Changing the practice of medicine: an interview with Mark Fishman

Mark Fishman has served as President of the Novartis Institutes for BioMedical Research (NIBR) since 2002, and in a former academic role was among the first to develop the zebrafish system for studying development and disease. Here, he recalls what it was like to ride the first real wave of zebrafish research, discusses industry-academia collaborations and provides a current perspective on drug development.

How did you become interested in science? My father was a physiologist and pulmonary physician, and his influence encouraged my interest in biology. As a family, we used to go to explore marine biology in Maine, and I became interested in fish and other marine animals from a young age. Later, I worked in different labs as a technician, usually on fish physiology, during the summers.

Where and with whom did you train? I trained in Medicine at Harvard, and then did my residency and cardiology training at Massachusetts General Hospital. I then did a postdoc at the NIH with Phil Nelson and Marshall Nirenberg. I worked mainly on synaptic development during that time. It wasn’t until later that I learned genetics, in part during a sabbatical with Phil Leder at Harvard.

What has been the most exciting period of your career? Scientifically, it has to be the zebrafish screens. Setting them up, getting the first glimmers of success and then beginning to discover steps of organ formation, for the first time anywhere. We had a great team of colleagues, and all felt we were discovering not just genes but the overall logic of vertebrate development.

You were among the first people to adopt the zebrafish as a model for basic research. What made you choose this organism? At that time, I was thinking about areas that were still completely unexplored – where we were missing paradigms. In particular, I had been considering how we could approach the formation of vertebrate organ systems. I played with a few different approaches – chick, fruit fly and so on – and I eventually realised that zebrafish genetics was the way to go. I used to have dinner regularly with a friend of mine, Bob Horvitz. Bob was one of the inventors of the nematode system, and I was getting quite envious of his ability to dissect cell-fate decisions in that animal. Speaking with him really convinced me that genetics was the way to go. I then read of the work by George Streisinger, Chuck Kimmel and Monte Westerfield on zebrafish. George Streisinger was the person that first showed that the zebrafish was a genetically tractable system, but he died soon thereafter. Chuck and Monte continued to do work on zebrafish embryology.

For me, this organism looked like an opportunity. So, Wolfgang Driever and I went on to set up a screen. I didn’t know at the time that we would be in such competition with someone else doing a similar screen at the same time – Janni [Christiane] Nüsslein-Volhard. I managed to explain to Janni that we had different interests: mine were in how organs formed, whereas she wanted to learn about early development and neurogenesis. So, in the end, the mentors that guided me into the zebrafish field were Bob Horvitz, over Chinese food, and Janni Nüsslein-Volhard, who started out as a competitor and became a close friend.

The zebrafish community is quite friendly; has it always been so? It was wonderful from the beginning. At that time, most people in the field came from one of three institutions: either Mass General where I was, from Janni’s institute in Tübingen, or from the Oregon group, where Monte Westerfield and Chuck Kimmel were based. We not only knew each other but also the technicians and the students in those groups. So, for the first few years, it was a very tight-knit community. It grew quickly, of course, but everyone has remained close. As the field exploded, we all realised there were so many directions to go. Janni and we did the first large-scale screens, but then all of the mutations we discovered had to be worked up, and that sustained a whole generation of postdocs. Now there have been many more screens, and many more exciting questions to work on. It remains a wonderful community.

When did you realise how powerful zebrafish was going to be in your research? There were three exciting phases to our early zebrafish work. The first eureka
moment, so to speak, was when we realised that certain mutations deleted discrete units of organs. That meant that organ morphogenesis would be decipherable. This wasn't a given, you see; it could have been that many mutations would affect the heart or the kidney or other organs, but that the effects would not be interpretable. The embryo or organ affected might simply have become a jumble of tissue. In fact, there was a lot of scepticism that a genetic approach would work to decipher organ development. Organs form relatively late, compared, for example, with early embryonic patterning decisions. Some predicted that mutations in genes with early and late roles would have phenotypes related only to the former. Would we ever find informative mutations, for example, about the fashioning of heart valves if the same genes were important to early patterning? But, it turned out to work! The first time that we saw a fish mutant missing heart valves, but with the rest of the body and organ relatively intact, we knew that we would be able to dissect the steps of organ development. We could define genetic 'units'.

