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Roger Perlmutter on shaping Amgen's R&D strategy

Interviewed by Christopher Watson

Roger M. Perlmutter
Executive Vice President, Research and Development, Amgen

Roger M. Perlmutter joined Amgen as executive vice president, Research and Development in January 2001. Dr. Perlmutter oversees the company's worldwide Research and Development Operations and is a member of Amgen's executive committee. Before joining Amgen, Dr.Perlmutter was executive vice president at Merck Research Laboratories. He also held positions as chairman, Department of Immunology, at the University of Washington; and he was an investigator for Howard Hughes Medical Institute from 1991 to 1997. Dr. Perlmutter received his bachelor's degree in 1973 from Reed College, Portland, Oregon, and his MD and PhD from Washington University, St. Louis, Missouri in 1979.

Your academic research focused on immunology – what attracted you to this field?
I started becoming interested in immunology as an undergraduate when I was in college. I attended a school in the US called Reed College in Portland, Oregon and ended up doing my senior thesis on the analysis of pharmacologic immunodepressants. So, in a way, I have sort of stayed with that for more than 30 years.

What were the factors that made you switch over from a successful academic career to industry?
I had a wonderful academic career and at the time I made the decision to leave I was chairman of the Department of Immunology at the University of Washington, a member of the Departments of Medicine and Biochemistry as well as a member of the Howard Hughes Medical Institute, and I was doing work that I enjoyed very much. However, I had always wanted to be involved in drug discovery and I had worked as a consultant and a member of the scientific advisory boards for a number of pharmaceutical companies, so I had come to know the process, as far as one can from the outside. I had flirted with the idea of trying to move into the pharmaceutical industry, then the opportunity came to join Merck and I had a deep respect for their capabilities. I guess the second thing I would say is that I always believed that there was a tremendous scientific opportunity at the interface between synthetic organic chemistry and molecular biology and I was very interested in the idea of harnessing synthetic organic chemistry to explore and interpret biological processes. Using synthetic chemistry as a tool to understand biology is not something that one can do very well in a university setting. Synthetic chemistry is not well represented in most academic universities – certainly not at most medical schools – whereas fine chemistry reaches its apotheosis in the pharmaceutical industry. Therefore, industry was a place where you could actually have a good interface between synthetic organic chemistry and molecular biology and that was extremely appealing to me.

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What do you miss about the academic environment?
First of all, time to think! What one misses most about the academic setting, frankly, is scholarship. That is, throughout one's academic research career, from the time one pursues an advanced degree in biomedical research, the goal is to gain an extraordinary depth in some narrow subject area. And so, in one particular area you know all of the published literature. It is a very narrow area, but you know it all, and you can approach that particular topic with deep scholarship. My problem in the pharmaceutical industry is that I end up being a mile wide and a millimetre deep and I very much miss the confidence that comes from knowing all that can be known in one particular area.

What role do you think academia has in drug discovery?
I think academia has always had the leading role in terms of identifying targets and that

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will continue. Even with constraints in funding for biomedical research, you are still talking about US$28 billion at the NIH and a substantial fraction of that supports exploratory research. No pharmaceutical company can hope to deploy more than perhaps US$100 million at the most for exploratory research so target identification is an area where academia will continue to really shine. The history of broad-spectrum interaction between industry and academia over the last 20 years is chequered at best. However, the relationships that have proven productive are those that were formed at the grassroots between investigators who shared a common interest, where industry provided funds to support research, and university investigators contributed to the critique of industry's efforts. This has worked time and time again. Broad-based relationships between industries and academic institutions, frankly, have not.

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What are the reasons for this?

