at 10 o'clock in the morning and goes down at 3. And so it tends to be dark a lot and the Swedes at this time of year are also really desperate for parties so my theory is that they have this party that goes from, you know, the darkest time of year, and they have it every year because they have to have this party because every year it gets dark and unpleasant…But to make the party more interesting each year they have these honored guests. And your job, as a Nobel laureate, is to be the honored guest that year. So you go to all these parties and these people are really happy to have you there and they're great hosts…The Swedes also like things formal in the sense that they have parties where they go and dress up and they have these formal parties with social customs…And even though they're wearing these formal clothes they will leap up in the middle of the dinner and stand on the table and sing these songs and then get back down and—a lot of really wonderful parties, wonderful spirit…What is the nicest thing, for me, is just the memory of being in Stockholm and wearing these clothes and all the little things that kind of happened to you that are kind of like vacation like memories. I met the king of Sweden twice…Those are the kinds of things that you remember and that's actually the thing, for me, that was the most valuable thing about the Nobel Prize. This out of the ordinary thing happened in my life…but that was cool. Sweden was cool.

Q: They fly you and your family over to Stockholm. Is it business class, first class?

They flew me first class, yes. Actually we offered our girls, our children, the opportunity—we had to pay for their tickets, but we would let them fly first class with us or they could fly coach and take the difference, keep the difference themselves. Naturally, being, you know, smart kids, they took coach. But then they convinced the stewardesses on the airplane, because they were children of a Nobel Laureate, to bump them up into first class anyway. So they got the money and they also flew first class.

Q: And they provide you with all the fancy clothing?

Well I rented my clothes. That's my one regret, I should have bought my tux.

Q: When are you ever going to need to wear one again?

I know but it would've been nice to have it. You know, you can go into the closet and put it on. I could, you know, wear it to departmental Christmas parties, any of those things.

Q: But you can wear the medal.

I could wear the medal, yeah. I haven't— I don't know what to do with the medal…Actually, what I did is, I put it in a safety box in the bank in Princeton and haven't seen it for five years but I assume it's still in the box somewhere. I mean I'm not going to go in, open up the box and fondle the medal on occasion. That's not what you really want to do with your life.

Q: Do you remember getting the phone call?

Oh yeah. Vaguely…They called, my wife picked up the phone, she handed it over to me. I, uh, well, I thought it was a wrong number. Why would someone call from Sweden? They made the announcement on [Monday] Oct 12. Before they make the public announcement in Sweden they call the people who receive the prize. If you're in the States, 10:30 Sweden time is 5:30 am US time. It was a year that I was teaching freshman, and had set up a class, a freshman seminar, and I realized I had organized the class but I hadn't really prepared everything. It was coming to the end of the weekend and I realized it was going to be a true disaster. The class was at 1 o'clock on Monday and it was midnight [on Sunday] and I was thinking 'how is it going to be possible to organize this into a successful class?' And I realized I was headed for a major teaching disaster on Monday and there was no solution. I thought I'll get up early on Monday and I'll go into the lab and work all day to try to rescue this class because it's going to be a disaster and nothing is going to save me. Then I went to bed and at 5:30 [in the morning] there was this phone call. Saved…And they announce this [publically] and then the phone starts ringing and these people are calling from Buenos Aires and Hong Kong and want to know what you're going to do with the money, what does [the prize citation] mean. I went into the lab and started sorting flies and then, of course, all these people come in and the University organizes a press conference. So you really become like a famous person and you're in the newspaper and on the news and reporters are calling to get interviews…it doesn't last very long. The next day, Tuesday, reporters were already beginning to call up and cancel their interviews for Wednesday because you're already old stuff…

Q: What about the class?

Ah. I taught the class, of course. But it was great, I mean, I didn't get any more preparation in, but the kids were all convinced the stuff must be important. Nothing like good will on the part of your student population to help with a class…The University sent over people to photograph during class because it was like 'ah, he wins the Nobel award and still he goes into his class and teaches his freshman.'

Q: So you had no idea, you weren't expecting this? In the back of your mind, you weren't thinking…

Even in the back of my mind I was not thinking it…I didn't expect it to happen. My sense is that some of the awards, and I think in my mind this is true of Physics, that Physics is such an advanced science that it's pretty clear, the history of Physics, the major accomplishments of Physics, you can look at Physics and…there is a much stronger consensus of what are the major accomplishments in physics than there is in biology… But of course the reason we're all biologists is we're not smart enough to be physicists. If we were smart enough to be physicists we could probably be smart enough to sit around and think about what would be the great experiments. But since we're biologists we have to accept the basic humility of our situation that we're not smart enough and the

field isn't advanced enough to allow us to approach science that way. So the only thing that we can do is go to the lab and try to come up with the best experiment to do and then struggle desperately to get it to work…It's really a crapshoot to think that you would ever get a Nobel award in Medicine and Physiology because there are hundreds of experiments that are in many respects comparable, in terms of their impact, to yours. And so you don't anticipate it, if you're smart. You just sit around, and do your experiments and enjoy being a biologist and then…maybe.

Q: It obviously doesn't seem to have lessened your scientific motivation at all. Or has it?

No.

Q: What has changed? Do you do less lab work, more lecturing…

No. I decided that I wouldn't let it change anything in my life, so I don't do any less lab work. It obviously changes some things. People are actually interested in what I have to say. They sometimes call up and want to get opinions on a lot of things that I don't know anything about. Probably the University is happier that I'm there. I probably have more cache in terms of, I could ask for things if I ever wanted it and I might have a better chance of getting it. All of that is probably true but I pretend, in my own mind, like it's not true because it's easier to live your life if you don't assume those things. In reality it has changed my life, but it hasn't really changed it that much. I think because I was happy with my life before. I am happy in the lab. I go into the lab every morning, I sort my flies, I do my experiments, I struggle with administration, I struggle with my teaching, I struggle with all my other jobs. I still try to get in four to six hours a day at the bench.

Q: Actually at the bench?

Yeah. I don't always succeed, but mostly it's in the range of four hours a day.

Q: It's a little unusual for a senior investigator to still…

It's easy. Again, because if I were doing something really complicated, like molecular biology, or—but working with flies is so easy that you, even a PI can do it.