Second, we started to find sets of mutations that affected specific physiological functions; for example, the rhythm or contractility of the heart. This meant that we could look at developmental physiology for the first time in a genetic way. These kinds of mutations couldn't be studied in mice because the corresponding mouse mutants would die in utero. By contrast, the fish embryo lives by diffusion for a few days. So, we realised that the zebrafish would allow us to study biological functions that are intractable in other animals.

Third, we started to discover zebrafish models of human disease. For example, we found a mutant with a phenotype similar to a type of human porphyria. We also found many mutations that caused cardiac arrhythmias or heart failure. Each mutation could then point to a gene that was potentially involved in human disease. We also found that these mutant embryos could be used for screening of potential drugs that ameliorate the phenotype.

For me, the fact that these complex functions were decipherable was breathtaking. We could assemble all of these mutations we found in a way that would enable us to start looking at pathways underlying the formation and function of tissues.

What do you think is an important next step for the zebrafish field?
At the moment, I think that there's pretty good evidence that we can begin to dissect behaviour in the zebrafish. The models are tricky, and sometimes of questionable relevance to humans, and fish are simpler than humans in terms of the complexity of their neural networks – but I have confidence that we will be able to extrapolate from fish to human behaviour.

“Moving to an industry environment was the hardest thing I've ever done – harder even than being a medical intern. It was a whole new way of thinking that I hadn't experienced before”

How did you come to be President of NIBR?
It was completely out of the blue. I was in an academic position at Mass General, and I wasn't even aware that Novartis was a pharmaceutical company. I had no relationships with other pharmaceutical companies, aside from receiving some funding from time to time. I was called up by Dr Vasella, the CEO of Novartis, to ask if I would meet for dinner to discuss running research. I said that I would be delighted to have dinner, but not to change jobs. I was completely happy: I was Chief of Cardiology and our work with zebrafish was going beautifully. In the end, I did end up meeting him to discuss research programmes, many times in fact, and we ended up becoming friends. Ultimately I decided to take the position for several reasons: because of my confidence that Dr Vasella really wanted me to reinvent drug discovery in Novartis; because it looked like an incredible scientific challenge; and, mostly, because I convinced myself that this way I could have a major impact on medicine. In fact, my son, about 10 at the time, put it most succinctly: “Dad”, he said, “I love your zebrafish, don't get me wrong, but don't you think it would be more important to make medicines?”

Moving to an industry environment was the hardest thing I've ever done – harder even than being a medical intern. It was a whole new way of thinking that I hadn't experienced before.

An important part of translating basic science to the clinic is collaborating with industry. From an industry perspective, what makes a potential academic project attractive?
I can't tell you what every company considers, but I'll try to explain how Novartis looks at its relationships. Working with academia is extremely important for us: it expands our horizons and acts as a quality control. We have many long-standing collaborations with academic groups, as well as an academic advisory board that criticises our research programmes. The basis of academic relationships for us is the scientist-to-scientist collaboration. We hire outstanding scientists, and they collaborate with other scientists internally and externally. We've tried to remove the barriers so that scientists can work together and publish together, just as they would anywhere else.

Another way we establish collaborations is through groups that come to us with a project. This certainly happens, and it can happen at an early stage or a late stage of a project. Even through that route, however, there has to be someone inside that serves as a champion. If someone in NIBR is excited, then we might be interested in it. This is because we run each collaboration as an integrated programme – it's not as if we're at a distance, providing funding and then stepping away. For us, it's not that different from how collaborations are forged in academia.