The most important reason is that the interest of an academic institution and the interests of industry are not aligned, and are not easy to align. The fundamental goal of an academic institution is the acquisition and dissemination of new knowledge, full stop. We in industry are trying to make drugs, a wholly different enterprise. Academic researchers treasure perplexing, inexplicable and highly reproducible results, because a career can be made out of such things. The last thing in the world I want in industry is findings that are perplexing, inexplicable and highly reproducible! Instead, I would love to have (you never have it, by the way) is a target that can be approached for a disease wherein everything lines up from the time the target is selected; every experiment I do thereafter works exactly the way you would expect time and time again. A university professor would hate that. There is nothing there for them to build a career on. Therefore, the interest of the university and the interests of companies end up being really quite different. They start from the same point of view of saying 'wouldn't it be nice to discover something important', but they diverge immediately. As a result, these broad-based interactions I spoke of end up being quite problematic. I also think it is very difficult for a university to build the infrastructure necessary to do drug discovery, because a lot of critically important but unsurprising results must be adduced and documented. It is hard to motivate people in universities to do these things and you can't publish the results.

Why did you decide to make the move from Big Pharma to biotech?

This actually was a very easy decision. First of all, Merck is a wonderful company. However, Merck is also a big, old established company with more than 100 years' history. In such companies, it is hard to introduce new initiatives. I had the idea that drug discovery really needed to change a lot, that we needed to speak differently about drug discovery and to do so we needed to build a different kind of drug discovery organization. Within about 30 seconds of visiting Amgen I knew that this was a terrific place for me. Amgen had never had a head of research and development before. I am the first. Therefore, it was an opportunity to paint on a very broad canvas.

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How do you think you have shaped Amgen's R&D strategy?

I brought to Amgen four guiding principles that inform our strategy in research and development. The first was: focus on grievous illness. You might say, 'Of course. What else would you do?' But the fact of the matter is, by virtue of the strength of franchises that have been established in the traditional pharmaceutical industry, much effort is expended in engineering modest improvements to existing therapeutics as a means of supporting the franchise. There is a substantial amount of work on lifecycle extension that has to be done just to preserve the base of the company. When I came to Amgen there were really only two (albeit extraordinarily successful) products. There was little need to support existing franchises, which gave us the opportunity to think more broadly about the people who could really benefit from our best efforts.

'In a traditional pharmaceutical company, you have one hammer and everything looks like a nail.'

The second guiding principle was to be modality independent. In a traditional pharmaceutical company, you have one hammer and everything looks like a nail. A traditional pharmaceutical company looks for a disease target that can be approached with a potent, orally bioavailable, once daily, highly selective molecule, that can be manufactured in existing facilities and packaged in a blister pack. In my view, because it is so hard to make a drug that actually works, why would we want to limit ourselves to any particular modality? I don't care if the target is best approached using a protein therapeutic, an antibody, a small molecule, a nucleic acid, a cell based therapy, I don't care what it is. I want to fit the tool to the task – to ask the question, 'What is the best possible target?' To do that, you have to build a research organization that is comfortable working in all of these different modalities. In a traditional pharmaceutical company, it is relatively difficult to build an interdisciplinary research organization that addresses topics at the interfaces between chemistry, biology, molecular biology and so on. My feeling is that the most interesting science is always going on at the interfaces between conventional disciplines. Amgen was a place where I could build an interdisciplinary group that would focus on those interfaces and that is exactly what we have done. If I am proud of anything I have achieved in the last four or five years here at Amgen, it is that – building a research organisation where interdisciplinary science is emphasized. I don't think anyone has a research organisation like Amgen in the industry, period. It is very different.

The third guiding principle is: 'Do the experiment in people'. That has two parts to it. The first is 'do an experiment' and the second is 'do it in people'. Here is the fundamental reason why I make the statement that way. If it is the case that pre-clinical models have almost no predictable

