interview

Mark Fishman on changing the grammar of drug discovery

Interviewed by Christopher Watson

Mark Fishman,
President, Novartis Institutes for BioMedical Research

Mark C. Fishman is President of the Novartis Institutes for BioMedical Research, President and CEO of the Novartis Institutes for BioMedical Research, Inc. and a member of the Executive Committee of Novartis AG. He leads all worldwide discovery research activities of Novartis in the US, Europe, and Japan. Prior to accepting his current post, Dr. Fishman was Professor of Medicine at Harvard Medical School, and Chief of Cardiology and Director of the Cardiovascular Research Center at the Massachusetts General Hospital. As a scientist, Dr. Fishman, contemporaneously with Dr. Nusslein-Volhard, introduced the zebrafish as a genetic model system for vertebrate development. He is also the author of the best-selling medical textbook, *Medicine*. A graduate of Yale College and Harvard Medical School, Dr. Fishman completed his Internal Medicine Residency, Chief Residency, and Cardiology training at the Massachusetts General Hospital. He serves on several editorial boards, has worked with numerous national policy and scientific committees, and is a member of the American Academy of Arts and Sciences.

Could you outline Novartis's rationale for organising the company's research activities under the umbrella of the Novartis Institutes for BioMedical Research (NIBR)? How is this different to the efforts of competitor companies?

I suspect that it arose from a recognition that the discovery process is key to the future of pharmaceuticals and the question of how to best make a discovery engine for pharmaceuticals. The conclusion was that a dedicated entity was needed where all of the components were focused on the mission. That means not only the scientific part, but the administrative part and strategic alliances, and this led to this new entity called the NIBR. I really can't comment on what competitors are doing, I don't know in detail and it is not even appropriate for me do try to do so. However, there is a sense I have that there is a novelty to this and it represents a clear-eyed focus on science and medicine.

What are the main strategic goals for NIBR for the next couple of years?

The initial years, and we are still in the midst of these initial years, are concerned with building and recruiting. The fastest phase of recruitment is completed and we have done it much more quickly than we could have anticipated; we now have almost 900 people here in Cambridge. But there is probably still another year or two of more aggressive than usual recruiting.

For me it is very important to establish the new sociology of science – a critical, thoughtful and open approach with which to launch the new programme. Clearly in the next few years we have to make sure we have a smooth system for the transition from preclinical pipeline to the clinic. It's extremely important to me that we keep the focus here on the patients.

When do you expect to see the large investment in the NIBR producing tangible results?

We already are. I think we can see it in two ways. First, the Proof of Concept trial, which is the clinical trial approach that we are taking, is quite expeditious and focused and has permitted us to more rapidly complete some trials, some of which I talked about at the FRESCO analyst conference a couple of months ago. The clinical Proof of Concept trial is a mechanistic trial of efficacy, using small populations of patients with very well-defined disorders, and is accomplished with alacrity. In standard parlance, it combines current Phase 1 and 2a studies. Secondly, we have already reduced the late attrition in the preclinical pipeline so I think the quality controls that we have put in place have gone up. Early attention to whether the compound actually has

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drug-like properties, classically left until just before the clinic (such as toxicology or metabolism studies), means we select the most robust candidate for clinical trial. If you are asking when some entity will be brought through that was totally started within the confines of a new programme, I think the standard would be getting to the clinic in seven years or so; we would like to see it in five. I think we can do that. Our goals are to get more into the clinic in the next five years.

What are the challenges of co-ordinating research strategy and operations across two continents and two different cultures?
I never really look at science as a monolithic structure and I think we should cherish some of the differences between people. The issue of course is making sure that we have a unity of purpose and quality of science. So, aside from some continuous jetlag on my part, it's not really a big problem.

Integration seems to be very much at the heart of NIBR. How are different scientific disciplines being integrated there?
It is an interesting question. I think at the end of the day, the best integration occurs at the lab level. The post-doctoral fellow in the genomics lab works with the young scientist in the chemistry lab, who has a particular relationship to the oncology group, and so on. We foster those sorts of interactions in several ways. The first, of course, is by arranging regular presentations amongst the groups, as well as across the different continents. Second, we have a policy of rewarding those who are open and share information, both at a formal and informal level. Finally, we have a set of ambassadors, including myself, who are sort of like little honeybees cross-pollinating. They form a group that we call the Programme Office, which is dedicated specifically to this cross-fertilisation.

What are the biggest challenges for an academic scientist coming into the commercial environment?
I think every academic scientist will come in with a different approach and will have different issues. For me, the biggest issue is that I want to know everything thoroughly and there is no way to learn this except on the job, and the breadth of this is immense. I don't think any field of science is as broad as drug discovery.

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Prior to taking up your place, you did a two-month 'crash course' at Harvard Business School. Did that prepare you for the rigors of the pharmaceutical industry?
Well, I did learn finance and accounting and economics, but I am not sure that I would call Harvard the real world! What was helpful to me, joking aside, was actually meeting my classmates there, who were engaged in business, and learning what motivated them, what they like, what they were troubled by in the business community, how they responded and what were the issues that they were most concerned about. That actually helped me a lot in terms of understanding that part of my new colleague community.