When we look at projects in general – whether internally or externally – we're looking for projects that will change the practice of medicine. We're looking for projects where there is something intrinsic that represents a wonderful new opportunity. This might be something at a technical level – something that will jump-start a programme or serve as a platform for many of the different disease programmes we have here at Novartis. But we get a huge number of opportunities presented to us every month, often from groups that think they've found the next great drug. Many are overly optimistic about how quickly their project can be made into a medicine. If only it were that simple! Of the 20 new drugs approved each year by the FDA, only about five are directed at truly new targets. When it comes to drug development, we're not talking about a high success rate. So, one alternative we've started here is on occasion not to collaborate per se, but to act as pro bono advisors. We
might ask whether they’ve really thought about the safety concerns, point out cases where a compound will never make it as a drug, or when there are already ten similar drugs out there – whatever the case may be.

“When we look at projects in general…we’re looking for projects that will change the practice of medicine”

Much academic research is focussed on understanding rare and neglected diseases. Many companies aren’t interested in developing therapies for such diseases because they aren’t likely to be profitable. What is NIBR’s take on this? For us, rare diseases are central to our mission. In fact, we’re working on 50 of them. In particular, we try to work on rare diseases where the mechanism is relatively clear, and where we think we can exploit that fundamental mechanism more broadly, once we have a drug for it. For example, we had an antibody to interleukin-1, which would traditionally have been studied in the context of rheumatoid arthritis or another complex inflammatory disease. Instead, we focussed on testing it in the context of CAPS [cryopyrin-associated periodic syndrome, comprising several rare autoinflammatory disorders], and we were able to get the studies done quite quickly and the drug registered rapidly. The same pathway involved in CAPS is involved in the pathology of gout, systemic onset idiopathic juvenile arthritis and possibly atherosclerosis. So, we look at these rare diseases as models, and we begin the process of going into the clinic by looking at a rare disease, or at least a subset of the population that can be defined. We aren’t interested in studying all rare diseases, such as rare diseases of inherited metabolism (such as Gaucher disease and others) – not because they’re not important, but because the targets or therapies that exist aren’t something we can see how to rapidly expand to other more common indications.

Many other companies are also dedicated to studying rare and neglected diseases, although I don’t know how they make their decisions. And of course Francis Collins has set up an NIH Institute, part of which functions to facilitate the study of rare and neglected diseases, which has hopefully helped to increase work on these as well. I think that the approach encouraged at the NIH is quite similar to what we’re doing at Novartis. Overall, research in this direction will evolve because, at the moment, we are aware of ~6000 Mendelian disorders, and we know the cause of 3000 of them. Undoubtedly, we’ll know the cause of many others soon as well. But we will also begin to uncover heritable disorders that aren’t strictly Mendelian through next-generation sequencing. So, the possibility of looking at subpopulations will expand, and people will have to grapple with this in both industry and academia.

Another interesting point related to developing drugs for rare diseases is that, once you have a treatment for a disease, I believe more and more patients will be diagnosed than when it was believed hopeless. I suspect the subconscious of a physician will search more readily for rare diseases in their patient when they know of a potential therapy. I cannot prove this; it’s just a suspicion.

What area of drug development are you most excited about at the moment?

I don’t like to pick favourites among our programmes, but the reality is that a programme gets more exciting as it gets close to the clinic. So, anything where we’re close to getting into patients is exciting. At the early end of this process, I’m excited about our efforts in regenerative medicine, where we are trying to find molecules that will capture the activity of intrinsic stem cells and tissues. I believe that will help to address some chronic diseases of aging.

What area of medicine do you think will see the most advances in drug development in the coming years?

In a practical way, I think we’ll see the most change in oncology, in terms of the number of medicines reaching registration, simply because there are so many coming through now. In the discovery realm, I think that regenerative medicine will be important, and possibly psychiatry, because genetic studies of psychiatric diseases are beginning to reveal the genes responsible for many of these diseases. It’s unlikely that these findings will lead to new medicines within the next decade, but in terms of the discovery process I think those diseases will be important.

If you could go back to the bench now and start a new project, what would you do?

If I had to start now, I would seriously consider studying the genetics of psychiatric diseases, both in humans and in model organisms.

Any advice for young scientists?

What I found best is to work on what you love. Choose a problem that interests you, and a tractable approach for addressing it. I would not consider too much what is fashionable, because the world changes all the time.

What would our readers be surprised to know about you?

I’m an adult-onset cello player.