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value for human disease, why bother to use them? Why bother developing four different animal models of asthma and testing drugs in each one of those four, hoping to find the one that works best in all four, when none of them has any predictive value in human asthma? Why don't we just stop doing that? The disease that we want to study is human asthma, hence we should be doing the experiment in patients. However, if you are going to do an experiment in patients we have an ethical responsibility to actually do an experiment, to adduce interpretable results. So, if I introduce a potential drug candidate, I want to know that I hit the target and the pathway that I wanted to hit, in the relevant cells, in patients with the disease. Often in the conventional pharmaceutical development paradigm the best information you have is simply the concentration of free drug in the plasma that is associated with the therapeutic effect in an animal model, which we can all agree has no predictive value. And so you simply go to humans and say, 'well, let's achieve the same concentration'. Under these circumstances, when the drug doesn't work (and drugs almost always fail in such studies) you don't know whether you actually hit a target and the target was no good, or whether you never actually hit the target and the target might have been fine. You can't draw any conclusions from those kinds of phase II studies.

To address this concern we have spent quite a bit of time building a medical sciences group here at Amgen, which consists of people cross-trained in medicine and in basic research, with the goal of developing the assay systems and the biomarkers necessary to show that any potential drug that we introduce into people really hits the target it is supposed to hit. What I had said to our basic researchers from the outset is 'we will not bring forward a molecule that you think could be a drug unless you can tell me how I will test that it actually hits the target in people'. We therefore deploy our biomarker working groups and our medical sciences groups right from the beginning to try to develop the tools necessary to study the disease in people. That often means that we have to do a series of phase zero studies in people with the disease, where we ask questions about what we can measure, what the signal to noise ratio is and so on. I would say, in terms of status report on this effort, we are doing well in our medical sciences group but we still have a long way to go. There is a lot that needs to be done to develop non-invasive techniques for studying biochemical pathways in humans but we have certainly made the commitment and we save ourselves the, what I think is, ill-advised expense of trying to build better animal models as a means of studying human disease. It seems to me that we have the animal model – it is humans you need to study.

'It seems to me that we have the animal model – it is humans you need to study.'

The last guiding principle is something that I refer to as 'seamless integration'. I want to have a completely integrated approach to the drug discovery process all the way from our basic research group right through to the sales team. I want to have marketing people at our basic research meetings, not because we want marketers to tell us how to do basic research; they can't do that. However, there are insights that come from the market place that are almost impossible to obtain by any other method, and we need to have an appreciation of that. Moreover, marketers need to have an understanding of basic research. Amgen is engaged in exploring targets that, by and large, nobody else is pursuing. We have made a commitment as a company to focus on pioneering approaches to therapy. That is what we see as our niche in the world. And so, any time you are approaching completely new targets, there is a lot of work that has to be done, both internally to understand what the nature of the target is but also externally so that people understand how best to use a product as it comes from the basic science level. And for this reason we have integrated the whole process. George Morrow, our head of Sales and Marketing, and I work very closely – we do everything but keep house together. It is unusual because in the traditional pharmaceutical industry R&D and sales and marketing are often at sword's point.

So those are the four guiding principles that I brought to Amgen and it explains, I think, why it was attractive for me to come here, because it would have been essentially impossible for me to introduce that kind of approach to R&D, not only at Merck, but at any other hundred-year-old corporation that is already very successful.

What drugs in the Amgen pipeline are you most excited about?

AMG 162 is a remarkable drug candidate. It represents a completely novel approach to the treatment of bone disease. In this case, we have an antibody directed against a protein called RANK ligand, which we at Amgen, over a period of years, have shown is the principal regulator of bone resorption. We have shown that a single injection of the antibody directed against RANK ligand can suppress bone resorption almost completely for six months or more. This offers the opportunity to basically immunise people passively against excess bone resorption of the kind that occurs in postmenopausal osteoporosis, in male senile osteoporosis, in drug-induced osteoporotic disease, even potentially in metastatic disease. This is a completely different approach to treating bone disease and we think it is an approach that will be superior to anything that exists now and will dramatically reduce fracture rates.