The recently announced collaboration between NIBR and The Broad Institute to look for underlying genetic causes of Type II diabetes is a very progressive step on the part of a private pharma company because findings will be made public for other scientists to use. What are the key benefits for Novartis in this initiative?
There are several. First, it rapidly advances our own agenda. We have a big commitment to understanding diabetes and adopting novel approaches to that disease, and understanding how that patient population can be subdivided. Second, it allows our scientists to continue learning and to continue being challenged by experts in a field that is constantly changing. It also gives us a new cadre of potential recruits that might join Novartis in the future.

Was it a struggle to convince the Novartis Board to take this approach?
No, I wouldn't say that there was really a struggle. It did require some explanation, and there were certainly some quizzical looks around the table, but I think that they were exerting a very reasonable desire to understand what the benefits were and once they did they were supportive.

This approach will presumably be used in other therapeutic areas?
Yes, we are always open to this. The nature of the academic partner is extremely important in this of course. There needs to be a real understanding that this is a partnership between the groups and that the scientists on both sides are valued for what they bring to the table. This is not, by any means, sponsored research – this is a joint scientific effort.

You have emphasized the importance of studying pathways in searching for drug targets and understanding disease. Does our ability to define these disease-related pathways and networks really help in the drug discovery process?
The notion of pathways is really a shorthand for figuring out how to incorporate the genome into drug discovery. I believe it is simply not feasible to work through 24,000 genes one by one. It is much more sensible, and practical, to look at them in these connected networks. This is one of the great lessons we have learned from developmental biology. Embryology looked like a completely intractable field for molecular biologists until they began to understand that there were these interconnected pathways that played out again and again and again; once to make the gastrula, then to make the segments and then later to make the bones. It is a very simplifying process.

'I cannot think of a greater challenge than making medicines.'

There seems to be a greater fascination in the industry now with basic academic biological research and the NIBR and your appointment would seem to be indicative of this. Is such a curiosity-driven approach compatible with such a market-driven industry?
I think it depends on how you define science. As Peter Medawar once said, science is the art of the feasible. I may be misquoting him a bit, but his point is that science is not about aimless curiosity. Great science always revolves around solving great challenges. I cannot think of a greater challenge than making medicines.

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In your opinion, when will advances in genomics and proteomics begin to impact on the discovery pipeline?
I think they are right now. The drugs that target activated pathways in cancer were not discovered so long ago and they are now already taken for granted. Those have been very powerful, basically genomic-based approaches. If you ask when the essential grammar of the discovery process will change, this still needs greater linkage between the genome and the disease. That is, I think, a process that will be continuous, but my guess is that drug discovery will look very different in seven to ten years than it does now.

During the development of Gleevec the collaboration with patients was much deeper. Will that continue and how will you ensure this?
As a physician, I can tell you I believe it is extremely important, for many reasons, to keep the patients involved. Let me give you an example of some of the ways we go about it. All of the disease-area groups at NIBR have to meet with patients during the year to find out what the disease really means to them. So, all of the scientists here should have some familiarity with the reality of the disease that they are studying. I work regularly and meet regularly with various advocacy groups to understand what they need and there are some areas where we are trying to work together. Therefore, patient care really permeates our whole discovery process.

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What new advances and technologies are you excited about at the moment?
Personally, I still am convinced that the application and the understanding of developmental genetics holds great promise for the discovery of new medicines and the potential of this is still untapped to a large degree. If you asked me about a technical advance, I would say a key one would be molecular imaging for understanding how these processes play out *in vivo*.

Who or what has been your greatest inspiration?
I can't say that there is any one person, rather an amalgam. I was fortunate in having a father who is committed to both medicine and science. As I matured in the field, I was also fortunate to have many close friends who are great scientists, such as Janni Nuesslein-Volhard and Bob Horvitz, now both Nobel laureates, who taught me that no challenge was too great as long as you understood where you were trying to go. The other key inspiration for me is people who have enough breadth to incorporate artistic or scientific motivations with very practical ones. There are those who are journalists and also fiction writers, such as Gabriel García Márquez, or those who are scientists, such as Leonardo, who are very engaged with their society.

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When counting sheep does not help: the growing incidence of sleep disorders

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> ***'O weary night, O long and tedious night, Abate thy hour! ... And sleep, that sometimes shuts up sorrow's eye, Steal me awhile from mine own company.'***
> Helena, *'A Midsummer Night's Dream'*, by William Shakespeare

We humans spend a third of our lives sleeping; an activity (or passivity) essential to our health and general well-being. Although sleep requirements between individuals vary, on average we indulge in a good seven to nine hours every night. Sleep is regulated by the hypothalamus, which releases specific neurotransmitters, such as serotonin, γ-aminobutyric acid (GABA), adenosine and endogenous opiates, all of which induce sleep. Electroencephalogram readings from sleeping subjects show that sleep oscillates between two states – passive, resting sleep and rapid-eye movement (REM) sleep, during which dreams occur.

Impact of sleep disorders

The term 'sleeping disorder' can mean any of a number of complaints, including insomnia, parasomnia (the symptoms of which include sleepwalking and night-terrors), narcolepsy, obstructive sleep apnoea, 'jet-lag syndrome', disturbed biological and circadian rhythms and restless leg syndrome. Current therapeutic treatments tend to target the symptoms of these disorders, rather than the underlying pathophysiology – often the precise cause of a sleeping disorder is, in fact, a different disorder entirely.

In the USA alone, the number of sleep disorder clinics and specialist physicians has

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