I would also mention, in terms of novelty and as an illustration of how we think about disease and modalities here, AMG 531, which is Amgen's first peptibody. In this case, we have designed a peptide that is an agonist at the thrombopoietin receptor, which governs the production of platelets. We have then taken that peptide and conferred upon it pharmaceutically acceptable properties by virtue of linking it covalently to the Fc region of immunoglobulin. As a result, we get a long-lived injectable molecule that is an extremely potent agonist at the thrombopoietin receptor, but that does not raise concerns about immunogenicity, which other thrombopoeitin agonists have. We then went on to look at whether we can use our thrombopoeitin agonist to treat an autoimmune disease called immune thrombocytopenic purpura (ITP). This is a fairly rare disease, about 90,000 people in the US have this disease at any given time. In this disease people make an antibody attack

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against their own platelets and destroy their own platelets. The general approach to this disease is immunosuppression, which is only partly effective and has many side effects. Therefore, we wanted to determine whether we could produce more platelets than are destroyed in individuals with the disease by stimulating the thrombopoeitin effect. We have gone on to show that we can do that very effectively. In our phase II studies we can take most of those with low platelet counts and bring them back into an acceptable range with weekly injections of AMG 531, and our phase III studies for that molecule are scheduled to begin soon. So that is a really exciting new approach to a disease where we sort of re-conceptualised the whole thinking about it. That is the kind of thing that Amgen does very well.

You are Chairman of the Board of the Institute of Systems Biology (ISB). What sparked your interest in systems biology?

This is a longstanding discussion that Lee Hood and I have had. Lee is the president of the ISB, a founder of the Institute and a close friend and mentor over a period of about 25 years now. With the availability of parallel analytical tools such as microarrays and mass spectrometry for looking at, broadly speaking, protein expression, it became apparent that it was going to be possible to think quite differently about biological processes and how we explore them. In the past, mathematical modeling and theoretical biology hasn't had much of a role. I remember having these kinds of discussions as a graduate student about the distinction between physical scientists, where there were experimentalists and theorists, and biologists, where the theorists and the experimentalists were embodied in the same individual. There hasn't been much of a role for theoretical biologists.

Now, with the availability of these kinds of datasets, one can begin to develop mathematical models and then test those models in a very robust way. This is one of those situations where the most interesting science is going on at the interface between conventional disciplines, where physical scientists, computer scientists, biologists and chemists can all interact together and speak the same language. The ISB was born from that kind of thinking. The ISB is not quite five years old and at the time, while I was at Merck, I considered joining Lee Hood in establishing the Institute, because I found the idea so compelling and so interesting scientifically, but I couldn't give up on the idea of doing a better job with drug discovery, so I settled for being Chairman of the Board.

How is Amgen implementing systems approaches? Are there any in-house efforts in this direction?

At Amgen we have not done much to implement systems biology as a tool. I think it is way too early, frankly. I think there will come a time when it will be enormously valuable, but at the moment I think it is an academic discipline. We at Amgen have a deep commitment to parallel analytical tools, both in the protein and DNA areas, and we have computer models for analysing those data sets, but we don't really take a systems biology approach here. What we have done is try to have a look at what is going on not just at the ISB, but in the other systems biology groups that have been established around the country. We therefore take advantage of some of that input, but we haven't brought it in-house yet.

You are a director of Stem Cell Inc., a company focused on the use of adult stem cells to treat disease. What role do you see stem cells playing in future drug design efforts?

I would say that I have always been interested in working at the cutting edge of large scientific disciplines, whether that is systems biology, molecular biology or stem cell biology. I think that the potential for stem cells as a means of cell replacement in degenerative disease is enormous. From a biological perspective, understanding the process of differentiation and of self-renewal, has to me always been an extremely interesting area. Recently, a lot of progress has been made in terms of characterizing stem cells. I don't have the time and opportunity to stay close to this field as an academic discipline, but I can remain aware of what is going on in the stem cell field through my involvement with Stem Cells Inc. I think that the potential for stem cells as therapeutics will emerge over time, and it is going to emerge through companies like Stem Cells Inc. I would like to help craft that future.

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